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LIST OF ABBREVIATIONS

Abbreviation	Definition
ABS	absolute
ACQ	Asthma Control Questionnaire
ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
anti-IgE	anti-immunoglobulin E (omalizumab)
AQLQ	Asthma Quality of Life Questionnaire
AST	aspartate aminotransferase
ASUI	Asthma Symptom Utility Index
AUC	area under the curve
BL	baseline
BLA	Biologics License Application
CAC	Carcinogenicity Assessment Committee
CAE	clinical asthma exacerbation
$C_{av,ss}$	average concentration at steady state
cGMP	current Good Manufacturing Practices
CI	confidence interval
C_{max}	maximum concentration
CPK	creatine phosphokinase
CRF	case report form
ECG	electrocardiogram
EIB	exercise-induced asthma
ELISA	enzyme-linked immunosorbent assay
EoE	eosinophilic esophagitis
EOS	eosinophils
EOT	end of treatment
ER/ED	emergency room/emergency department
EU	Europe
FAAN	Food Allergy and Anaphylaxis Network

Abbreviation	Definition
Fab	fragment antigen-binding
FAS	Full Analysis Set
Fc	fragment crystallizable
FDA	Food and Drug Administration
$FEF_{25\%-75\%}$	forced expiratory flow during the middle half of the forced vital capacity
FEV_1	forced expiratory volume in 1 second
FU	follow-up
FVC	forced vital capacity
GI	gastrointestinal
GINA	Global Initiative for Asthma
HLT	high level term
ICH	International Conference on Harmonisation
ICS	inhaled corticosteroid
IgG	immunoglobulin
IL-5	interleukin-5
ITT	intent-to-treat
iv	intravenous
IVRS	Interactive Voice Recognition System
KM	Kaplan-Meier
LABA	long-acting beta-agonist
LS	least squares
LTRA	leukotriene receptor antagonist
mAb	monoclonal antibody
MAR	Missing At Random
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputations
MID	minimal important difference
MMRM	mixed effect model for repeated measures
NA	not applicable
NAEPP	National Asthma Education and Prevention Program
ND	not done
NIAID	National Institute of Allergy and Infectious Disease

Abbreviation	Definition
NMAR	Not Missing At Random
NMSC	non-melanoma skin cancer
NOEL	no-observed-effect level
NS	not significant
OLE	open-label extension
OCS	oral corticosteroid
PBO	placebo
PCT	placebo-controlled trial
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
POC	proof of concept
PPK	population pharmacokinetics
% predicted FEV_1	actual FEV_1 divided by standard predicted FEV_1 times 100%
PRN	pro re nata (as needed)
PT	preferred term
PY	patient-years
qPCR	quantitative polymerase chain reaction
RES	reslizumab
RR	rate ratio
SABA	short-acting beta-agonist
SAD	single ascending dose
SAE	serious adverse event
sc	subcutaneous
SD	standard deviation
SE	standard error
SEER	Surveillance Epidemiology and End Results
SIR	standardized incidence ratio
SMQ	standardized Medical Dictionary for Regulatory Activities query
SOC	system organ class
Teva	Teva Global Branded Pharmaceutical Products R & D, Inc.
ULN	upper limit of normal
URTI	upper respiratory tract infection

Abbreviation	Definition
US	United States
WD	withdrawal
Wk	week

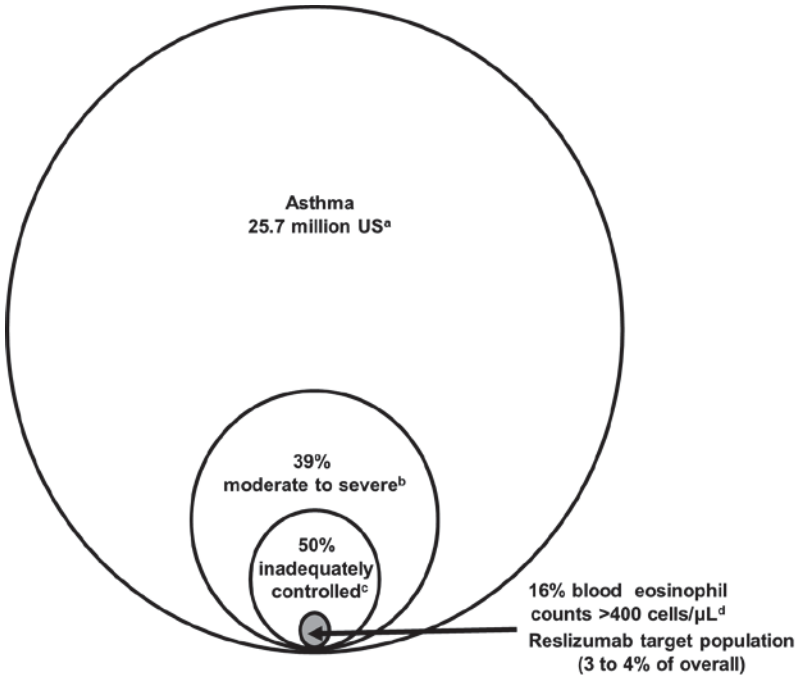
1. EXECUTIVE SUMMARY

Unmet Medical Need and Introduction: Asthma is a common heterogeneous disease defined clinically by respiratory symptoms, including shortness of breath, cough, wheezing, and chest tightness associated with variable expiratory airflow limitation, affecting over 25 million adult patients in the United States (US) (CDC 2014). Of these, 39% of patients are estimated to have more severe asthma (Murphy et al 2012). Despite substantial improvements in the treatment of asthma and the use of guideline-based therapy, approximately 50% of adult US asthma patients have inadequately controlled asthma (CDC 2015). A proportion of these patients with inadequately controlled asthma who require emergency room (ER) visits and hospitalizations due to exacerbations drive a substantial amount of the cost burden associated with asthma treatment. Treatments that can reduce the risk of future asthma exacerbations and improve measures of current impairment address a major unmet need in asthma management in the US today.

Eosinophilic inflammation in asthma has emerged as a distinctive asthma phenotype (Walford and Doherty 2014, Wenzel et al 1999, Wenzel 2012). Airway eosinophilia has been associated with worse lung function and risk for developing exacerbations in patients with asthma (Green et al 2002, Jatakanon et al 2000, Leuppi et al 2001, Louis et al 2000, Miranda et al 2004, ten Brinke et al 2001). Blood eosinophil levels have been recognized as a more practical and relevant biomarker for identifying patients with active airway eosinophilia who could benefit from anti-interleukin-5 (IL-5) therapy. A higher blood eosinophil level is more predictive of the presence of sputum eosinophilia and has been shown to be associated with worsening lung function and exacerbation risk (Horn et al 1975, Ulrik 1995, Malinovschi et al 2013, Tran et al 2014, Zeiger et al 2014).

In a recent cohort study of medical record data of primary care patients 12 to 80 years of age with asthma, 16% had blood eosinophil counts greater than 400 cells/μL (Price et al 2015). Teva estimates that exacerbation prone asthma patients with elevated blood eosinophil counts, that despite medium- to high-dose inhaled corticosteroid (ICS) therapy, represent approximately 3% to 4% of the total asthma patients in the US (Figure 1).

Figure 1: The Unmet Need and Reslizumab Target Population



a. CDC 2014.
b. Murphy et al 2012.
c. CDC 2015.
d. Price et al 2015.

Reslizumab (CEP-38072) is a humanized anti-IL-5 monoclonal antibody (immunoglobulin [IgG]-G4 kappa) that specifically addresses an unmet medical need for asthmatic patients with elevated blood eosinophils who are uncontrolled on currently available treatments. Results of the Phase 3 safety and efficacy program demonstrate that reslizumab 3.0 mg/kg every 4 weeks significantly reduces asthma exacerbations, improves lung function, and relieves symptoms in patients with asthma and elevated blood eosinophils whose symptoms are inadequately controlled on medium to high doses of ICS-based standard-of-care therapy. The overall safety profile was acceptable and similar to that seen in patients treated with placebo.

Proposed Indication and Appropriate Patients for Reslizumab Treatment: Clinical data showed that an elevated blood eosinophil level (indicative of currently active airway inflammation) is an important condition for overall reslizumab efficacy. The reslizumab clinical program evaluated patients with varying degrees of asthma severity in order to identify the appropriate patients who could benefit from reslizumab treatment. The proposed indication reflects the spectrum of asthma severity evaluated in the clinical program. Teva will work with the Food and Drug Administration (FDA) on the indication language that best informs physicians and health care providers on the appropriate patient population who could benefit from treatment.

Teva has proposed the following indication: "*Reslizumab is a treatment to reduce exacerbations, relieve symptoms, and improve lung function in adult and adolescent patients (12 years of age and above) with asthma and elevated blood eosinophils whose symptoms are inadequately controlled on inhaled corticosteroids.*"

The results from the reslizumab clinical program support that the patient population with the greatest likelihood of achieving clinical benefit are exacerbation-prone asthma patients with elevated blood eosinophils whose symptoms are inadequately controlled on medium- to high-dose ICS-based therapies, particularly National Asthma Education and Prevention Program (NAEPP) treatment guidelines for asthma steps 4 to 6 (Section 2.1.1, Figure 3).

Clinical Development Program: The reslizumab clinical development program is composed of 14 clinical studies, including 6 Phase 3 studies, 4 Phase 2 studies, and 4 Phase 1 studies, with 2195 patients or healthy subjects exposed to at least 1 dose of reslizumab (with a total of 2155 patient-years of exposure in the 13 Teva-sponsored studies [n=2187]). Of these patients, 1781 were patients with asthma from 8 studies and 1596 received the proposed dose and regimen (3.0 mg/kg dose every 4 weeks).

The primary support for the efficacy of reslizumab 3.0 mg/kg every 4 weeks in moderate to severe asthma is based on the results from 3 Phase 3, randomly assigned, double-blind, placebo-controlled studies in the intended target population with elevated blood eosinophils (≥400 cells/µL at screening). They include one 16-week primary lung function study (Study 3081) and 2 replicate 52-week primary asthma exacerbation studies (Studies 3082 and 3083). An additional randomly assigned, double-blind, placebo-controlled Phase 3 16-week lung function study (Study 3084) enrolled asthma patients, irrespective of baseline eosinophil count. Key inclusion criteria for the Phase 3 program are given in Table 1 below.

Table 1: Major Inclusion Criteria in Phase 3 Studies

	Study 3081, 3082, and 3083	**Study 3084**
Age	12-75 years; global	18 to 65
FEV_1 reversibility	≥12%	Same
Inadequately controlled	ACQ7 score ≥1.5	Same
Background medication	At least medium ICS[a] ± another controller	Same
Screening blood eosinophils	≥400/µL	ANY
Study 3082 and 3083 only		
Maintenance OCS allowed	≤10 mg/day[b]	
≥1 exacerbation in previous. 12 months	Required	

[a] Daily ICS dose ≥ fluticasone 440 µg or equivalent.
[b] Prednisone or equivalent.
ACQ=Asthma Control Questionnaire; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; ICS=inhaled corticosteroid; OCS=oral corticosteroid.

The frequency of clinical asthma exacerbation (CAEs) over 52 weeks was selected as the primary endpoint for Studies 3082 and 3083. A CAE was defined as a worsening of asthma that required a medical intervention that was above and beyond the patient's usual care. The definition accommodated medical interventions including hospitalization, new or increased use of systemic corticosteroid, increased use of ICS, and other emergency treatments for asthma. Worsening asthma was based on worsening asthma symptoms or decreased lung function. All events were adjudicated by 3 asthma experts independent of Teva, blinded to treatment assignment, who made the determination if an event met the criteria for an asthma exacerbation.

Dose Justification: The observed clinical results support the safety and efficacy of the proposed therapeutic dose (3.0 mg/kg) and regimen (every 4 weeks) of reslizumab for the treatment of patients with evidence of active eosinophilic airway inflammation based on elevated eosinophil counts.

- Dose up to 1.0 mg/kg in unselected asthma patients produced reduction in blood eosinophils, however, did not show any clinical effect.
- A 3.0-mg/kg dose every 4 weeks was subsequently evaluated in a Phase 2 proof of concept study (Study Res-5-0010) testing in patients selected for evidence of active eosinophilic inflammation (sputum eosinophils ≥3%) on the hypothesis that higher doses may be required to suppress tissue eosinophilia and provide clinical benefits. The choice of the 4-week dosing interval for Study Res-5-0010 was supported by the elimination half-life of reslizumab, which is approximately 24 days. The results of Study Res-5-0010 demonstrated that the 3.0-mg/kg dose administered every 4 weeks markedly suppressed airway eosinophilia with corresponding improvements in Asthma Control Questionnaire (ACQ) score and lung function (forced expiratory volume in 1 second [FEV_1]).
- In Study 3081, an additional low dose of 0.3 mg/kg was effective in improving FEV_1, ACQ, and Asthma Quality of Life Questionnaire (AQLQ) scores. The treatment effect for these measures was largest for the 3.0-mg/kg dose, as was the magnitude of blood eosinophil reduction. Only the 3.0-mg/kg dose produced improvement in forced vital capacity (FVC; a marker of air trapping), supporting that higher exposures may be needed.
- Pharmacokinetic/pharmacodynamic modeling was used to explore the exposure-response relationship using clinical data from patients with asthma and elevated eosinophils for measures of asthma control (FEV_1 and ACQ) for doses of 0.3 to 3.0 mg/kg. This analysis demonstrated that the 3.0-mg/kg dose provided the greatest benefit relative to lower doses.

Efficacy: All 3 Phase 3 studies in the target population met their primary efficacy endpoints (improvement of FEV_1 at 16 weeks in Study 3081 and reduction in the annual rate of CAEs in Studies 3082 and 3083). In addition, reslizumab consistently improved FEV_1 and patient-reported measures of asthma control (ACQ and Asthma Symptom Utility Index [ASUI] scores) and quality of life (AQLQ). The published minimal important difference (MID) for ACQ and AQLQ (0.5 units for both) was not achieved relative to placebo treatment for the overall population. This is not unexpected when taking into consideration that approximately 80% of the enrolled population were receiving reslizumab (or placebo) on top of standard of care consisting of medium to high doses of ICS with a long-acting beta-agonist (LABA) (Bateman et al 2015a). The overall efficacy profile is summarized in Table 2.

Table 2: Key Efficacy Findings: Treatment Effects over 16 and 52 Weeks (Patients Aged ≥12 years Treated with Reslizumab 3.0 mg/kg)

	16 Weeks			52 Weeks	
	Study 3081	**Study 3082**	**Study 3083**	**Study 3082**	**Study 3083**
Reduction in annualized rate of CAEs					
All CAE events				✓ (primary)	✓ (primary)
CAE events requiring systemic corticosteroids				✓	✓
CAE events resulting in hospitalization or ER visit				NS	NS
Other variables					
FEV_1	✓ (primary)	✓	✓	✓[a]	✓[a]
ACQ score	✓[a]	✓	✓	✓[a]	✓[a]
AQLQ total score	✓[a]	✓	✓	✓[a]	✓[a]
ASUI score	✓[a]	✓	✓	✓[a]	✓[a]
SABA use	✓[a]	NS	NS	NS	NS
Blood eosinophil count	✓[a]	✓[a]	✓[a]	✓[a]	✓[a]
Other lung function					
FVC	✓[a]	✓	✓	✓	✓
$FEF_{25\%-75\%}$	NS[a]	NS	✓[a]	NS	✓[a]

[a] Not controlled for multiplicity.

Note: Reduction in the rate of CAEs was an annualized measure and was therefore not performed at 16 weeks.

✓=p≤0.05; ACQ=Asthma Control Questionnaire; AQLQ=Asthma Quality of Life Questionnaire; ASUI=Asthma Symptom Utility Index; CAE=clinical asthma exacerbation; $FEF_{25\%-75\%}$=forced expiratory flow during the middle half of the forced vital capacity; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; NS=not significant (p>0.05); SABA=short-acting beta-agonist.

In the randomized population, reslizumab 3.0 mg/kg every 4 weeks reduced the annual rate of CAEs by 50% and 59% relative to placebo in Studies 3082 and 3083, respectively. A prespecified analysis demonstrated that reduction in events requiring systemic corticosteroids (the most frequent type of utilized medical intervention) was consistent with the primary analysis (55% and 61% reductions in the annual CAE rate relative to placebo for Studies 3082 and 3083, respectively). The time to first event was significantly longer for reslizumab than for placebo in both studies. Finally, trends in health care utilization including the need for hospitalization or ER visit favored reslizumab treatment, although not significant.

Patients treated with reslizumab 3.0 mg/kg showed improvements in lung function and asthma symptoms relative to placebo that were evident after the first dose, at the first week 4 assessment, and maintained throughout the treatment period. In Studies 3081, 3082, and 3083, statistically significant improvements (increases) in FEV_1 ranging from 0.110 to 0.155 L relative to placebo were observed over the 16-week treatment period in all 3 studies (controlled for multiplicity). Increases in FEV_1 were sustained through week 52 for the 2 exacerbation studies (0.090 to 0.126 L over the 52-week treatment period; 0.123 to 0.145 L at week 52).

In all 3 studies, patients receiving reslizumab 3.0 mg/kg reported fewer asthma symptoms compared with patients receiving placebo as demonstrated by statistically significant improvements in ACQ and ASUI scores over 16 weeks, which were evident by week 4 and

sustained over the 52-week treatment period. Asthma-related quality of life based on AQLQ score was also improved at week 16 (first AQLQ assessment) and over 52 weeks.

Study 3084 was similar to Study 3081 (16-week FEV_1) except that it was limited to adult patients who were unselected for screening blood eosinophils: patients who had a blood eosinophil count above and below 400 cells/μL were enrolled. The results demonstrated nonsignificant effects of reslizumab on the overall unselected population and no meaningful benefit with reslizumab in patients with blood eosinophil cutoffs <400 cells/μL. In contrast, the subset of patients with blood eosinophils ≥400 cells/μL demonstrated a large treatment effect.

Certain key subgroups (ie, adolescent, black, and US patient subgroups) did not demonstrate a reduction in the annualized CAE rate. These studies were not designed to determine efficacy in smaller subgroups. There is no clear reason why the disease state for the subgroups in question would differ meaningfully from the overall population. This is supported by the fact that reslizumab produced the expected changes in blood eosinophil levels and lung function (FEV_1) in the 3 subgroups in question, indicative of a therapeutic response. Given the consistent efficacy across multiple measures of asthma control (including exacerbation reduction) for the overall randomized population, we believe that the apparent lack of effect on exacerbation events in adolescent, US region, and black subgroups is likely due to chance imbalances in baseline asthma control in these small subpopulations.

Safety: The safety profile of reslizumab is well characterized based on 2155 patient-years of exposure from 2187 patients and on subjects who received at least 1 dose of reslizumab in sponsored clinical studies, including pediatric and long-term safety data.

Reslizumab, administered as an intravenous (iv) infusion 3.0 mg/kg every 4 weeks, demonstrated an acceptable safety profile. The overall incidence of adverse events was lower in the reslizumab group than that in the placebo group (67% and 81%, respectively). The most frequently observed adverse events (≥5% observed for reslizumab) were of the types expected for the study population (ie, asthma, nasopharyngitis, upper respiratory tract infection, headache, and sinusitis). There were no adverse event types in the reslizumab-treated patients that had an incidence that exceeded by more than 1% the incidence in the placebo-treated patients. There were no deaths related to reslizumab or asthma worsening in the reslizumab program. Serious adverse events occurred more frequently overall in the placebo-treated patients than in the reslizumab-treated patients (9% versus 6%, respectively), and the incidence of discontinuation due to adverse events was similar in the two groups (5% for each group).

Anaphylactic reactions were associated with reslizumab infusions in 3 patients in the asthma placebo-controlled studies. All cases occurred during infusion or within 20 minutes after completion of the infusion and fully resolved with treatment at the study site). Reslizumab is an iv infusion and will be administered under the supervision of a health care professional capable of managing the risk of anaphylaxis as is done with other currently available therapies used in the treatment of asthma. Teva is committed to ensuring that patients and health care providers are properly informed about the anaphylaxis risk via the Prescribing Information and Patient Information. Additionally, Teva intends to make nurse trainers available to patients and health care professionals to help ensure the appropriate use of reslizumab.

Uncommon, non–severe/serious reports of myalgia occurred in a higher frequency in reslizumab-treated asthma patients (10/1028 [0.97%]) than in placebo-treated patients (4/730 [0.55%]).

These adverse events were transient, with no evidence of muscle injury, myositis and rhabdomyolysis (Section 5.7.4).

The profile of other specific adverse events of special interest (namely malignancies, infections, and cardiovascular events) showed no increased risk following reslizumab treatment.

Except for the pharmacological effect of reduced eosinophils, there were no clinically meaningful differences or patterns of abnormality for any clinical laboratory tests, and variable value shifts were similar in each group. There were no clinically meaningful differences or potentially clinically important trends in vital signs, electrocardiogram (ECG) intervals, or overall ECG assessments.

Patients in the reslizumab group had a lower incidence in the overall concomitant medications commonly used to treat worsening asthma and/or allergic and infectious comorbidities (ie, antibacterials for systemic use, antihistamines for systemic use, corticosteroids for systemic use, and nasal preparations).

Long-term Safety Data: There is a substantial cohort (756 patients) of reslizumab-treated asthma patients who were treated for greater than 12 months. The adverse event profile of patients exposed to >12 months of treatment was similar to that of the overall population. There were no increases in overall adverse events over time (including the specific adverse event of special interest), and no new events of concern arose with longer-term use. Of note, there were no anaphylactic reactions reported after 12 months.

Pediatric Safety Data: A total of 253 pediatric patients from 5 to 19 years of age with eosinophilic esophagitis (EoE) or asthma have been treated with reslizumab at doses up to 3.0 mg/kg. The majority of these pediatric patients (167 patients, 66%) were treated with reslizumab for more than 2 years. The reslizumab-treated pediatric population had a similar safety profile as the placebo-treated population as well as with the overall population.

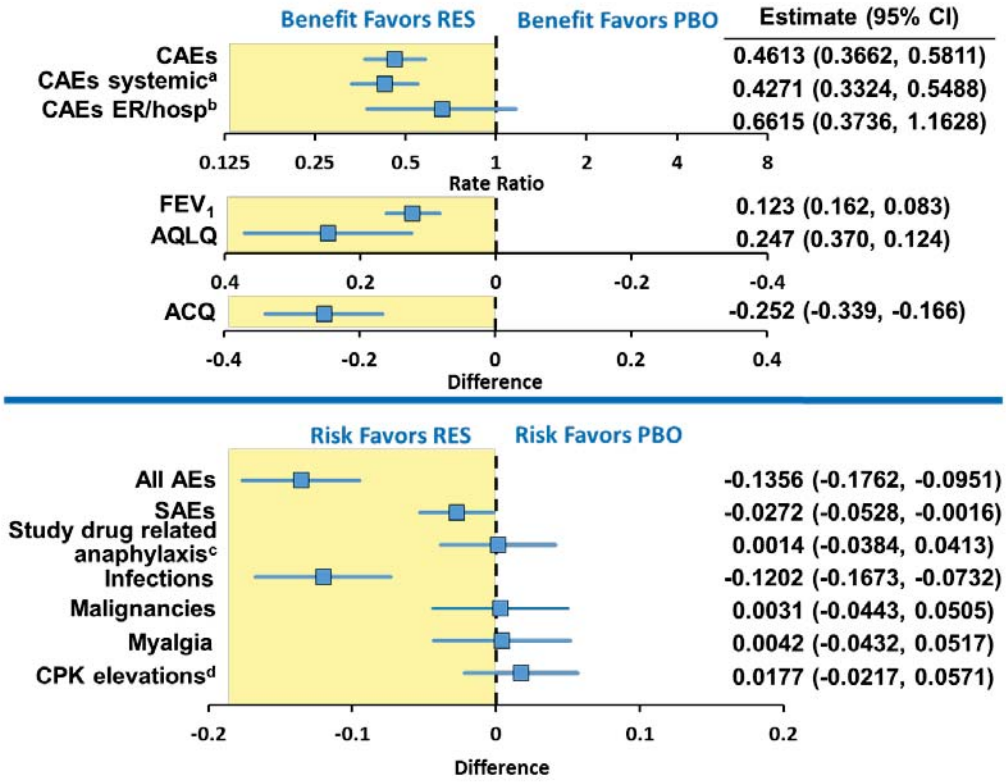
Immunogenicity: The overall incidence of at least 1 positive anti-drug antibody (ADA) formation was 5% in the Phase 3 asthma studies; these were generally low titer, frequently transient, and had no observed impact on exposure of reslizumab, blood eosinophil reduction, FEV_1 improvement, or associated with adversity. The presence of ADA was not associated with hypersensitivity reactions.

Benefit-Risk Profile: Asthma with elevated blood eosinophils has been recognized as a distinct phenotype associated with an increased risk for exacerbations and lower lung function. Reslizumab was developed as a targeted therapy for this phenotype—specifically, exacerbation-prone asthma patients with elevated eosinophils whose symptoms remain inadequately controlled by medium- to high-dose ICS-based therapies.

An overall positive benefit-risk profile of reslizumab 3.0 mg/kg every 4 weeks has been demonstrated in the target population based on the following (as shown in Figure 2):

- reduction in asthma exacerbations and improvements in lung function, asthma symptoms, and asthma-related quality of life
- a well-characterized and acceptable safety profile based on 2155 patient-years of exposure

Figure 2: Summary of Reslizumab Benefit and Risk



a. CAEs requiring use of systemic corticosteroids.
b. CAEs requiring ER or hospitalization.
c. The patient population utilized for the assessment of drug-related anaphylaxis totaled 2072 patients from studies with treatment using multiple doses of reslizumab (ie, not single-dose studies). See Section 5.7.1 for a more detailed description.
d. CPK result based on data from all patients with a normal baseline value and a treatment emergent elevation to ≥ 1.25 ULN (i.e. heathy volunteer grade 1 and above). See Section 5.7.4 for a more detailed description.

ACQ=Asthma Control Questionnaire; AE=adverse event; AQLQ=Asthma Quality of Life Questionnaire; CAE=clinical asthma exacerbation; CI=confidence interval; CPK=creatine phosphokinase; ER=emergency room; FEV_1=forced expiratory volume in 1 second; PBO=placebo; RES=reslizumab; SAE=serious adverse event.

The measures of clinical benefit include the CAE assessments (integrated cohort from the two 52-week exacerbation studies [3082 and 3083]) as well as the asthma control and impairment assessments over 16 weeks (integrated cohort from Phase 3 Studies 3081, 3082, and 3083). Full discussions of these efficacy measures are found in Section 4.2. The variables displayed to show the risk profile of reslizumab are based on the patient populations from the randomized asthma placebo-controlled trials (PCTs) (Studies Res-5-0010, 3081, 3082, 3083, and 3084), except as noted for anaphylaxis. Full discussions of these safety parameters are found in Section 5. Point estimates of the risk differences are provided at the right side of each parameter and include 95% confidence intervals (CIs) of the estimate (also displayed as lines within the figure).

Based on the totality of the efficacy and safety data, Teva believes that reslizumab 3.0 mg/kg every 4 weeks demonstrates a positive benefit-risk profile in in exacerbation-prone asthma patients with elevated blood eosinophils who have limited treatment options.

2. INTRODUCTION

Asthma is a common heterogeneous disease defined clinically by respiratory symptoms, including shortness of breath, cough, wheezing, and chest tightness associated with variable expiratory airflow limitation. Approximately 25.7 million adults in the US are currently diagnosed with asthma (CDC 2014). Uncontrolled asthma leads to a significant clinical impact and increase in healthcare utilization, including 14.2 million unscheduled office visits annually (National Ambulatory Medical Care Survey 2010), 1.8 million ER visits annually (National Hospital Ambulatory Medical Care Survey 2011), approximately half a million hospitalizations annually (National Hospital Discharge Survey 2010), and approximately 3600 asthma-related deaths per year (National Vital Statistics Report 2013). In addition, school-age children with asthma miss a total of 10.5 million school days and adults with asthma miss a total of 14.2 million work days due to asthma annually (National Center for Health Statistics 2011). Despite availability of safe and effective therapies with national guidelines supporting their use, there remains considerable morbidity and mortality from asthma justifying the need for new treatments that can address this unmet need.

2.1. Unmet Medical Need and Role of Reslizumab in Treating Asthma with Elevated Eosinophils

2.1.1. Current Treatment of Asthma

Both patient-related (eg, genetic) and environmental factors can influence the development of asthma, or trigger asthma-related symptoms (Bacharier et al 2008, Ege et al 2011, GINA 2014, Vijverberg et al 2011). Despite this variability, the dominant pathologic feature of asthma is airway inflammation, and for this reason, anti-inflammatory controllers (eg, ICS) constitute the cornerstone of asthma therapy. Figure 3 shows the current NHLBI treatment guidelines for asthma. ICS is the preferred treatment for persistent asthma. The ICS dose is increased, and non-ICS controller medications should be added, in a stepwise fashion, according to the severity and/or frequency of symptoms.

"Asthma control" refers to the extent to which the manifestations of asthma have been reduced or removed by treatment (Taylor et al 2008) and includes the domains of current impairment and future risk (particularly risk of asthma exacerbation). As such, the goals of therapy proposed by the NAEPP (NAEPP 2007) are to:

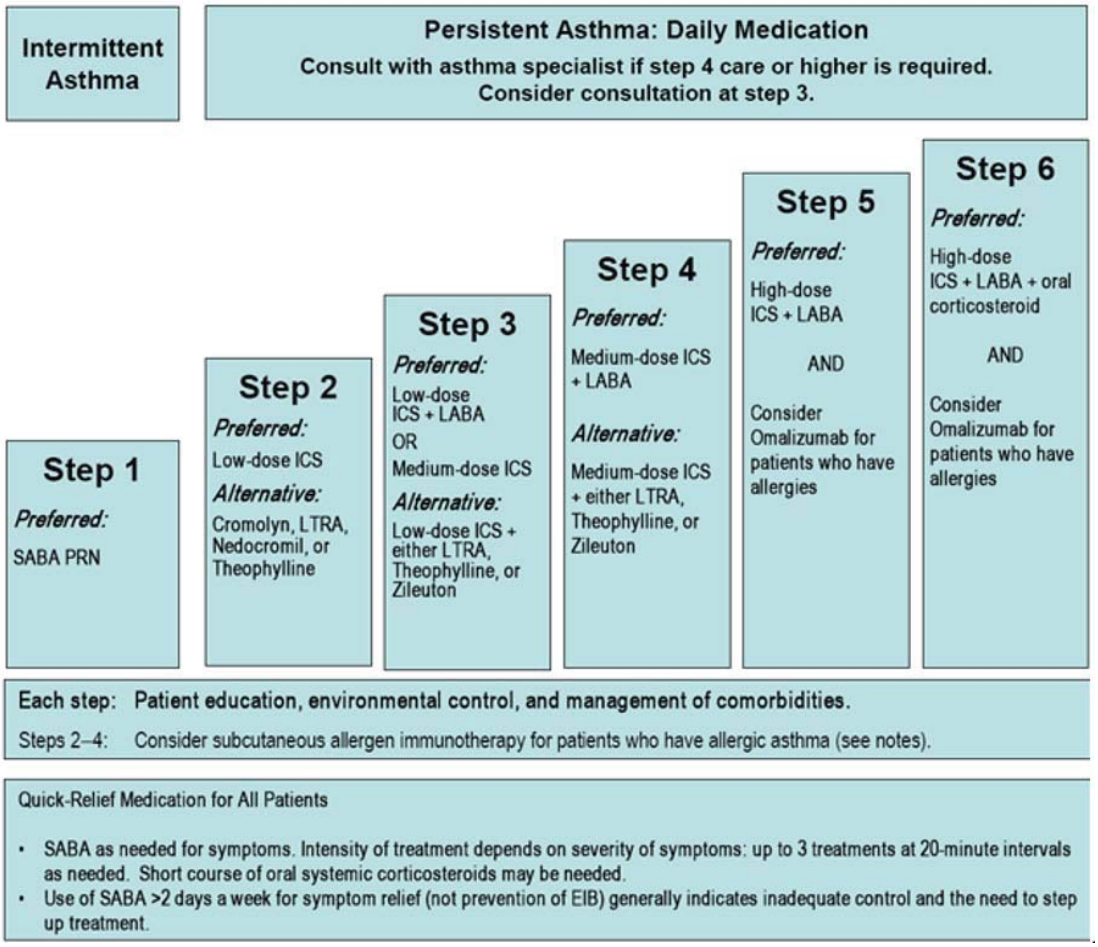
- prevent asthma symptoms,
- reduce the use of inhaled rescue therapies,
- maintain (near) normal pulmonary function,
- maintain normal activity levels,
- meet patients'/families' expectations, and
- reduce risk, including preventing asthma exacerbations, preventing loss of lung function, and avoiding adverse effects of treatment.

In patients already being treated for asthma, guidelines classify disease severity based on the intensity of treatment defined both by the dose level and by the class of the controller medication

required to achieve good asthma control. However, these guidelines do not take asthma phenotype into account (see Section 2.1.3 for further details).

The reslizumab asthma clinical development program evaluated patients whose symptoms remain inadequately controlled despite use of medium- to high-dose ICS-based regimen (steps 4 to 6; Figure 3) and who have evidence of ongoing eosinophilic inflammation. The severity of asthma in these patients despite receiving the recommended treatment supports the need for new therapies that can improve their clinical disease.

Figure 3: Current NHLBI Treatment Guidelines for Asthma



Source: NAEPP 2007.

EIB=exercise-induced asthma; ICS=inhaled corticosteroid; LABA=long-acting beta-agonists; LTRA=leukotriene receptor antagonist; NHLBI=National Heart, Lung, and Blood Institute; PRN=pro re nata (as needed); SABA=short-acting beta-agonist.

2.1.2. Unmet Medical Need

Despite substantial improvements in the treatment of asthma and the use of guideline-based therapy, approximately 50% of adult asthma patients in the US have inadequately controlled asthma (CDC 2015) and an estimated 39% of asthma patients have more severe disease (Murphy et al 2012).

The large observational cohort study (TENOR) of 4756 patients (3489 adults aged ≥18 years, 497 adolescents aged 13 to 17 years, and 770 children aged 6 to 12 years) concluded that, regardless of age, patients with severe or difficult-to-treat asthma demonstrated high rates of health care use and substantial asthma burden despite receiving multiple long-term controller medications (Chipps et al 2012). In this study, recent history of asthma exacerbation was the strongest predictor of future asthma exacerbations.

In patients with asthma whose symptoms remain inadequately controlled on a medium- to high-dose ICS-based regimen, there are few therapeutic alternatives beyond the add-on treatment with oral corticosteroids (OCSs) and/or (for patients with perennial allergies) anti-IgE (eg, omalizumab).

2.1.3. Influence of Elevated Airway and Blood Eosinophils on Asthma Control

Eosinophilic inflammation in asthma has emerged as a distinct asthma phenotype (Walford and Doherty 2014, Wenzel et al 1999, Wenzel 2012). Airway eosinophilia has long been associated with the key pathophysiological and clinical features of asthma, including airway remodeling with associated persistent airflow limitation and poor clinical control with risk of asthma exacerbation (Balzar et al 2005, Green et al 2002, Jatakanon et al 2000, Leuppi et al 2001, Miranda et al 2004, Petsky et al 2012, Robinson 1995, Saglani et al 2007, ten Brinke et al 2001, Wenzel et al 1999). Recent studies have shown that higher blood eosinophil levels are also specific for predicting sputum eosinophilia (Fowler et al 2015, Westerhof et al 2015) and represent a simple and reliable biomarker for identifying patients with asthma and active eosinophilic airway inflammation.

Higher blood eosinophil levels are associated with worse lung function in patients with asthma (Horn et al 1975, Ulrik 1995). Additionally, a higher blood eosinophil level has been shown to be associated with worsening lung function and exacerbation risk (Malinovschi et al 2013, ten Brinke et al 2001, Tran et al 2014, Zeiger et al 2014).

In a recent cohort study of medical record data of primary care patients 12 to 80 years of age with asthma, 20929 (16%) of 130248 patients had blood eosinophil counts greater than 400 cells/µL (Price et al 2015). During the outcome year, these patients experienced significantly more severe exacerbations (adjusted rate ratio [RR]: 1.42; 95% CI: 1.36, 1.47) and acute respiratory events (RR: 1.28; 95% CI: 1.24, 1.33) than those with blood eosinophil counts of 400 cells/µL or less. For this study, a severe exacerbation was defined according to the American Thoracic Society/European Respiratory Society definition as an asthma-related hospitalization, attendance at an accident and ER, or a prescription of acute OCS.

Elevated blood eosinophils are emerging as an important biomarker for patient selection to determine who could benefit from anti- IL-5 therapy. Teva anticipates that exacerbation prone asthma patients with elevated blood eosinophil counts, that despite medium- to high-dose ICS therapy, represent approximately 3% to 4% of the US asthma population and could benefit from eosinophil-targeted therapies.

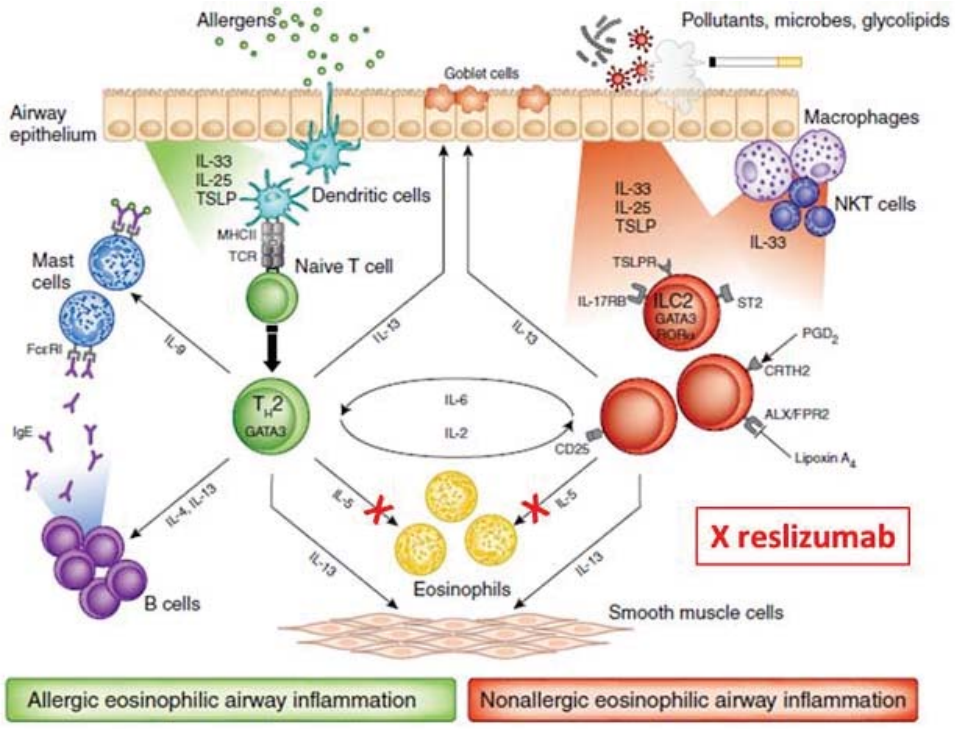
2.2. Reslizumab for Inadequately Controlled Asthma: Mechanism of Action

IL-5 is a key cytokine responsible for the differentiation of human eosinophils in the bone marrow and for their activation, resulting in chemotaxis, release of preformed toxic granule proteins and mediators, and cytokine synthesis. Importantly, IL-5 is a critical survival factor for eosinophils at sites of inflammation.

Reslizumab is a humanized anti-IL-5 monoclonal antibody (mAb; IgG-G4 kappa). It contains the complementarity determining regions (CDRs) of the rat anti-human IL-5 39D10 antibody grafted onto human frameworks. Reslizumab binds to a specific epitope on the IL-5 molecule, which appears to be important for its biological activity (Zhang et al 1999).

In in vivo studies, reslizumab showed biological activity in several species: mouse (B6D2F1/J and CD-1 strains), guinea pig, rabbit, and cynomolgus monkey, including species used for reproductive toxicology and repeat-dose toxicology evaluations. Reslizumab inhibited eosinophilia in the lungs or skin and reduced airway hyperresponsiveness after antigenic challenge in sensitized animals (Egan et al 1999). In asthma patients, single doses of reslizumab reduced circulating eosinophils in a dose-related manner (Kips et al 2003). Figure 4 illustrates key sources of IL-5 in the airway. It is notable that IL-5 can also be produced as a result of non-allergic stimuli. This figure was augmented to depict the inhibition of IL-5 by reslizumab treatment, thereby disrupting the influence of the cytokine on eosinophils and subsequent inflammation.

Figure 4: Sources of IL-5 Driving Eosinophilic Airway Inflammation



Source: Adapted from the original to show sites of reslizumab action (Brusselle et al 2013).
IL=interleukin; NKT=natural killer T-cells; TSLP=thymic stromal lymphopoietin; TSLPR=thymic stromal lymphopoietin receptor.

2.3. Proposed Indication and Dosage

Reslizumab was studied in exacerbation-prone, symptomatic patients with moderate to severe asthma and elevated blood eosinophil levels in order to determine the population who would benefit from anti-IL5 therapy. Teva is proposing the following indication for reslizumab:

- Reslizumab is a treatment to reduce asthma exacerbations, relieve symptoms, and improve lung function in patients (aged 12 years and above) with asthma and elevated blood eosinophils whose symptoms are inadequately controlled on ICSs.

The proposed indication reflects the spectrum of asthma severity evaluated in the clinical development program. Teva will work with the FDA on the indication language that best informs physicians and health care providers on the appropriate patient population who could benefit from treatment.

2.4. Description of Active Substance

Reslizumab is produced using a typical process for monoclonal antibodies using recombinant DNA technology in the murine myeloma NS0 expression system. The manufacturing process for reslizumab drug substance is divided into upstream (inoculum expansion, cell culture, and harvest) and downstream (purification, bulk formulation, and filling) steps.

Extensive testing is implemented to confirm the key attributes of the reslizumab drug substance, namely, strength (protein concentration), identity (tryptic peptide map, BIAcore binding assay), purity (reduced and nonreduced sodium dodecyl sulfate capillary gel electrophoresis, gel permeation high-performance liquid chromatography, and capillary isoelectric focusing), potency, and safety (bioburden, endotoxin, murine host cell deoxyribonucleic acid by quantitative polymerase chain reaction [qPCR], protein A enzyme-linked immunosorbent assay [ELISA], murine host cell protein ELISA, mycoplasma testing, in vitro virus assay, minute virus of mouse by qPCR, and electron microscopy for retrovirus-like particles).

2.4.1. Pharmaceutical Form, Strength and Presentation

2.4.1.1. Active Pharmaceutical Form

Intravenous (iv) reslizumab drug product is a single-use sterile solution for infusion presented as 100 mg in a 10-mL glass vial. The drug product for infusion is formulated as 10 mg/mL of reslizumab in 20-mM sodium acetate, 7% sucrose, pH 5.5.

The drug product appears as a clear to slightly hazy/opalescent solution or colorless to slightly yellow/yellow solution. As seen with many other monoclonal antibodies, proteinaceous particles may be present in the drug product, which appear as translucent-to-white amorphous particulates. As a precaution and typical practice, an inline filter is used when administering reslizumab intravenously.

2.4.1.2. Good Manufacturing Practices Status

The reslizumab drug substance is manufactured using current Good Manufacturing Practices (cGMP) by well-established mammalian cell culture and purification processes. The drug product is manufactured using cGMP by traditional aseptic manufacturing processes.

There are no antibiotics or animal- or human-derived materials used in the cell culture or in the purification steps in manufacturing the reslizumab drug substance. The master and working cell banks used for the production of reslizumab have been confirmed to be free from contamination by mycoplasma, adventitious viruses, bacteria, molds, and other yeasts.

Through the implementation of appropriate controls in all phases of production, product and process-related impurities are monitored and limited. The validated manufacturing process is well established, and the same process and scale used for the Phase 2/3 clinical studies are proposed for the commercial supply. The manufacturing process follows relevant FDA and International Conference on Harmonisation (ICH) guidance for monoclonal antibodies and every batch of product undergoes extensive quality control testing.

2.4.2. Alpha Gal Presence in Reslizumab

During their review, the FDA requested information pertaining to galactose 1,3 alpha-galactose (alpha gal) in reslizumab. Alpha gal is a mammalian oligosaccharide epitope that is regarded as foreign in humans and some primate species and has been associated with 1.) delayed-onset anaphylaxis (following consumption of meat) and 2.) immediate-onset anaphylaxis during the first exposure (seen with cetuximab) (Commins and Platts-Mills 2013).

Humans are routinely exposed to alpha gal glycosylated proteins in their diet, and antibodies against alpha gal are present in all non-immunocompromised human subjects. Studies suggest that the IgG antibodies against alpha gal constitute about 1% of circulating IgGs in human subjects, apes, and Old World monkeys (Galili et al 1984). IgE to the carbohydrate epitope alpha gal has been linked to patients in the southeastern United States who experience delayed anaphylaxis after eating red meat (Mullins et al 2012). It is currently thought that tick bites are responsible for the development of IgE directed against alpha gal; although, the exact mechanism is unknown (Steinke et al 2015).

Severe, rapid onset hypersensitivity reactions have been observed with cetuximab (Erbitux®), a chimeric mouse-human IgG1 antibody directed against the epidermal growth factor receptor used to treat squamous cell carcinoma of the head and neck and metastatic colorectal cancer (ERBITUX US Prescribing Information 2015). These hypersensitivity reactions to cetuximab occurred with the first infusion and almost exclusively in the southeastern US (Chung et al 2008, Maier et al 2015, O'Neil et al 2007). It was later determined that the presence of preexisting IgE directed against alpha gal was responsible for these reactions to cetuximab (Chung et al 2008). The cetuximab anaphylaxis reactions raised questions if other biologic products which contain alpha gal epitopes could result in similar risks for individuals sensitized to alpha gal.

The gylcan component of cetuximab contains approximately 30% alpha gal, located primarily on the fragment antigen-binding (Fab) region (binding domain), with a minimum level located on the fragment crystallizable (Fc) region of the antibody. The amount of alpha gal required to trigger an anaphylactic response is unknown; however, IgE binding has been implicated as an important catalyst in this pathology (Chung et al 2008, Lammerts van Bueren et al 2011). Anti-alpha gal IgE binding to cetuximab was shown to be directed exclusively to the highly exposed glycans in the Fab variable region (Chung et al 2008). The location of alpha gal on the

Fab region of cetuximab could provide a means by which cross-linking of IgE on the surface of mast cells could occur, resulting in the rapid onset of an anaphylactic response (Chung et al 2008).

2.5. Key Regulatory History

This section includes a summary of key interactions with the FDA regarding the iv reslizumab clinical program.

Based on clinical feedback and recommendations received from the FDA from the 18 August 2010 End-of-Phase-2 meeting, the Phase 3 asthma program included the following studies using a blood eosinophil selection criterion of ≥400 cells/μL to define the clinical phenotype of eosinophilic airway inflammation in asthma:

- two 52-week Phase 3 studies (Studies 3082 and 3083) that evaluated the effect of reslizumab (3.0 mg/kg every 4 weeks) on the incidence of asthma exacerbations
- one 16-week Phase 3 study (Study 3081) that evaluated the effect of reslizumab at 2 dose levels (0.3 and 3.0 mg/kg every 4 weeks) on FEV_1
- one 16-week Phase 3 study (Study 3084) that evaluated the effect of reslizumab (3.0 mg/kg every 4 weeks) on FEV_1 in patients unselected for blood eosinophils in order to understand the efficacy of reslizumab in patients with a blood eosinophil count that did not meet the programmatic definition of elevated blood eosinophils (≥400 cells/μL)

The FDA noted that robust, clinically meaningful results from Studies 3082 and 3083 (ie, studies in patients with a blood eosinophil count of ≥400 cells/μL at baseline), in conjunction with results from Study 3084, would support a threshold value of blood eosinophils ≥400 cells/μL for the purpose of the proposed package insert (Type C meeting request written response, 17 May 2013). The FDA also agreed that the proposed revised definition of CAEs (refer to Section 3.5) and the plan for independent adjudication of these events appeared reasonable.

Subsequently, Teva met with the FDA to discuss the planned Biologics License Application (BLA) for reslizumab (Type B meeting, 15 January 2015). In general, the FDA agreed with Teva's planned BLA that was received by the FDA on 30 March 2015. The BLA includes data from 14 clinical studies, summary details of which are presented in Table 3 and Table 34. The 120-Day Safety Update was submitted on 27 June 2015, providing a comprehensive integrated immunogenicity report and the final long-term, open-label extension (OLE) Study 3085 safety data, which were shown to be consistent with data included in the original BLA.

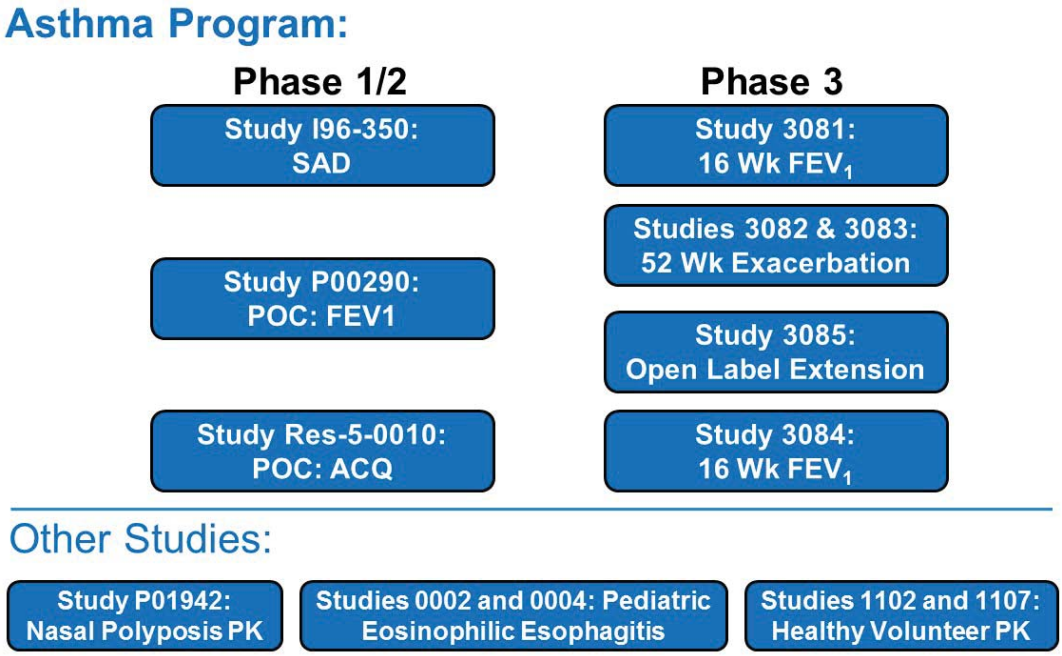
3. CLINICAL DEVELOPMENT PROGRAM

3.1. Overview of Clinical Development Program

The reslizumab clinical development program comprises 14 clinical studies, including 2195 patients or healthy subjects exposed to at least 1 dose of reslizumab. Populations studied include healthy subjects (pharmacokinetic [PK] studies) and patients with asthma, EoE, hypereosinophilic syndrome, eosinophilic gastroenteritis, and nasal polyposis. Of these patients,

1781 were patients with asthma, of whom 1596 received the 3.0 mg/kg dose every 4 weeks. Figure 5 provides an overview of the sponsored clinical trials that inform the safety and efficacy reslizumab for this BLA.

Figure 5: Development Landscape: Studies in Asthma and Other Studies Supporting the BLA



ACQ=Asthma Control Questionnaire; FEV_1= forced expiratory volume in 1 second; POC=proof of concept; PK=pharmacokinetics; SAD=single ascending dose; Wk=week.

3.1.1. Summary of Studies Supporting Dose, Efficacy, Blood Eosinophil Inclusion, and Safety of Reslizumab in Asthma

The design details of 8 studies in asthma are given in Table 3. A summary of the key studies is as follows:

- **Studies supporting the proposed labeled reslizumab dose 3.0 mg/kg** include early phase studies (ie, Studies I96-350, P00290, and Res-5-0010), which tested doses from 0.03 mg/kg through 3 mg/kg in patients with asthma, with and without evidence of eosinophilic inflammation.

  In patients with elevated blood eosinophils, Phase 3 Study 3081 tested the 3.0 mg/kg dose of reslizumab plus 1 additional dose (0.3 mg/kg) as part of a 16-week lung function study (FEV_1).

  Only the 3.0 mg/kg dose was tested in the two 52-week exacerbation studies. Dose justification is discussed in Section 3.2.

- **Confirmation of reslizumab efficacy in the targeted population** is primarily based on the two 52-week exacerbation studies (ie, Studies 3082 and 3083). In addition, the lung function study (ie, Study 3081) provided complementary shorter-term efficacy results (16 weeks). The clinical efficacy of reslizumab is detailed in Section 3.5.1.

- **Study 3084 in patients with and without elevated blood eosinophils** confirmed the utility of an elevated blood eosinophil count of 400/µL in predicting a clinical response to reslizumab (discussed in Section 3.3.2).
- **Integrated analyses to support the efficacy and to examine subgroups include the following:**
  - for CAEs: Studies 3082 and 3083
  - for other efficacy measures: Studies 3081, 3082, and 3083
- **Integrated analyses supporting the safety of the proposed labeled reslizumab dose (3.0 mg/kg) and regimen (every 4 weeks) for efficacy include the following:**
  - placebo-controlled asthma studies: Res-5-0010, 3081, 3082, 3083, and 3084
  - asthma studies including open-label: Res-5-0010, 3081, 3082, 3083, 3084, and 3085

Supportive integrations were also constructed to investigate rare events (such as anaphylaxis) and consist of "all reslizumab studies" (any indication including healthy subjects and patients), "all reslizumab studies with multiple doses administered," and "all asthma studies" (any dose, any regimen).

Table 3: Description of Clinical Asthma Studies Supporting Dose, Efficacy, Blood Eosinophil Inclusion, and Safety

Study number/ Phase	Design	Target population	Dose group (n)	Primary objective	Key efficacy results
I96-350/ Phase 1	Single-ascending reslizumab doses, multicenter, randomized, double-blind, placebo-controlled study	Patients with asthma. Age: ≥18 years	<0.1 mg/kg: (6) 0.3 mg/kg: (6) 1.0 mg/kg: (12) PBO: (8)	Safety, tolerability, pharmacokinetics, biologic activity, and lung function	Reslizumab doses ≥0.3 mg/kg reduced blood EOS within 24 hours • 1.0 mg/kg more durable than 0.3 mg/kg
P00290/ Phase 2	12-week, repeat-dose, multicenter, randomized, evaluator-blind, parallel-group, placebo-controlled study first dose on day 1 and a second dose at week 12	Patients with asthma. Age: ≥18 years	0.3 mg/kg: (72) 1.0 mg/kg: (75) PBO: (68)	Lung function. (as well as pharmacokinetics, safety, and tolerability)	Reslizumab 0.3 mg/kg and 1 mg/kg: no clinical effect observed • Blood EOS reduced with both doses (greater in 1.0 mg/kg than in 0.3 mg/kg)

Table 3: Description of Clinical Asthma Studies Supporting Dose, Efficacy, Blood Eosinophil Inclusion, and Safety (Continued)

Study number/ Phase	Design	Target population	Dose group (n)	Primary objective	Key efficacy results
Res-5-0010/ Phase 2	15-week, randomized, double-blind, placebo-controlled, parallel-group Reslizumab iv infusion every 4 weeks for 4 doses	Patients with asthma whose symptoms were inadequately controlled with inhaled corticosteroids Sputum EOS ≥3% Age: 18 to 75 years	3.0 mg/kg: (53) PBO: (53)	Asthma control (ACQ score - change from baseline to EOT [week 15 or early withdrawal] between the groups)	Reslizumab 3.0 mg/kg (produced • Increase in ACQ (p=0.054) • Increase in FEV_1 (p=0.005) • Trend for decreased exacerbations • 82% reduction from baseline in sputum EOS
3081/ Phase 3	16-week, randomized, double-blind, placebo-controlled, parallel-group Reslizumab iv infusion every 4 weeks for 4 doses	Patients with asthma whose symptoms were inadequately controlled with inhaled corticosteroids Blood EOS ≥400 cells/μL Age: 12 to 75 years	0.3 mg/kg: (104) 3.0 mg/kg: (106) PBO: (105) <u>Stratification factor:</u> presence of historical exacerbation	Lung function (FEV_1 - overall change from baseline over the 16 weeks of treatment)	Reslizumab 0.3 mg/kg and 3.0 mg/kg produced • Statistically significant[a] improvement in FEV_1; numerically larger for 3.0 mg/kg vs 0.3 mg/kg • Increase in ACQ; numerically larger for 3.0 mg/kg than for 0.3 mg/kg • Increase in AQLQ at the 3.0-mg/kg dose level • Increase in FVC and $FEF_{25\%-75\%}$ only with 3.0 mg/kg • Dose-related reduction in blood EOS 3.0 mg/kg >0.3 mg/kg
3082/ Phase 3 3083/ Phase 3 (replicate studies)	52-week, randomized, double-blind, placebo-controlled, parallel-group Reslizumab iv infusion every 4 weeks for 13 doses	Patients with asthma whose symptoms are inadequately controlled with inhaled corticosteroids Blood EOS ≥400 cells/μL Age: 12 to 75 years History of 1 or more exacerbations	3082: 3.0 mg/kg: (245) PBO: (244) 3083: 3.0 mg/kg: (232) PBO: (232) <u>Stratification factor:</u> OCS use at baseline	Asthma exacerbations (frequency of adjudicated CAEs during the 52-week treatment period)	Reslizumab 3.0 mg/kg (relative to placebo) produced • Statistically significant reduction in CAEs (50% in 3082 and 59% in 3083) and prolonged the time to 1st exacerbation • Statistically significant improvement in FEV_1, AQLQ, ACQ, ASUI

Table 3: Description of Clinical Asthma Studies Supporting Dose, Efficacy, Blood Eosinophil Inclusion, and Safety (Continued)

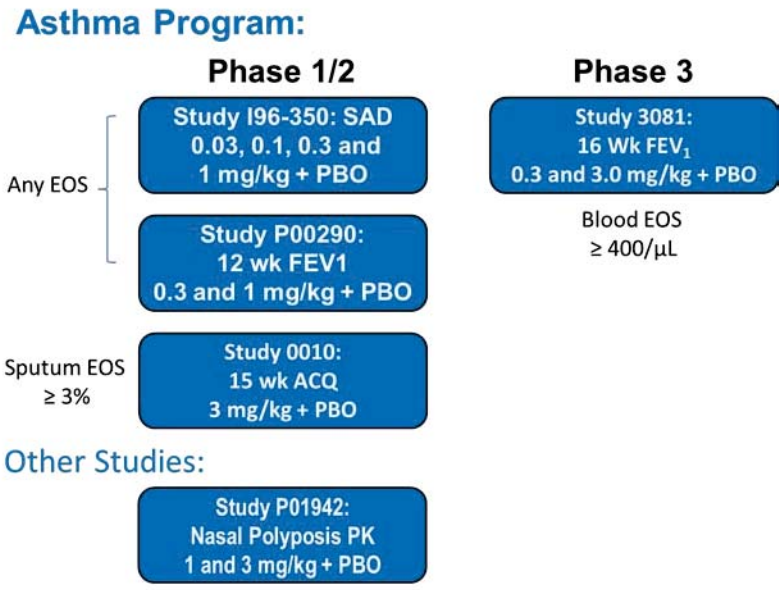
Study number/ Phase	Design	Target population	Dose group (n)	Primary objective	Key efficacy results
3084/ Phase 3	16-week, randomized, double-blind, placebo-controlled, parallel-group Reslizumab iv infusion every 4 weeks for 4 doses	Patients with asthma whose symptoms were inadequately controlled with inhaled corticosteroids Any EOS Age: 18 to 65 years	3.0 mg/kg: (398) PBO: (98) <u>Stratification factor:</u> presence of historical exacerbation	Lung function (FEV_1 - change from baseline to week 16)	Reslizumab 3.0 mg/kg (relative to placebo) produced • Modest, non-significant FEV_1 improvement in the overall population • Increase in FEV_1 and ACQ7 in the subgroup with baseline blood EOS ≥400 cells/µL • No meaningful differences observed in FEV_1 or ACQ7 in patients <400 cells/µL as a group
3085[b]/ Phase 3	Open-label extension Reslizumab iv infusion every 4 weeks up to 24 months	Patients with asthma who were previously enrolled in Study 3081, 3082, or 3083	3.0 mg/kg: (481 reslizumab-naïve, 1051 total)	Long-term safety	Improvements observed during prior double-blind treatment were maintained for up to 2 years of treatment.

[a] Statistically significant improvement: p≤0.05 and controlled for multiplicity.
[b] Study 3085 was ongoing at the time of data cutoff for the BLA submission (01 September 2014) and is now complete.
ACQ=Asthma Control Questionnaire; AQLQ= Asthma Quality of Life Questionnaire; ASUI= Asthma Symptom Utility Index; CAE=clinical asthma exacerbation; EOS=eosinophils; EOT=end of treatment; $FEF_{25\%-75\%}$=forced expiratory flow during the middle half of the forced vital capacity; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; OCS=oral corticosteroid; PBO=placebo.
Note: All studies were multicenter. See Section 9.4 for study statistical considerations.

3.2. Justification for the Reslizumab 3.0 mg/kg Dose for Asthma

Studies that informed the 3.0 mg/kg dose and the 4-week dosing regimen are depicted in Figure 6.

Figure 6: Reslizumab Studies Supporting the 3.0 mg/kg Dose Selection



ACQ=Asthma Control Questionnaire; EOS=eosinophils; FEV_1=forced expiratory volume in 1 second; PK=pharmacokinetics; PBO=placebo; SAD=single-ascending dose.

The justification of the 3.0 mg/kg dose is summarized below:

- Early studies in unselected asthma patients showed that single doses of reslizumab <0.3 mg/kg had minimal effect on blood eosinophil levels. Doses ≥0.3 mg/kg, while able to suppress blood eosinophil counts, did not meaningfully affect FEV_1 (Studies I96-350 [single-ascending doses] and P00290 [2 doses 12 weeks apart]).
- A 3.0 mg/kg dose every 4 weeks was subsequently selected for the Phase 2 proof of concept study (Study Res-5-0010) testing in patients selected for evidence of active eosinophilic inflammation (sputum eosinophils ≥3%) on the hypothesis that higher doses may be required to suppress tissue eosinophilia and provide clinical benefits. The choice of the 4-week dosing interval for Study Res-5-0010 was supported by the elimination half-life of reslizumab, which is approximately 24 days. The Study Res-5-0010 results demonstrated that the 3.0 mg/kg dose administered every 4 weeks markedly suppressed airway eosinophilia, with corresponding improvements in ACQ score and lung function (FEV_1).
- In Study 3081, an additional low dose of 0.3 mg/kg was effective in improving FEV_1, ACQ, and AQLQ scores. The treatment effect for these measures was largest for the 3.0-mg/kg dose, as was the magnitude of blood eosinophil reduction. Only the 3.0 mg/kg dose produced improvement in FVC (a marker of air trapping), supporting that higher exposures may be needed.
- Following the conclusion of the Phase 3 clinical studies, PK/pharmacodynamic (PD) modeling was used to explore the exposure-response relationship using clinical data from patients with asthma and elevated eosinophils for measures of asthma control

(FEV_1 and ACQ) for doses of 0.3 to 3.0 mg/kg. This analysis demonstrated that the 3.0 mg/kg dose provided the greatest benefit relative to a lower dose.

3.2.1. Studies in Unselected Asthma

The results of early dose explorations in unselected asthma patients (the single-ascending dose Study I96-350 and the lung function Study P00290) demonstrated the following:

- Significant blood eosinophil reductions were effected by reslizumab doses ≥0.3 mg/kg in both studies.
- No significant clinical improvements (FEV_1 or asthma symptoms) were observed when reslizumab was dosed up to 1.0 mg/kg every 12 weeks × 2 doses in unselected asthma patients (primary analysis at 4 weeks; Study P00290).

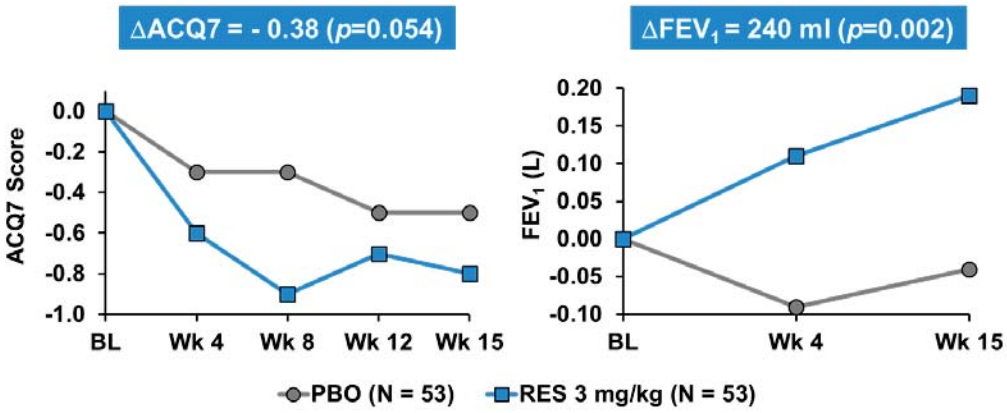
In addition, single doses of reslizumab (1.0 and 3.0 mg/kg) or placebo were evaluated in a PK study in patients with nasal polyposis (Study P01942). In this study, both dose levels produced significant blood eosinophil reductions (largest for the 3.0 mg/kg dose). In addition, the overall safety profile of reslizumab in single doses up to 3.0 mg/kg was similar to that of placebo, which was considered supportive for subsequent dose selection in a Phase 2 study with active airway eosinophilia.

3.2.2. Study Res-5-0010 in Targeted Asthma: Sputum Eosinophils

Given the above observations, it was hypothesized that suppression of tissue eosinophilia may require doses that were at the higher end of the range and that were also shown to be safe. Therefore, the 3.0 mg/kg dose was selected for further development in targeted asthma.

Study Res-5-0010 tested the 3.0 mg/kg dose every 4 weeks for 15 weeks in asthma patients whose symptoms were inadequately controlled by medium- to high-dose ICS (± another controller) and with sputum eosinophils ≥3%. Results from this proof-of-concept study demonstrated a trend toward improved asthma control based on the ACQ score (primary efficacy) plus substantial improvement in pulmonary function based on FEV_1 ($p<0.05$) [Figure 7]. In this study, 4 doses of reslizumab 3.0 mg/kg were observed to have a safety profile comparable to that of placebo.

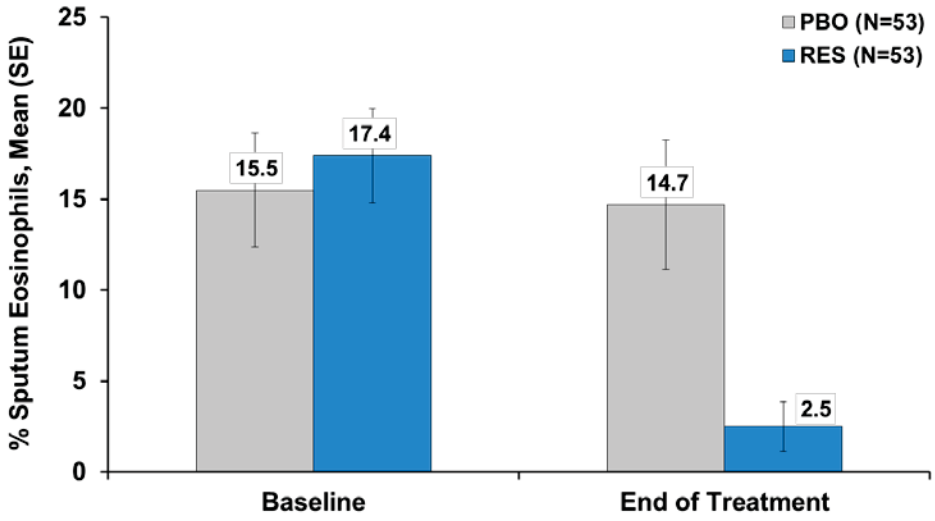
Figure 7: Mean Changes from Baseline over Time in ACQ and FEV_1 (Study Res-5-0010)



ACQ=Asthma Control Questionnaire; BL=baseline; FEV_1=forced expiratory volume in 1 second; PBO=placebo; RES=reslizumab; WK=week.

The improved asthma control with reslizumab treatment was also accompanied by large reductions in sputum eosinophils (mean: -82%) [Figure 8].

Figure 8: Induced Sputum Eosinophil Levels from Baseline to End of Therapy (Study Res-5-0010)



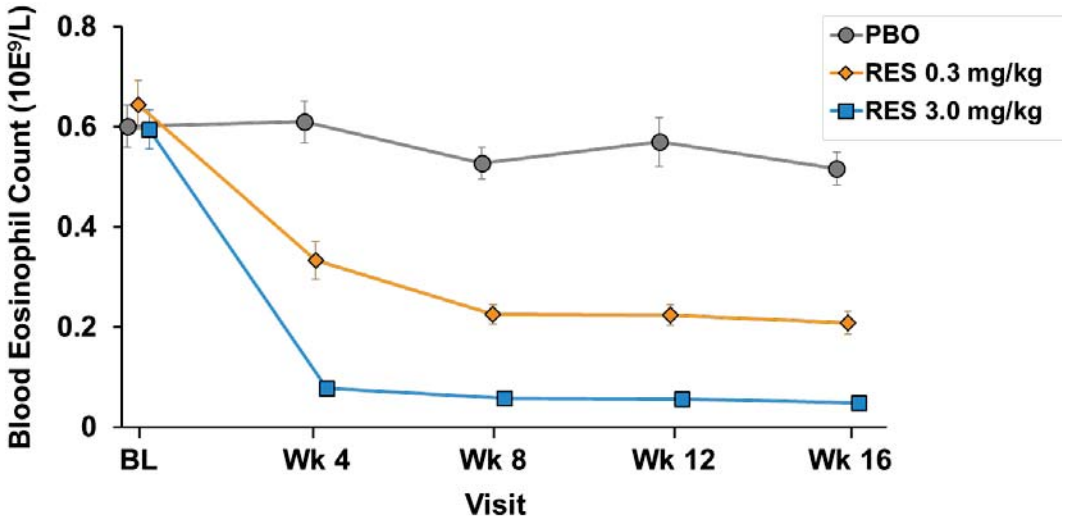
PBO=placebo; RES=reslizumab; SE=standard error.

3.2.3. Study 3081 in Asthma Patients with Elevated Blood Eosinophils

Additional support for the 3.0 mg/kg dose comes from Phase 3 Study 3081 that evaluated the efficacy of the proposed reslizumab dose (3.0 mg/kg) and a dosage 1 log level lower (0.3 mg/kg) in asthma patients with elevated blood eosinophils (≥400 cells/μL). Patients all had reversible asthma and had to be inadequately controlled (ACQ ≥1.5) during screening on medium to high doses of ICS ± another asthma controller (78% of the randomized population was using an

ICS + LABA). Figure 9 shows the dose-related changes observed for blood eosinophil counts for the treatments in Study 3081.

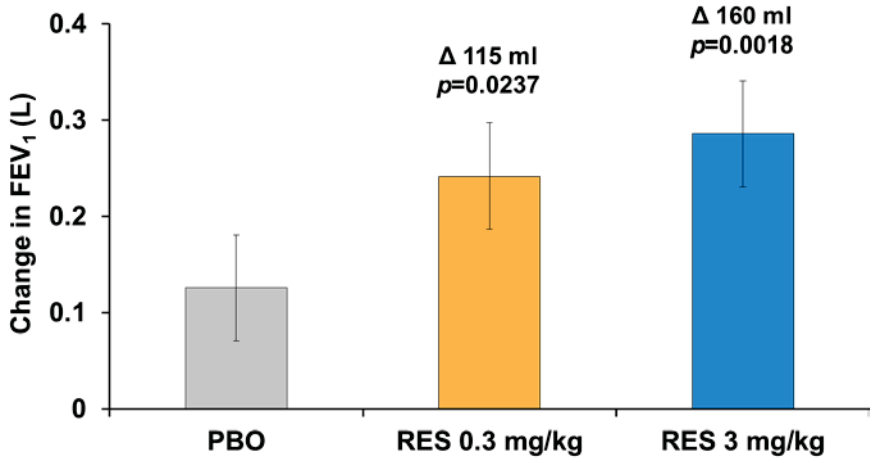
Figure 9: Blood Eosinophil Count by Treatment Group over Time (Study 3081)



Data are actual means±standard error of the mean.
PBO=placebo; RES=reslizumab; Wk=week.

Both dose levels produced significant improvements in FEV_1 over the treatment period (primary efficacy), which were larger for the 3.0 mg/kg level (160 vs 115 mL for reslizumab 3.0 and 0.3 mg/kg, respectively; Figure 10). Results at 16 weeks were similar (165 and 129 mL, respectively).

Figure 10: Mean Change in FEV_1 over 16 Weeks (Study 3081)



FEV_1=forced expiratory volume in 1 second; PBO=placebo; RES=reslizumab.

Secondary efficacy endpoints were not controlled for multiplicity (nominal p values indicated) and were considered supportive. Regarding other lung functions, only the 3.0 mg/kg dose

showed meaningful changes in FVC and forced expiratory flow during the middle half of the forced vital capacity ($FEF_{25\%-75\%}$), indicating that higher doses would be necessary to improve small airway physiology where asthma pathology primarily resides (Table 4). Both doses of reslizumab improved quality of life and asthma symptoms; improvements in the ACQ and AQLQ were larger for reslizumab 3.0 mg/kg versus 0.3 mg/kg (Table 4).

Table 4: Summary of Reslizumab Treatment Effect Versus Placebo over 16 Weeks by Dose Level (Study 3081)

Efficacy variable	Change vs placebo[a] (over 16 weeks)	
	Reslizumab 0.3 mg/kg	Reslizumab 3.0 mg/kg
FVC (L)	0.048	0.130*
$FEF_{25\% 75\%}$ (L/s)	0.030	0.233
AQLQ score[b]	0.278	0.359*
ACQ7 score	-0.238*	-0.359*
ASUI score	0.051*	0.047*
SABA use (puffs/day)	-0.7*	-0.6*

[a] Not controlled for multiplicity.
[b] The first AQLQ assessment was at Week 16.
* $p \leq 0.05$.
ACQ=Asthma Control Questionnaire; AQLQ=Asthma Quality of Life Questionnaire; ASUI=Asthma Symptom Utility Index; $FEF_{25\%-75\%}$=forced expiratory flow during the middle half of the forced vital capacity; FVC=forced vital capacity; LS=least square; SABA=short-acting beta-agonist.
Note: Treatment effect shown is the treatment difference calculated as LS mean of reslizumab minus the LS mean of placebo.

Importantly, there was no observed difference in the safety profile of the 0.3 and 3.0 mg/kg doses, supporting the 3.0 mg/kg iv dose as providing the greatest benefits with an acceptable safety profile. Study 3081 is further discussed in Sections 3.4 and 3.5.1 (Patient Selection and Efficacy Results) as part of the efficacy basis for the proposed package insert.

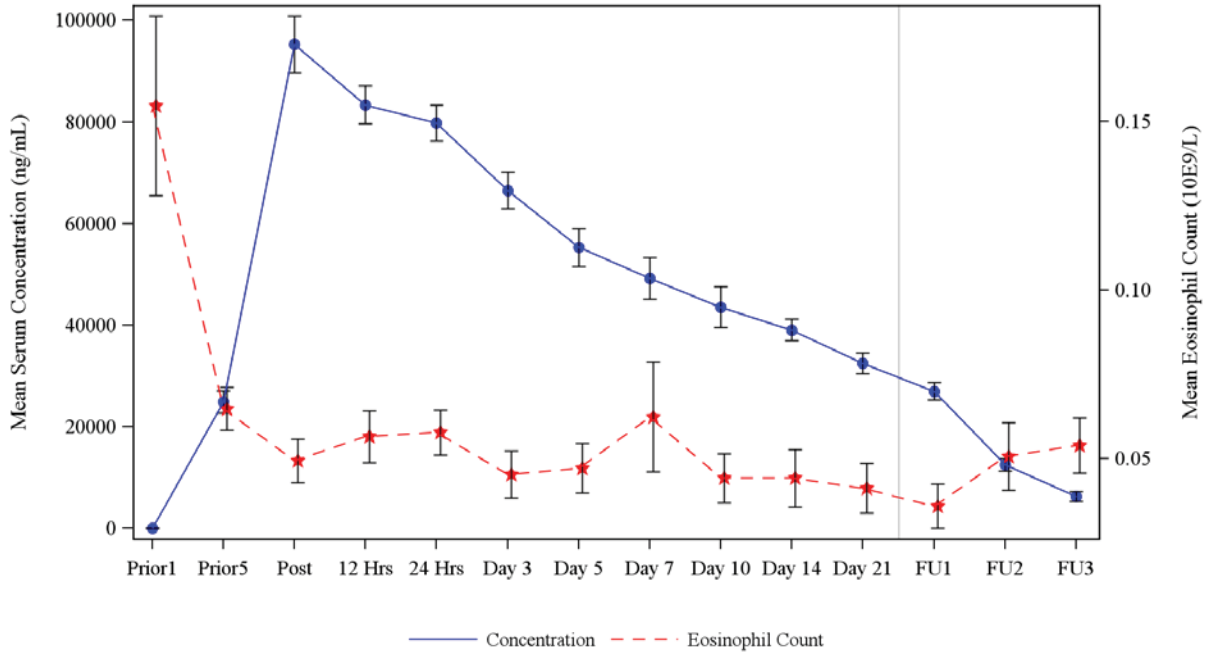
3.2.4. Pharmacokinetics, Pharmacodynamics, and Pharmacokinetic/Pharmacodynamic Relationships

The PK characteristics of reslizumab, the time course of its PD effects, and its PK/PD relationships provide additional justification for selecting the 3.0-mg/kg dose administered every 4 weeks as the therapeutic dosing regimen. Key relevant PK, PD, and PK/PD findings are presented below. Additional results along with the methods for population PK (PPK) and PK/PD modelling are provided in Section 9.5.2.

Weight-based dosing for iv reslizumab is supported by PPK analyses, which demonstrated that heavier body weight resulted in more rapid clearance and larger volume of distribution, with increases of approximately 50% to 60% in these parameters for a 2-fold increase in weight. These increases translate into shorter half-life and lower exposures at higher weights for a given fixed dose of reslizumab. Therefore, weight-based dosing is needed in order to produce similar exposures across the full population.

The 4-week dosing interval of reslizumab is supported by the elimination half-life (ie, 24 days) and the indirect relationship between reslizumab drug concentrations and blood eosinophil levels, where decreases in eosinophils at steady state are well sustained through 28 days postdose then begin to return toward baseline (Figure 11).

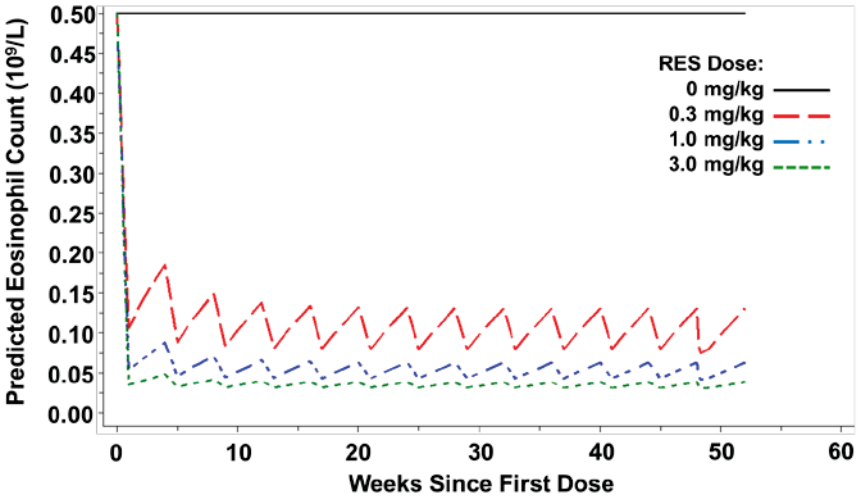
Figure 11: Mean Serum Concentration (±SE) Versus Mean Eosinophil Counts After Administration of 5 Doses of Reslizumab 3.0 mg/kg Every 4 Weeks in Healthy Subjects from Study 1102



FU1=First Follow-Up (28 ± 2 days after the last dose); FU2=Second Follow-Up (56 ± 2 days after the last dose); FU3-Third Follow-Up (84 ± 2 days after the last dose); SE=standard error.

Dose- and exposure-response relationships for blood eosinophils, pulmonary function tests, and ACQ scores in patients were examined over the dose range studied in the clinical program. Graphical assessment of exposure-response for CAEs in Study 3082 was also performed; however, no exposure-response relationship was apparent. Given that only the 3.0 mg/kg dose was tested opposite a CAE endpoint and that asthma exacerbations are sporadic/rare events, this result is not unexpected. The model used to explore these relationships incorporated pooled results from early and late-phase asthma studies that assessed both PK and efficacy variables and included only patients with evidence of eosinophil-mediated disease (either sputum ≥3% or blood eosinophilia ≥400 cells/µL). The results demonstrate that the predicted decrease in eosinophil count is maximal for the 3.0 mg/kg dose and exhibits limited fluctuation over the 4-week dosing interval compared to lower doses (Figure 12).

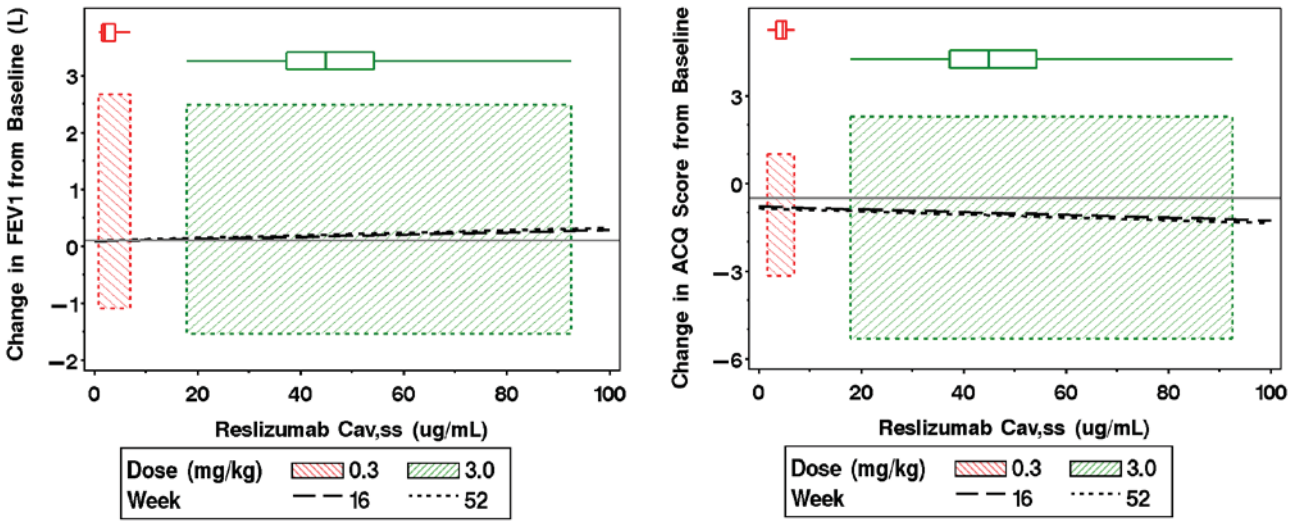
Figure 12: Model-Predicted Eosinophil Counts by Weeks Since First Dose and by Dose



Model based on Studies I96 350, P00290, Res-5-0010, 3081, and 3082.

Consistent with the observed dose-related improvements, a statistically significant correlation between the predicted average serum concentration and change from baseline in FEV_1 and ACQ scores was observed, with improvement in both measures occurring with increasing reslizumab exposure (Figure 13).

Figure 13: Change from Baseline in FEV_1 (Left) and Asthma Control Questionnaire Score (Right) Versus $C_{av,ss}$ with Final Pharmacokinetic/Pharmacodynamic Model-Predicted Lines Overlaid for Weeks 16 and 52



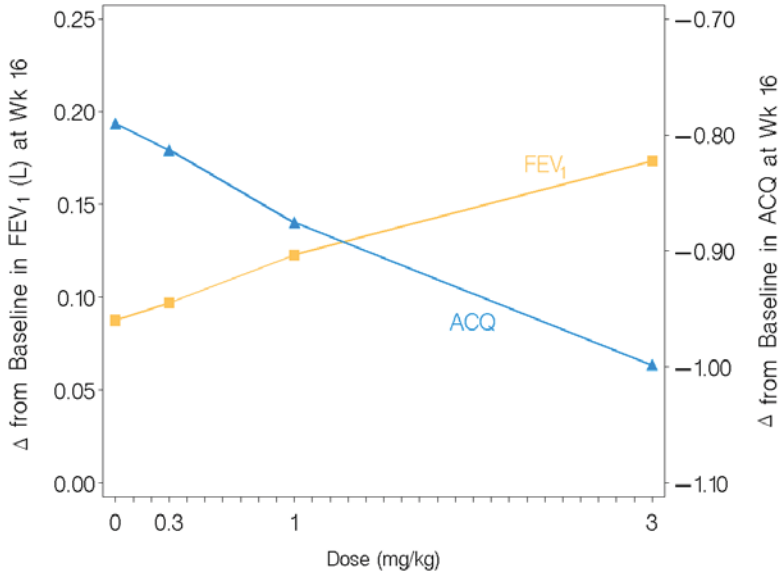
ACQ=Asthma Control Questionnaire; $C_{av,ss}$=average concentration at steady state; FEV_1=forced expiratory volume in 1 second.

Notes: The horizontal gray line represents a 100-mL improvement in FEV_1 (left) and a 0.5-point decrease in ACQ score (right).

The dashed and dotted lines represent the model-predicted FEV_1 scores (left) and ACQ scores (right) assuming the median $C_{av,ss}$ for an every-4-week dosing regimen for a white female patient with median age (47 years) and BMI (27 kg/m^2) at 16 and 52 weeks. The red shaded area represents the range of exposure and response values for the 0.3-mg/kg dose, and the green shaded area represents the range of exposure and response values for the 3.0-mg/kg dose. The box and whiskers at the top of the figures show the median, with 25th and 75th percentiles (box) and 5th and 95th percentiles (whiskers) for $C_{av,ss}$ values for the 0.3-mg/kg (red) and the 3.0-mg/kg (green) dose levels.

The established PPK and PK/PD models were used to simulate PD response by dose for an average person at the end of treatment. The responses for FEV_1 and ACQ by dose at 16 weeks are overlaid in Figure 14 and demonstrate that the previously discussed dose-related reductions in blood eosinophil counts corresponded with a dose-dependent increase in predicted FEV_1 and decrease in ACQ with the 3.0 mg/kg dose providing the largest effects.

Figure 14: Model-Predicted[a] FEV_1 and ACQ Score by Dose − Change from Baseline at Week 16



The median Cav,ss of 0, 4.8, 18.1, and 44.2 ug/mL for reslizumab doses of 0, 0.3, 1, and 3 mg/kg were used to obtain the model—predicted FEV1 and ACQ scores.

[a] FEV_1: Studies P00290, Res 5 0010, 3081, and 3082; ACQ: Studies Res-5-0010, 3081, and 3082.

ACQ=Asthma Control Questionnaire; $C_{av,ss}$=average concentration at steady state; FEV_1=forced expiratory volume in 1 second; PK=pharmacokinetic; Wk=week.

Data from Study 3083 were not included because PK samples were collected only in the event of a serious adverse event or an adverse event leading to withdraw in that study.

Note: The model is based on data in patients ≥12 years of age with sputum eosinophils ≥3% or blood eosinophils ≥400 cells/μL.

Therefore, results from the clinical studies and PK/PD modelling support that the 3.0 mg/kg dose provides greater benefits relative to lower doses of reslizumab.

3.3. Selection of the Blood Eosinophil Cutoff for Phase 3

3.3.1. Defining Elevated Blood Eosinophils for Reslizumab Based on Specificity

An elevated blood eosinophil count was selected as a practical surrogate of airway eosinophilia for the Phase 3 reslizumab studies because it has been shown to correlate with disease severity and can be easily obtained by health care professionals. A blood eosinophil inclusion criterion of ≥400 cells/μL was chosen based on the analysis of published data (Farooqui et al 2009, van Veen et al 2009) [Table 5], the results of which indicated that this cutoff would have a high specificity for sputum eosinophilia (≥3%), thereby aligning with the Phase 2 Study Res-5-0010 population. In addition, the high specificity would help to exclude patients who do not have airway eosinophilia and, therefore, would be less likely to benefit from reslizumab treatment. Several recent publications have confirmed the specificity of this relationship between sputum and blood eosinophils (Fowler et al 2015, Westerhof et al 2015) [Table 5].

Table 5: Sensitivity and Specificity of Blood Eosinophil Count for Sputum Eosinophils At Least 3% from External Data Sources

Characteristic	Blood eosinophil cutoff (cells/µL)	Sensitivity (%)	Specificity (%)
Farooqui et al[a]	≥400	72	83
van Veen et al[b]	≥400	60	94
Westerhof 2015 (adult onset asthma)[c]	>90	96	26
	>410	36	95
Fowler 2015 (severe asthma)[d]	>150	78	53
	>300	60	84
	>450	49	97

[a] Derived from Farooqui et al 2009.
[b] Derived from van Veen et al 2009.
[c] Westerhof et al 2015.
[d] Fowler et al 2015.

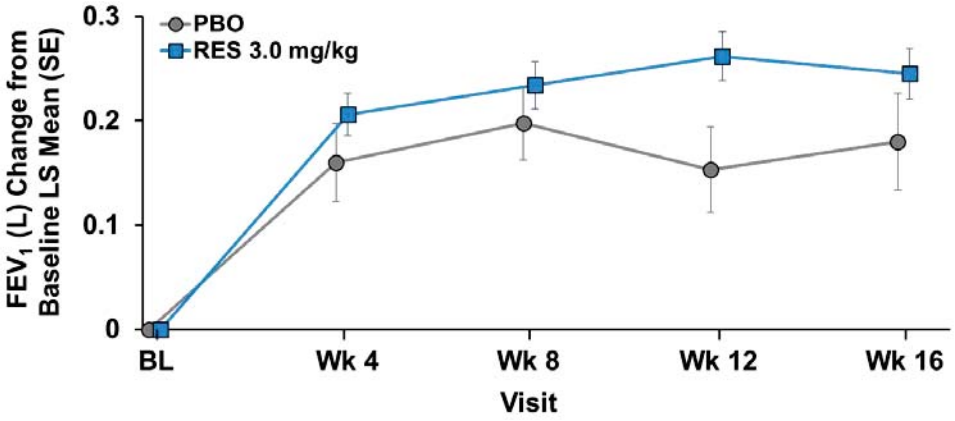
3.3.2. Study 3084: Influence of Baseline Blood Eosinophil Level on Reslizumab Efficacy

The effect of reslizumab in unselected asthma patients was explored in Study 3084. The design and study population were the same as those of Study 3081 (4 doses of reslizumab 3.0 mg/kg [n=398] vs placebo [n=98] over 16 weeks in patients whose symptoms were uncontrolled on medium- to high-dose ICS ± another controller) except that it was conducted in adult patients only (from 18 to 65 years of age) and there was no blood eosinophil inclusion threshold.

A positive relationship was observed between baseline blood eosinophil levels and change from baseline in FEV_1 for reslizumab (slope: 0.0229), with a negative relationship observed for the placebo group (slope: -0.2778) based on linear regression; however, the interaction between baseline eosinophils and treatment did not achieve statistical significance (p=0.2407).

Overall, reslizumab produced modest effects on FEV_1 in an unselected asthma population, with a difference of 68 mL compared to placebo (Figure 15).

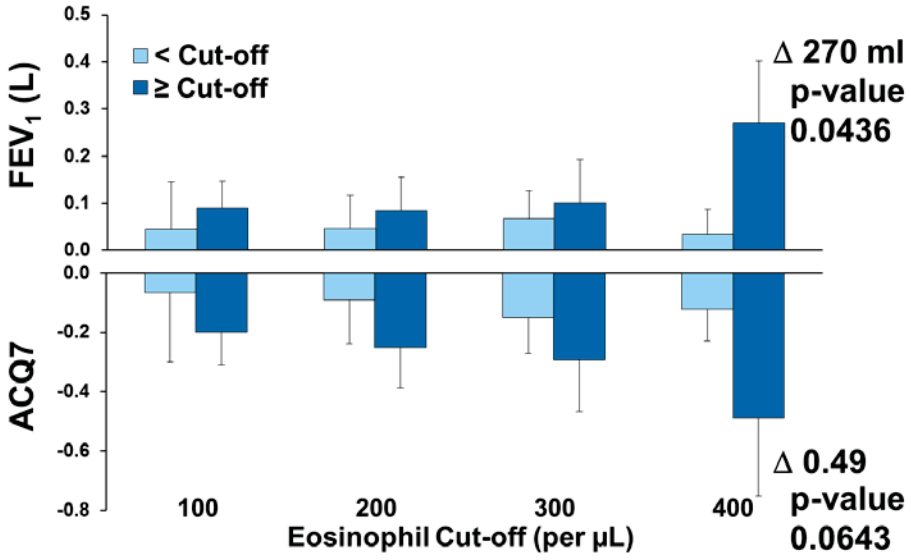
Figure 15: Least Squares Mean (±SE) of Change from Baseline to Each Visit in FEV_1 by Treatment Group for the Overall Population (Full Analysis Set; Study 3084)



BL=baseline; FEV_1=forced expiratory volume in 1 second; PBO=placebo; RES=reslizumab; SE=standard error; Wk=week.

A prespecified analysis by categorical blood eosinophil cutoffs showed a 270-mL improvement relative to placebo in the subset of patients with baseline blood eosinophil count of ≥400 cells/µL; in addition, the ACQ score was substantially improved in this subgroup. No meaningful treatment effects were observed at week 16 for the subset of patients with baseline eosinophil counts of <400 cells/µL indicating that lower blood eosinophil cutoffs did not predict treatment response to reslizumab (Figure 16).

Figure 16: Treatment Effect of Reslizumab versus Placebo on FEV_1 and ACQ Score by Baseline Blood Eosinophil Categories (Study 3084)



ACQ=Asthma Control Questionnaire; FEV_1=forced expiratory volume in 1 second.

3.4. Patient Selection

The inclusion criteria for the Phase 3 studies were intended to select adolescent and adult asthma patients who, beyond having likely active eosinophilic airway inflammation based on blood eosinophil counts, had symptoms that were inadequately controlled by a medium- to high-dose ICS-based treatment regimen. The efficacy basis for the proposed package insert includes Studies 3081, 3082, and 3083 in patients with inadequately controlled asthma and elevated blood eosinophils ≥400 cells/μL; the results of replicate 52-week Studies 3082 and 3083 are considered pivotal. Studies 3082 and 3083 included male and female adolescent and adult patients with the key inclusion criteria shown in Table 6. The inclusion criteria for Studies 3082 and 3083 were identical to those of Study 3081, except that patients were required to have at least 1 asthma exacerbation requiring systemic corticosteroid during the 12 months prior to screening and that maintenance OCS was allowed.

Table 6: Key Enrollment Criteria for Studies 3082 and 3083

Age	**12-75 years, global**
Background medication requirement	At least medium doses of ICS (≥440 μg of fluticasone or equivalent) ± another controller
Asthma control	ACQ7 score ≥1.5
FEV_1 reversibility	≥12%
Screening blood eosinophils	≥400 cells/μL
Maintenance OCS allowed[a]	≤10 mg/day
≥1 exacerbation in the previous 12 months	Required

[a] Prednisone or equivalent.
ACQ7=Asthma Control Questionnaire 7; FEV_1=forced expiratory volume in 1 second; ICS=inhaled corticosteroids; OCS=oral corticosteroids.

The Phase 3 inclusion criterion for inadequate asthma control was also based on an ACQ score ≥1.5. The ACQ has been validated against quality-of-life and physician global assessment in patients with asthma (Juniper et al 1999). A score of ≥1.5 predicts inadequate asthma control with a high degree of confidence (Juniper et al 2006) and endorsed by both Global Initiative for Asthma (GINA) and NAEPP guidelines (GINA 2014, NAEPP 2007).

3.4.1. Baseline Background Asthma Medication Dose

The reslizumab asthma clinical development program included patients with asthma whose symptoms were inadequately controlled on medium- to high-dose ICS ± another asthma controller.

The range of background therapy was chosen in order to adequately inform the benefit-risk profile of a novel add-on biologic across a reasonably broad range of asthma severities. Determination of asthma severity in patients already using an asthma controller is based on the treatment step and differs slightly depending on guidance (Table 7).

Table 7: Assessment of Asthma Severity in Patients Already Receiving Treatment

Asthma severity	Treatment guideline	
	GINA 2014 (adults and children >5 years)	**NAEPP 2007 (youth ≥12 years and adults)**
Intermittent	NA	Step 1: • As needed SABA
Mild	Step 1: • As needed SABA • Consider low-dose ICS Step 2: • Low-dose ICS (preferred) • Other options: LTRA or low-dose theophylline	Step 2: • Low-dose ICS (preferred) • Other options: cromolyn, LTRA, nedocromil, or theophylline
Moderate	Step 3: • Low-dose ICS/LABA (preferred) • Other options: medium-/high-dose ICS, low-dose ICS+LTRA or theophylline	Step 3: • Low-dose ICS+LABA or medium-dose ICS (preferred) • Other options: low-dose ICS + either LTRA, theophylline, or zileuton Step 4: • Medium-dose ICS+LABA (preferred) • Other options: medium-dose ICS + either LTRA, theophylline, or zileuton
Severe	Step 4: • Medium- to high-dose ICS/LABA (preferred) • Other options: high-dose ICS+LTRA or theophylline Step 5: • Referral for add-on treatment (eg, anti-IgE), add low-dose OCS, consideration of non-standard approaches and therapies (eg, sputum assessment, bronchial thermoplasty)	Step 5: • High-dose ICS+LABA (preferred) • Consider anti-IgE for patients with allergies Step 6: • High-dose ICS+LABA+OCS • Consider anti-IgE for patients who have allergies

Source: GINA 2014, NAEPP 2007.

anti-IgE=anti-immunoglobulin E; ICS=inhaled corticosteroids; GINA=Global Initiative for Asthma; LABA=long-acting beta-agonist; LTRA=leukotriene receptor antagonist; NAEPP=National Asthma Education and Prevention Program; OCS=oral corticosteroid; NA=not applicable; SABA=short-acting beta-agonist.

3.5. Efficacy Measures

The efficacy variables utilized in the Phase 3 placebo-controlled safety and efficacy studies in asthma were selected to comprehensively assess the 2 major domains of asthma control, including current impairment (lung function, symptoms, and quality of life) and future risk (asthma exacerbations) [Table 8]. For Studies 3082 and 3083, the primary efficacy measure was the frequency of CAEs over the 52-week treatment period. Secondary efficacy measures for Studies 3082 and 3083 including the time to first asthma exacerbation and change from baseline relative to placebo (FEV_1, AQLQ, ACQ, ASUI, short-acting beta-agonist [SABA] use, and blood eosinophils) over and/or at 16 weeks, depending on the measure, were controlled for multiplicity (see Section 9.4.1 for further detail). The primary efficacy measure for Study 3081 was the change in FEV_1 over 16 weeks for the 2 doses of reslizumab (0.3 and 3.0 mg/kg); analyses of other efficacy variables in Study 3081 were not controlled for multiplicity.

Table 8: Efficacy Variables for the Phase 3 Asthma Program

Study number	Study 3081	Study 3082	Study 3083
CAEs	--	X[a]	X[a]
Time to first CAE	--	X	X
Lung function (assessed monthly)			
FEV_1	X[b]	X	X
Other lung function (FVC, $FEF_{25\%-75\%}$)	X	X	X
Other asthma control measures (assessed monthly)			
ACQ score	X	X	X
ASUI score	X	X	X
SABA use	X	X	X
Quality of life measures (assessed beginning at week 16)			
AQLQ total score	X	X	X
Blood eosinophils monthly	X	X	X

[a] Primary efficacy variable for Studies 3082 and 3083 over 52 weeks.
[b] Primary efficacy variable for Study 3081 over 16 weeks.
ACQ=Asthma Control Questionnaire; AQLQ=Asthma Quality of Life Questionnaire; ASUI=Asthma Symptom Utility Index; CAE=clinical asthma exacerbation; $FEF_{25\%-75\%}$=forced expiratory flow during the middle half of the forced vital capacity; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity.

Clinical Asthma Exacerbations

The frequency of CAEs over 52 weeks was selected as the primary endpoint for Studies 3082 and 3083, in agreement with the FDA. An asthma exacerbation is generally regarded as a worsening of asthma that requires some medical intervention beyond the patient's usual care; however, there is no universally accepted definition of asthma exacerbation. As such, advice was sought from regulatory authorities regarding the definition used for Studies 3082 and 3083. The final definition, which incorporated feedback received from regulatory authorities, was as follows:

- medical intervention
  - either the use of a systemic corticosteroid or an increase in the use of ICS, or
  - asthma-related emergency treatment including at least 1 of the following:
    - unscheduled visit to the physician's office for nebulizer treatment or other urgent treatment to prevent worsening of asthma symptoms
    - visit to the ER for asthma-related treatment
    - asthma-related hospitalization

- plus evidence of asthma worsening (at least 1 of the following)
  - decrease in FEV_1 by 20% or more from baseline
  - decrease in peak expiratory flow rate by 30% or more from baseline on 2 consecutive days
  - worsening of symptoms or other clinical signs per physician evaluation of the event

To ensure uniformity, all asthma exacerbation events were adjudicated by a committee of 3 asthma experts independent of Teva who were blinded to the treatment assignment. An adjudication charter, including membership, was submitted to the FDA.

Prespecified subanalysis of asthma exacerbations included an analysis of those asthma exacerbations that required systemic corticosteroid use, hospitalization, and/or ER visit as an intervention. An analysis of exacerbations that resulted in hospitalization alone was performed post hoc.

3.5.1. Additional Rationale for the Selection of Efficacy Measurements and Statistical Considerations

Discussion of the rationale for the selection of the primary and secondary efficacy endpoints in Phase 3 Studies 3081, 3082, and 3083 (FEV_1 and other lung functions, SABA use, ACQ, ASUI, and AQLQ) is presented in Section 9.3. Statistical considerations for efficacy analyses are presented in Section 9.4.

4. EFFICACY

The efficacy discussion is focused on the results from 3 adequate and well-controlled Phase 3 Studies 3081, 3082, and 3083, which tested the proposed dose (3.0 mg/kg) and regimen (every 4 weeks) in asthma patients with elevated blood eosinophils whose symptoms were inadequately controlled on medium to high doses of ICS with or without another asthma controller.
The reduction in the rate of CAEs was measured over 52 weeks. Change over 16 weeks (can be viewed as a weighted average across all timepoints) was the principal analysis endpoint for current impairment measures (eg, improvement in FEV_1 and symptom scores), with other endpoints (analysis at specific time points) prespecified to help inform the onset and maintenance effect.

4.1. Patient Disposition and Demographics

The studies that support the efficacy evaluation of reslizumab are representative of the population of patients requiring treatment for asthma with elevated blood eosinophils and whose symptoms are inadequately controlled on medium- to high-dose ICS-based standard-of-care therapy (Table 6, Section 3.4.1, and Figure 3).

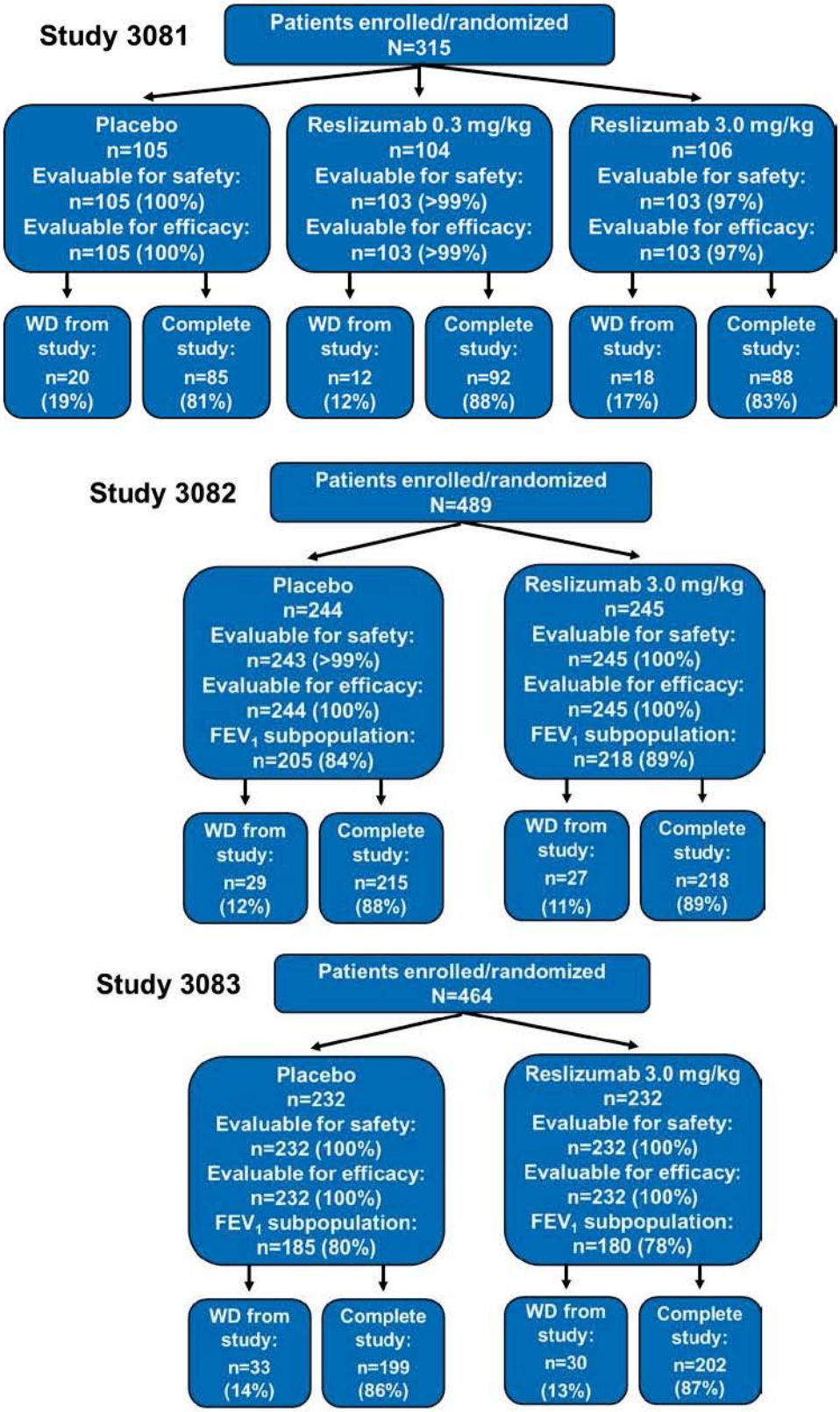
4.1.1. Disposition

A total of 1164 patients were randomized across Studies 3081, 3082, and 3083 (581 patients in the placebo group and 583 patients in the reslizumab 3.0 mg/kg group); an additional

105 patients were randomized to 0.3 mg/kg of reslizumab in Study 3081 (Figure 17). A total of 1010 patients (87%) completed the treatment phase of their respective studies: 500 patients (86%) in the placebo group and 510 patients (87%) in the reslizumab 3.0 mg/kg group.

The most frequent reason for discontinuation of study treatment in both groups was withdrawal of consent (5% of patients overall) and occurred at a similar rate between the placebo and reslizumab groups. Nearly all of the patients who completed the treatment phase also completed their respective studies (1007 patients [87%]), and the most frequent reason for withdrawal from the study was the same as the reason for discontinuation of study treatment (ie, withdrawal of consent). The proportion of patients in the reslizumab 3.0 mg/kg group who withdrew from their respective studies was similar to that in the placebo group.

Figure 17: Patient Disposition for Studies 3081, 3082, and Study 3083



FEV_1= forced expiratory volume in 1 second; WD=withdrawal.

4.1.2. Demographic and Baseline Characteristics

Demographics

Table 9 shows the demographic characteristics of subjects in Studies 3081, 3082, and 3083. The demographic characteristics of subjects were generally balanced between the placebo and reslizumab 3.0 mg/kg groups within a study. The Phase 3 asthma population was predominantly adult, female, and white. The observed female predominance is consistent with the adult asthma population. Patients from the US were represented in all 3 global studies, with a relatively small proportion represented in the 52-week asthma studies.

Table 9: Demographic and Baseline Characteristics by Treatment Group (Studies 3081, 3082, and 3083)

Demographic/baseline characteristic	Study 3081		Study 3082		Study 3083	
	Placebo (N=105)	Reslizumab 3.0 mg/kg (N=106)	Placebo (N=244)	Reslizumab 3.0 mg/kg (N=245)	Placebo (N=232)	Reslizumab 3.0 mg/kg (N=232)
Age (years), mean (SD)	44.2 (14.89)	43.0 (14.41)	46.7 (14.83)	46.6 (13.82)	47.5 (13.75)	46.4 (13.79)
Age group, n (%)						
12-17 years	5 (5)	5 (5)	7 (3)	6 (2)	4 (2)	8 (3)
18-64 years	93 (89)	99 (93)	212 (87)	224 (91)	208 (90)	207 (89)
≥65 years	7 (7)	2 (2)	25 (10)	15 (6)	20 (9)	17 (7)
Sex, n (%)						
Male	43 (41)	44 (42)	83 (34)	103 (42)	82 (35)	88 (38)
Female	62 (59)	62 (58)	161 (66)	142 (58)	150 (65)	144 (62)
Race, n (%)						
White	85 (81)	90 (85)	182 (75)	173 (71)	169 (73)	168 (72)
Black	7 (7)	5 (5)	20 (8)	14 (6)	4 (2)	6 (3)
Asian	0	2 (2)	33 (14)	50 (20)	21 (9)	16 (7)
American Indian or Alaskan Native	1 (<1)	0	0	0	4 (2)	7 (3)
Pacific Islander	1 (<1)	0	0	1 (<1)	1 (<1)	0
Other	11 (10)	9 (8)	9 (4)	7 (3)	33 (14)	35 (15)
Ethnicity, n (%)						
Hispanic or Latino	29 (28)	31 (29)	21 (9)	28 (11)	53 (23)	54 (23)
Non-Hispanic or non-Latino	74 (70)	75 (71)	223 (91)	216 (88)	178 (77)	177 (76)
Unknown	2 (2)	0	0	1 (<1)	1 (<1)	1 (<1)
BMI (kg/m^2), mean (SD)	27.7 (6.01)	27.4 (6.87)	28.0 (6.16)	27.7 (6.26)	27.0 (5.05)	27.0 (5.26)
Geographic region, n (%)						
United States	38 (36)	42 (40)	37 (15)	37 (15)	15 (6)	16 (7)
Other countries	67 (64)	64 (60)	207 (85)	208 (85)	217 (94)	216 (93)

BMI=body mass index; SD=standard deviation.

Baseline Disease Characteristics

There was a 2-week run-in period where patients maintained their usual ICS-based controller regimen. Table 10 displays the baseline disease characteristics for Studies 3081, 3082, and 3083. Overall, the baseline disease state measures for the Phase 3 asthma population were consistent with those for the intended asthma population (ie, inadequately controlled patients despite medium- to high-dose ICS-based therapy).

- The baseline disease characteristics were similar across reslizumab 3.0 mg/kg and placebo groups and across studies, except that the proportion of patients who experienced an exacerbation within the previous 12 months was lower for the lung function study (ie, Study 3081; not an inclusion requirement).
- Mean values of ACQ, ASUI, AQLQ, and lung function at baseline were consistent with those for the intended asthma population whose symptoms are inadequately controlled based on normal ranges for the respective measures.
- Between 76% and 87% of the patients were using an ICS plus an LABA at baseline. The proportion of patients on high doses of ICS ranged from 29% to 45%.
- In Studies 3082 and 3083, approximately 11% of patients were using low dose maintenance OCS therapy for their asthma.

Table 10: Baseline Disease Characteristics by Treatment Group (Studies 3081, 3082, and 3083)

Baseline disease characteristic	Study 3081		Study 3082		Study 3083	
	Placebo (N=105)	RES 3.0 mg/kg (N=106)	Placebo (N=244)	RES 3.0 mg/kg (N=245)	Placebo (N=232)	RES 3.0 mg/kg (N=232)
Asthma duration in years, mean (SD)	20.7 (14.49)	20.4 (15.64)	18.8 (14.20)	19.7 (15.19)	18.7 (13.28)	18.2 (14.43)
Asthma exacerbation within 12 months (Y/N), n (%)	57 (54)	60 (57)	242 (>99)	242 (99)	232 (100)	231 (>99)
Number of exacerbation in prior 12 months, mean (SD)	2.0 (1.27)	2.1 (1.63)	2.1 (2.31)	1.9 (1.63)	2.0 (1.78)	1.9 (1.58)
ACQ score, mean (SD)	2.47 (0.830)	2.59 (0.911)	2.76 (0.878)	2.66 (0.854)	2.61 (0.794)	2.57 (0.888)
Airway reversibility (%), mean (SD)	25 (15.6)	26 (18.6)	26 (18.1)	26 (15.5)	29 (23.7)	28 (16.1)
FEV_1 (L), mean (SD)	2.22 (0.813)	2.19 (0.792)	1.93 (0.791)	1.89 (0.726)	2.00 (0.668)	2.13 (0.785)
FEV_1/FVC, mean (SD)	0.67 (0.117)	0.68 (0.112)	0.64 (0.124)	0.64 (0.122)	0.67 (0.109)	0.67 (0.123)
% Predicted FEV_1, mean (SD)	71 (19.8)	70 (18.4)	65 (19.8)	64 (18.6)	68 (18.9)	70 (21.0)
AQLQ total score, mean (SD)	4.37 (1.205)	4.18 (1.230)	4.16 (1.088)	4.30 (1.121)	4.22 (1.079)	4.35 (1.022)
ASUI score, mean (SD)	0.67 (0.190)	0.66 (0.195)	0.61 (0.203)	0.63 (0.194)	0.65 (0.192)	0.66 (0.201)

Table 10: Baseline Disease Characteristics by Treatment Group (Studies 3081, 3082, and 3083) (Continued)

Baseline disease characteristic	Study 3081		Study 3082		Study 3083	
	Placebo (N=105)	RES 3.0 mg/kg (N=106)	Placebo (N=244)	RES 3.0 mg/kg (N=245)	Placebo (N=232)	RES 3.0 mg/kg (N=232)
Blood eosinophil count ($\times 10^9$ cells/L), mean (SD)	0.601 (0.4331)	0.592 (0.3878)	0.624 (0.5903)	0.696 (0.7677)	0.688 (0.6824)	0.610 (0.4115)
SABA use: daily average number of puffs in the past 3 days, mean (SD)	2.3 (2.20)	2.2 (2.56)	2.7 (3.18)	2.4 (2.82)	2.7 (2.41)	2.9 (2.82)
Total daily ICS dose[a] (μg), mean (SD)	757 (370.6)	814 (452.7)	848 (442.1)	824 (380.3)	757 (274.2)	856 (588.4)
Medium-dose ICS, n (%)	75 (71)	67 (63)	135 (55)	137 (56)	133 (57)	137 (59)
High-dose ICS, n (%)	30 (29)	39 (37)	109 (45)	108 (44)	99 (43)	95 (41)
Non-ICS controller drug,[b] n (%)	88 (84)	89 (84)	212 (87)	218 (89)	193 (83)	193 (83)
LABA use at baseline, n (%)	84 (80)	81 (76)	202 (83)	212 (87)	181 (78)	185 (80)
Leukotriene inhibitor, n (%)	24 (23)	27 (25)	68 (28)	57 (23)	44 (19)	40 (17)
OCS use, per CRF, n (%)	NA	NA	40 (16)	24 (10)	18 (8)	24 (10)

[a] Any ICS formulation; at least medium-dose ICS background is mandatory.
[b] Non-ICS controller=Yes if the medication belongs to any of the following categories: LABA, leukotriene inhibitors, long-acting muscarinic receptor antagonists, xanthine derivative bronchodilators, or chromone.
ACQ=Asthma Control Questionnaire; AQLQ=Asthma Quality of Life Questionnaire; ASUI=Asthma Symptom Utility Index; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; ICS=inhaled corticosteroid; LABA=long-acting beta-agonist; % predicted; FEV_1=actual FEV_1 divided by standard predicted FEV_1 times 100%; NA=not applicable; RES= reslizumab; SABA=short-acting beta-agonist; SD=standard deviation.

4.2. Efficacy Results

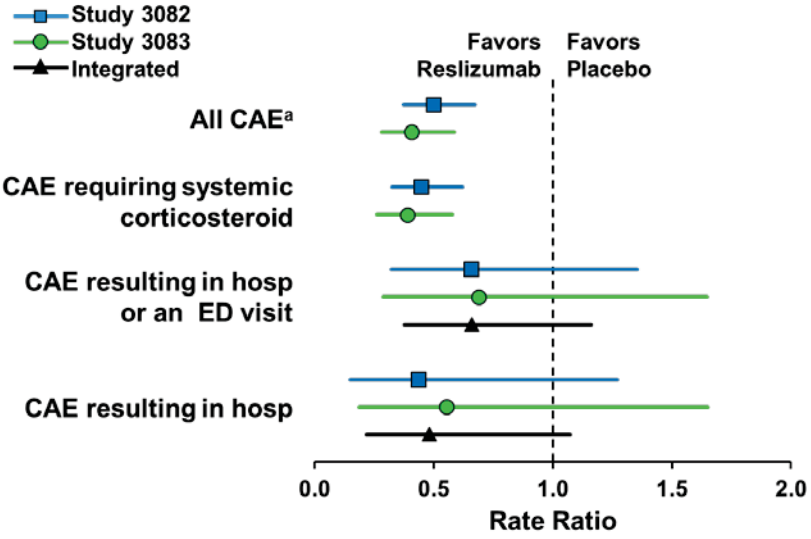
4.2.1. Frequency of Clinical Asthma Exacerbations over 52 Weeks (Studies 3082 and 3083)

The primary efficacy variable for Studies 3082 and 3083 was the frequency of CAEs per patient during the 52-week treatment period (see Section 3.5 for the per-protocol definition of CAE). In both studies, the primary analysis demonstrated a statistically significant reduction in CAE frequency over 52 weeks for patients in the reslizumab 3.0 mg/kg group compared with patients in the placebo group. The key findings are summarized in the following and detailed in Figure 18 and Table 11.

- 50% and 59% reductions were observed in the annual CAE rate relative to placebo in Studies 3082 and 3083, respectively (both with $p<0.0001$).
- The majority of patients (>80%) who experienced at least 1 CAE in either treatment group in Studies 3082 and 3083 were treated with systemic corticosteroids for ≥3 days. A prespecified analysis of this type of events resulted in 55% and 61% reductions in the annual CAE rate relative to placebo in Studies 3082 and 3083, respectively ($p<0.0001$ for both), consistent with the results of the primary analysis.

- Events leading to a hospitalization or an ER visit were less common. However, there were consistent trends toward a reduction in the rate of CAEs resulting in a hospitalization or a visit to the ER (31% and 34% reductions in Studies 3082 and 3083, respectively) and those requiring hospitalization alone (56% and 45% in Studies 3082 and 3083, respectively).

Figure 18: Clinical Asthma Exacerbations over 52 Weeks by Treatment Group (Studies 3082 and 3083 and Integrated Studies)



[a] This group comparison was controlled for type I error.
CAE=clinical asthma exacerbation; ED=emergency department.

Table 11: Overall Summary of CAE Frequency over 52 Weeks by Treatment Group (Studies 3082 and 3083 and Integrated Studies)

Variable	Study 3082		Study 3083		Integrated Studies 3082 and 3083	
	Placebo (N=244)	Reslizumab 3.0 mg/kg (N=245)	Placebo (N=232)	Reslizumab 3.0 mg/kg (N=232)	Placebo (N=476)	Reslizumab 3.0 mg/kg (N=477)
Overall CAE frequency over 52 weeks						
Number of patients with at least 1 CAE, n (%)	132 (54.1)	92 (37.6)	105 (45.3)	59 (25.4)	237 (49.8)	151 (31.7)
Primary endpoint: adjusted CAE rate	**1.80**	**0.90**	**2.11**	**0.86**	**1.81**	**0.84**
95% CI	1.37, 2.37	0.68, 1.21	1.33, 3.36	0.55, 1.35	1.43, 2.31	0.65, 1.07
CAE rate ratio (95% CI) p-value	0.50[a] (0.37, 0.67) <0.0001		0.41[a] (0.28, 0.59) <0.0001		0.46 (0.37, 0.58) <0.0001	
Frequency of CAEs requiring courses of systemic corticosteroids prescribed for ≥3 days over 52 weeks						
Number of patients with at least 1 CAE, n (%)	118 (48.4)	80 (32.7)	92 (39.7)	49 (21.1)	210 (44.1)	129 (27.0)
Adjusted CAE rate	1.60	0.72	1.66	0.65	1.54	0.66
95% CI	1.20, 2.15	0.53, 0.99	1.00, 2.74	0.40, 1.05	1.18, 1.9940	0.50, 0.86
CAE rate ratio (95% CI) p-value	0.45 (0.33, 0.62) <0.0001		0.39 (0.26, 0.58) <0.0001		0.43 (0.33, 0.55) <0.0001	
Frequency of CAEs resulting in hospitalization or a visit to the ER over 52 weeks						
Number of patients with at least 1 CAE, n (%)	21 (8.6)	22 (9.0)	12 (5.2)	9 (3.9)	33 (6.9)	31 (6.5)
Adjusted CAE rate	0.21	0.14	0.05	0.03	0.12	0.08
95% CI	0.11, 0.40	0.07, 0.27	0.01, 0.17	0.01, 0.12	0.07, 0.21	0.04, 0.14
CAE rate ratio (95% CI) p-value	0.66 (0.32, 1.36) 0.2572		0.66 (0.29, 1.65) 0.4020		0.66 (0.38, 1.17) 0.1510	
Frequency of severe CAEs resulting in hospitalization over 52 weeks						
Number of patients with at least 1 CAE, n (%)	11 (4.5)	9 (3.7)	8 (3.4)	5 (2.2)	NA	NA
Adjusted CAE rate	0.00[b]	0.00[b]	0.04	0.02	NA	NA
95% CI	0.00[b], 0.00[b]	0.00[b], 0.00[b]	0.01, 0.15	0.004, 0.09	NA	NA
CAE rate ratio (95% CI) p-value	0.44 (0.15, 1.27) 0.1285		0.55 (0.19, 1.65) 0.2885		NA	

[a] This group comparison was controlled for type I error.
[b] Calculated numbers were well below the rounding threshold of 2 significant digits after the decimal.
CAE=clinical asthma exacerbation; CI=confidence interval; ER=emergency room; NA=not applicable.
Note: See Section 9.4.1 for statistical methods.

The secondary efficacy endpoint, time to first CAE event, also favored reslizumab (Table 12 and Figure 19). The hazard ratio showed a reduction by 42.5% (p<0.0001) in Study 3082 and by 51.4% (p<0.0001) in Study 3083 for the reslizumab group.

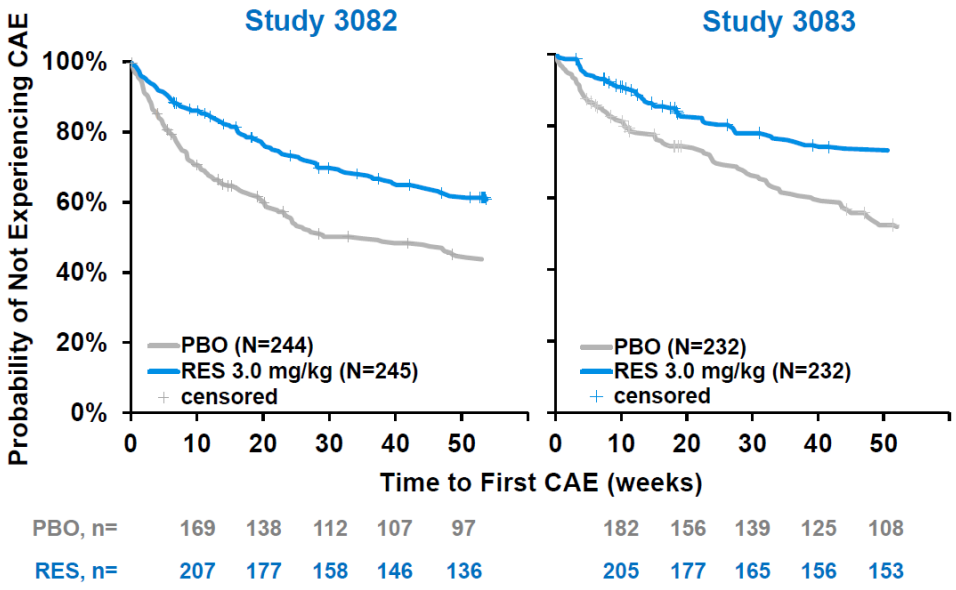
Table 12: Time to First CAE (Studies 3082 and 3083)

Statistic	Study 3082		Study 3083	
	Placebo (N=244)	Reslizumab 3.0 mg/kg (N=245)	Placebo (N=232)	Reslizumab 3.0 mg/kg (N=232)
KM estimate of probability of not experiencing a CAE by week 52 (95% CI)	44.2 (37.7, 50.5)	61.3 (54.7, 67.2)	51.9 (45.0, 58.3)	73.2 (66.8, 78.6)
Hazard ratio (95% CI) p-value	0.575 (0.440, 0.750) <0.0001		0.486 (0.353, 0.670) <0.0001	

CAE=clinical asthma exacerbation; CI=confidence interval; EOT=end of treatment; KM=Kaplan-Meier; OCS=oral corticosteroid; US=United States.

Notes: The CAEs counted were those that occurred between the completion of the first dose of study drug and 2 weeks after the EOT/early withdrawal visit.
The hazard ratio, its p-value, and confidence interval were estimated using stratified Cox regression model with baseline usage of OCS (yes or no) and geographical region (US or other) as stratification factors.
Primary analysis of overall CAE frequency over 52 weeks as well as secondary analysis of time to first exacerbation were controlled for multiplicity.

Figure 19: Time to First CAE by Treatment Group (Studies 3082 and 3083)



CAE=clinical asthma exacerbation; PBO=placebo; RES=reslizumab.

4.2.1.1. Sensitivity Analyses for the Primary Efficacy Endpoint

Missing data: A prespecified multiple imputations and post hoc tipping point (per FDA request at the pre-BLA meeting) were performed for the primary endpoint in each study. The percent of early discontinuations ranged from 11% to 15% in Studies 3082 and 3083 and were comparable

between the 2 treatment groups. Results support the robustness of the study results. More details on the methodology used can be found in Section 9.4.4.

Effect of protocol violations: Analyses were rerun excluding patients with protocol violations. The results were consistent with the primary efficacy analysis.

Effect of stratification errors: In an attempt to reduce potential imbalances in the level of asthma control between the placebo and reslizumab treatment groups, patients were stratified for OCS use (Study 3082 or 3083) on the day of randomization as part of the Interactive Voice Recognition System. In order to understand the impact of sporadic mis-stratification errors, efficacy analyses were rerun using OCS data from the medication case report form. The results of this analysis were consistent with those of the primary efficacy analysis.

4.2.2. Asthma Control Variables (Studies 3081, 3082, and 3083)

In addition to reducing the rate of CAEs, reslizumab 3.0 mg/kg consistently improved multiple measures of current asthma control, including lung function (FEV_1), asthma symptoms (ACQ and ASUI), and an asthma-related quality-of-life measure (AQLQ) from baseline to 16 and 52 weeks compared with placebo (Table 13).

Nonsignificant improvements in reliever SABA use were observed over the treatment period for both 52-week studies. The minimal improvements in this measure may be related to the reflective nature of the assessment (patient recalled number of inhalations) rather than to the daily diary.

Consistent with its mode of action, reslizumab 3.0 mg/kg produced sustained reduction in blood eosinophil counts over 16 and 52 weeks of treatment in all studies.

Table 13: Adjusted Mean Change in Asthma Control Variables from Baseline over 16 and 52 Weeks (Studies 3081, 3082, and 3083)

	Study 3081[a]		Study 3082[a]				Study 3083[a]			
	16 weeks		16 weeks		52 weeks		16 weeks		52 weeks	
Efficacy variable[b]	**Placebo (N=105)**	**Reslizumab (N=103)**	**Placebo (N=244)**	**Reslizumab (N=245)**	**Placebo (N=244)**	**Reslizumab (N=245)**	**Placebo (N=232)**	**Reslizumab (N=232)**	**Placebo (N=232)**	**Reslizumab (N=232)**
FEV_1 (L)	0.127 (n=103)	0.286 (n=102)	0.110 (n=241)	0.248 (n=243)	0.109 (n=241)	0.235 (n=243)	0.094 (n=227)	0.187 (n=230)	0.111 (n=227)	0.201 (n=230)
Adjusted mean difference	0.159[c,**]		0.137[c,**]		0.126[**]		0.093[c,**]		0.090[*]	
ACQ score	-0.494 (n=103)	-0.855 (n=101)	-0.676 (n=241)	-0.941 (n=242)	-0.764 (n=241)	-1.020 (n=242)	-0.660 (n=228)	-0.857 (n=230)	-0.800 (n=228)	-1.042 (n=230)
Adjusted mean difference	-0.361[**]		-0.266[c,**]		-0.255[**]		-0.196[c,**]		-0.242[**]	
AQLQ total score	0.781 (n=101)	1.140 (n=99)	0.695 (n=229)	0.933 (n=228)	0.789 (n=231)	1.091 (n=233)	0.777 (n=216)	0.987 (n=213)	0.889 (n=221)	1.123 (n=216)
Adjusted mean difference	0.358[*]		0.238[c,*]		0.302[**]		0.209[c,*]		0.234[**]	
ASUI score	0.082 (n=103)	0.129 (n=101)	0.109 (n=238)	0.167 (n=238)	0.127 (n=238)	0.188 (n=238)	0.080 (n=224)	0.115 (n=227)	0.113 (n=224)	0.149 (n=227)
Adjusted mean difference	0.047[*]		0.058[c,**]		0.061[**]		0.035[c,**]		0.036[**]	
SABA (puffs/day)	-0.3 (n=102)	-1.0 (n=102)	-0.36 (n=238)	-0.64 (n=240)	-0.42 (n=238)	-0.58 (n=240)	-0.44 (n=188)	-0.50 (n=180)	-0.55 (n=194)	-0.73 (n=192)
Adjusted mean difference	-0.632[*]		-0.276[c]		-0.152		-0.062[c]		-0.180	
FVC (L)	0.173 (n=103)	0.302 (n=102)	0.091 (n=241)	0.225 (n=243)	0.079 (n=241)	0.197 (n=243)	0.126 (n=227)	0.203 (n=230)	0.136 (n=227)	0.221 (n=230)
Adjusted mean difference	0.129[*]		0.134[**]		0.118[**]		0.077[*]		0.084[*]	
$FEF_{25\%-75\%}$ (L/sec)	-0.142 (n=103)	0.091 (n=1020	-0.053 (n=238)	0.039 (n=238)	-0.048 (n=238)	0.009 (n=238)	-0.260 (n=226)	-0.090 (n=230)	-0.227 (n=226)	-0.064 (n=230)
Adjusted mean difference	0.233		0.092		0.057		0.170[*]		0.163[*]	

Table 13: Adjusted Mean Change in Asthma Control Variables from Baseline over 16 and 52 Weeks (Studies 3081, 3082, and 3083) (Continued)

	Study 3081[a]		Study 3082[a]				Study 3083[a]			
	16 weeks		16 weeks		52 weeks		16 weeks		52 weeks	
Efficacy variable[b]	**Placebo (N=105)**	**Reslizumab (N=103)**	**Placebo (N=244)**	**Reslizumab (N=245)**	**Placebo (N=244)**	**Reslizumab (N=245)**	**Placebo (N=232)**	**Reslizumab (N=232)**	**Placebo (N=232)**	**Reslizumab (N=232)**
Blood eosinophils ($\times 10^9$ cells/L)	-0.035 (n=103)	-0.529 (n=102)	-0.118 (n=241)	-0.584 (n=243	-0.127 (n=241)	-0.582 (n=243)	-0.076 (n=226)	-0.555 (n=230)	-0.076 (n=226)	-0.565 (n=230)
Adjusted mean difference	-0.494**		-0.466**		-0.455**		-0.479**		-0.489**	

[a] The efficacy analysis set for Study 3081 was the Full Analysis Set, with all measurements included. The efficacy analysis set for Studies 3082 and 3083 was the Randomized Set (Section 9.4).

[b] Values shown are least-square mean changes over the specified period from baseline, apart from the week 16 AQLQ, which represents the change to week 16 (week 16 was the first timepoint where AQLQ was assessed).

[c] This group comparison was controlled for Type I error.

* $p \leq 0.05$.

** $p \leq 0.005$

ACQ=Asthma Control Questionnaire; AQLQ=Asthma Quality of Life Questionnaire; ASUI=Asthma Symptom Utility Index; $FEF_{25\%-75\%}$=forced expiratory flow during the middle half of the forced vital capacity; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; SABA=short-acting beta-agonist.

The published MID for ACQ and AQLQ (0.5 units for both) was not achieved for the overall population relative to placebo treatment. This is not unexpected when taking into consideration the fact that approximately 80% of the enrolled population were receiving reslizumab (or placebo) on top of standard of care consisting of medium to high doses of ICS with a LABA (Bateman et al 2015a). Except for ACQ for the 16-week lung function study, prespecified responder analysis favored reslizumab at the end of each respective study (Table 14).

Table 14: Proportion of MID Responders in the Placebo and Reslizumab Groups at the End of Each Study

	Study 3081 (at week 16)		Study 3082 (at week 52)		Study 3083 (at week 52)	
	Placebo (N=105)	Reslizumab (N=103)	Placebo (N=244)	Reslizumab (N=245)	Placebo (N=232)	Reslizumab (N=232)
ACQ, n (%)	49 (58) (n=84)	58 (64) (n=91)	137 (64) (n=215)	168 (77) (n=218)	123 (62) (n=200)	163 (81) (n=201)
p-value	NS[a]		0.0022[b]		<0.0001[b]	
AQLQ, n (%)	48 (48) (n=101)	63 (64) (n=99)	139 (65) (n=213)	163 (75) (n=218)	126 (64) (n=198)	147 (74) (n=200)
p-value	0.0189[a]		0.0272[b]		0.0305[b]	

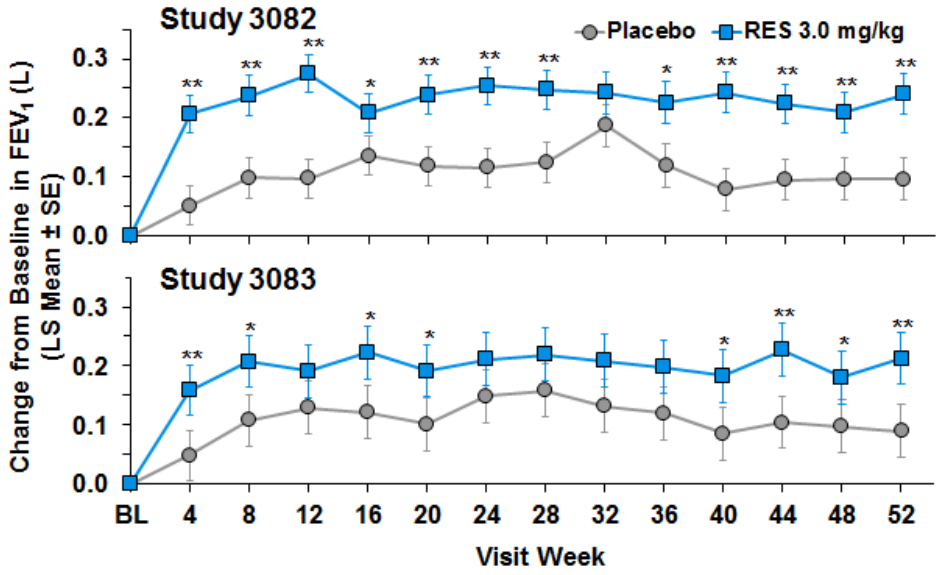
[a] The p-value for comparison in the active and placebo groups is obtained from the Cochran-Mantel-Haenszel test, stratified by age group and history of asthma exacerbation in the previous 12 months. Not controlled for multiplicity.

[b] The p-value for the between-group comparison is obtained from the Cochran-Mantel-Haenszel test, stratified by region and oral corticosteroids use at enrollment. Not controlled for multiplicity.

ACQ=Asthma Control Questionnaire; AQLQ=Asthma Quality of Life Questionnaire; MID=minimal important difference; NS=not significant.

The onset of treatment effect on measures of asthma impairment was observed at the first on-treatment assessment (week 4 for FEV_1, ACQ, and ASUI; week 16 for AQLQ) and sustained over the 52-week treatment period. This is shown for FEV_1 in Studies 3082 and 3083 (Figure 20).

Figure 20: Adjusted Mean (±SE) of Changes from Baseline in FEV_1 (Studies 3082 and 3083)



* p≤0.05 versus placebo.
** p≤0.005 versus placebo.
BL=baseline; EP=endpoint; FEV_1=forced expiratory volume in 1 second; LS=least squares; RES=reslizumab; SE=standard error.
Note: The majority of the timepoints were not controlled for multiplicity. p-values at the endpoint are nominal except at week 16.

4.3. Supportive Efficacy Results

4.3.1. Long-Term Efficacy

The treatment effect of reslizumab on the measures of pulmonary function (FEV_1), patient-reported outcomes (ACQ, AQLQ, and ASUI), and blood eosinophil counts persisted, without diminution, with repeated dosing of reslizumab 3.0 mg/kg for up to 1 year in Studies 3082 and 3083.

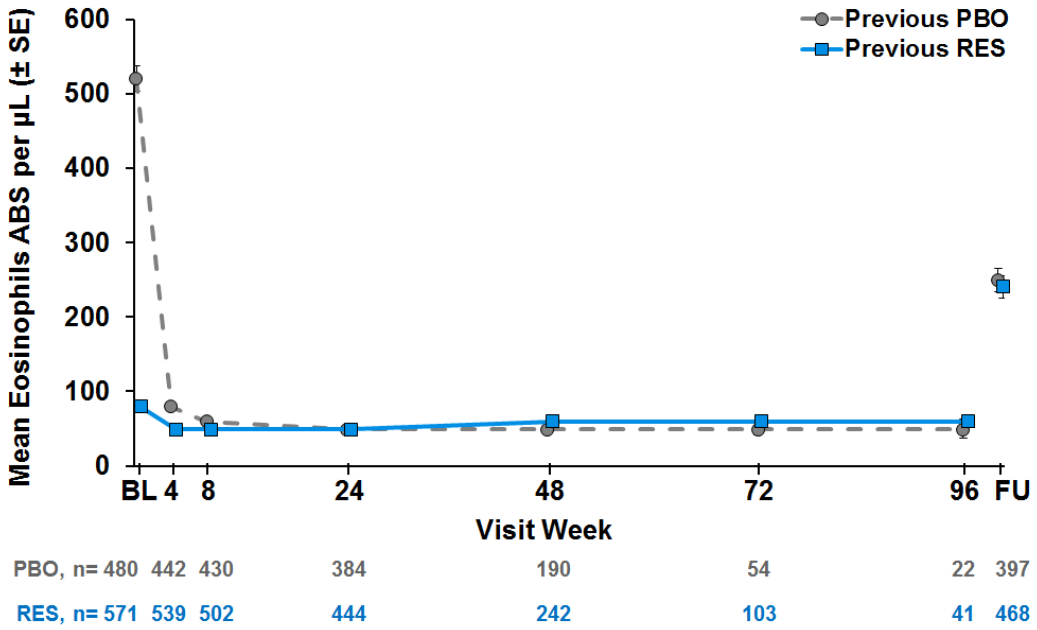
4.3.2. Persistence of Efficacy and Tolerance Effects

The OLE study (ie, Study 3085) enrolled eligible patients from Study 3081, 3082, or 3083. The primary objective of the OLE was to obtain additional safety data for reslizumab 3.0 mg/kg every 4 weeks relative to baseline for up to 24 months; however, efficacy assessments were continued during the open-label period. Efficacy variables included FEV_1, AQLQ score, ACQ score, ASUI score, and SABA use. All analyses were descriptive. Results from the OLE Study 3085 indicate that improvements in asthma control observed during the double-blind treatment period were sustained during the OLE.

The persistence of clinical efficacy after cessation of reslizumab dosing was not specifically evaluated in the Phase 3 studies. However, results demonstrated that blood eosinophils had

returned to near baseline at the 90-day follow-up visit (or approximately 4 months after the last scheduled dose of reslizumab) without evidence of a rebound effect. This was most robustly demonstrated in the OLE Study 3085, which had the largest number of follow-up blood eosinophil assessments (Figure 21). Thus, the clinical effects of reslizumab would be expected to wane after the last dose, with a gradual return to baseline symptoms (see also Section 5.11).

Figure 21: Mean (±SE) Blood Eosinophils at Each Visit by Double-Blind Treatment Group



ABS=absolute; BL=baseline; FU=follow-up; PBO=placebo; RES=reslizumab; SE=standard error.

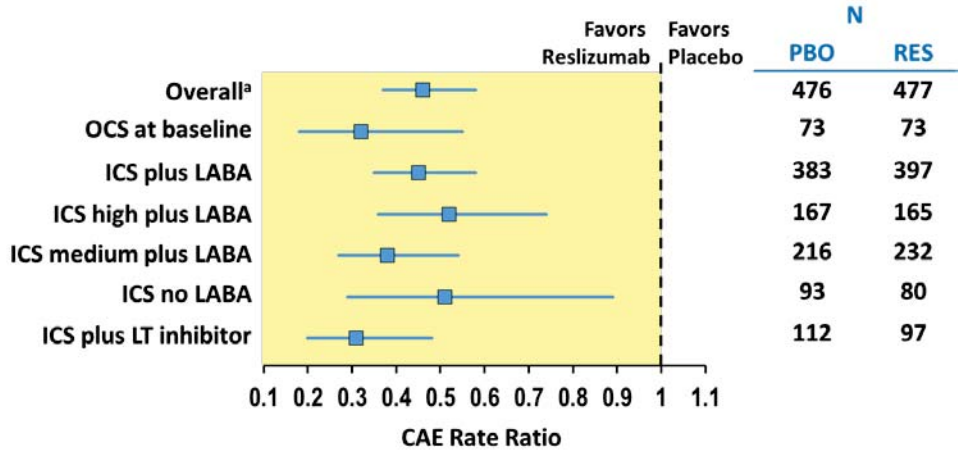
4.3.3. Influence of Background Medication and Demographic Factors on Reslizumab Efficacy

The Phase 3 reslizumab studies included male and female asthma patients of varied race, aged ≥12 years, from Europe, Asia, Oceana, and the Americas (including Canada, US, Mexico, and South America). A broad range of standard-of-care asthma medication was accommodated by the background inclusion (medium- to high-dose ICS ± another asthma controller medication). The influence of select intrinsic and extrinsic factors on the efficacy of reslizumab was explored.

4.3.3.1. Influence of Concomitant Background Medication on Reslizumab Efficacy

All patients were required to continue their background of medium to high doses of ICS; other asthma controllers were allowed. Analysis of efficacy by background medication demonstrated that reslizumab 3.0 mg/kg reduced the rate of CAEs over 52 weeks and improved FEV_1 irrespective of the type of baseline asthma controller medication (Figure 22 and Figure 23, respectively).

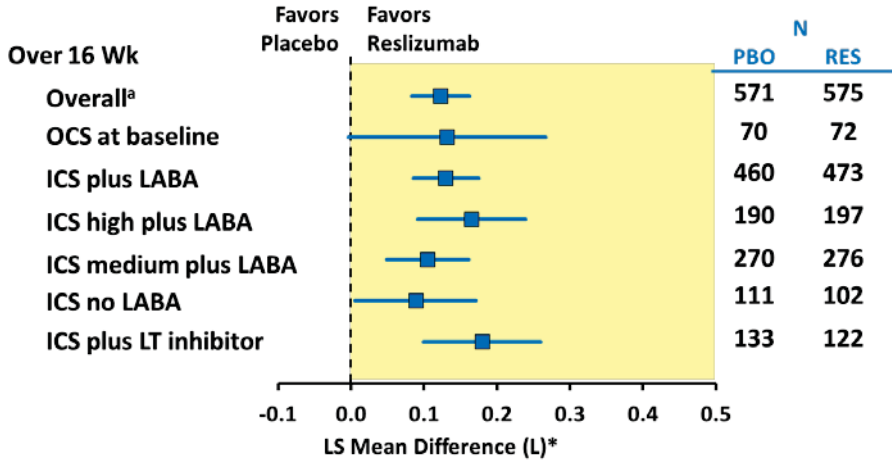
Figure 22: CAE Rates by Background Asthma Medication (Integrated Studies 3082 and 3083)



[a] At least medium dose ICS was required background for the reslizumab studies; additional asthma controllers were not mutually exclusive.

CAE=clinical asthma exacerbations; ICS=inhaled corticosteroids; LABA=long-acting beta-agonist; LT=leukotriene; OCS=oral corticosteroids; PBO=placebo; RES=reslizumab.

Figure 23: FEV_1 Improvement Over 16 Weeks by Background Asthma Medication (Integrated Studies 3081, 3082, and 3083)



*Reslizumab versus placebo.

[a] At least medium dose ICS was required background for the reslizumab studies; additional asthma controllers were not mutually exclusive.

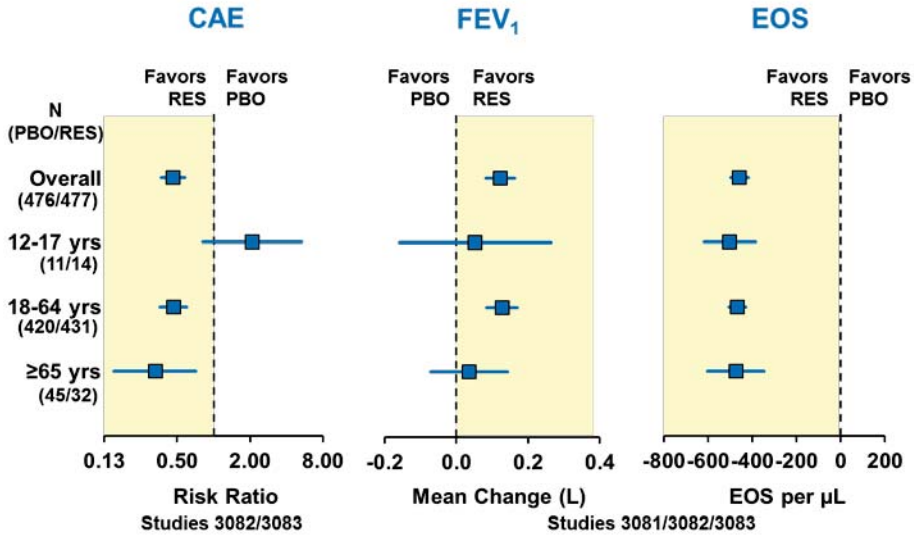
FEV_1=forced expiratory volume in 1 second; ICS=inhaled corticosteroids; LABA=long-acting beta-agonist; LS=least squares; ; LT=leukotriene; OCS=oral corticosteroids; PBO=placebo; RES=reslizumab.

4.3.3.2. Influence of Age, Race, and Region on Reslizumab Efficacy

Reslizumab reduced CAEs across most major demographic subgroups. However, a treatment effect on the frequency of CAEs relative to placebo was not observed in the following subgroups: patients aged 12 to 17 years (n=25), patients who were black (n=44), and patients from the US (n=105).

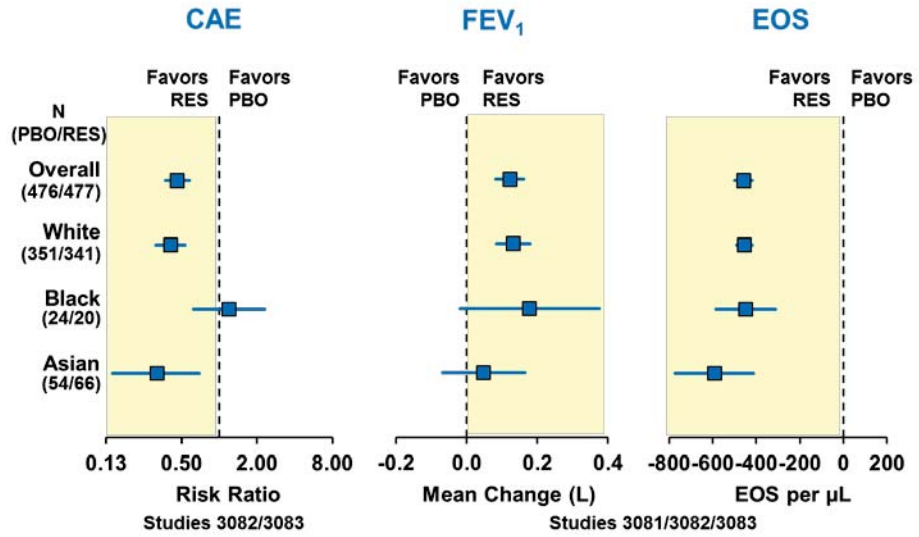
The effect of reslizumab on the subgroups of age, race, and region with respect to reduction of CAE, changes in lung function (FEV_1), and changes in blood eosinophil levels are shown in Figure 24, Figure 25, and Figure 26, respectively. CAE and FEV_1 were used to assess efficacy in these subgroups since these were the primary and/or key secondary efficacy measures in the 3 pivotal efficacy studies.

Figure 24: Reslizumab Effect by Age Subgroup (Integrated Studies)



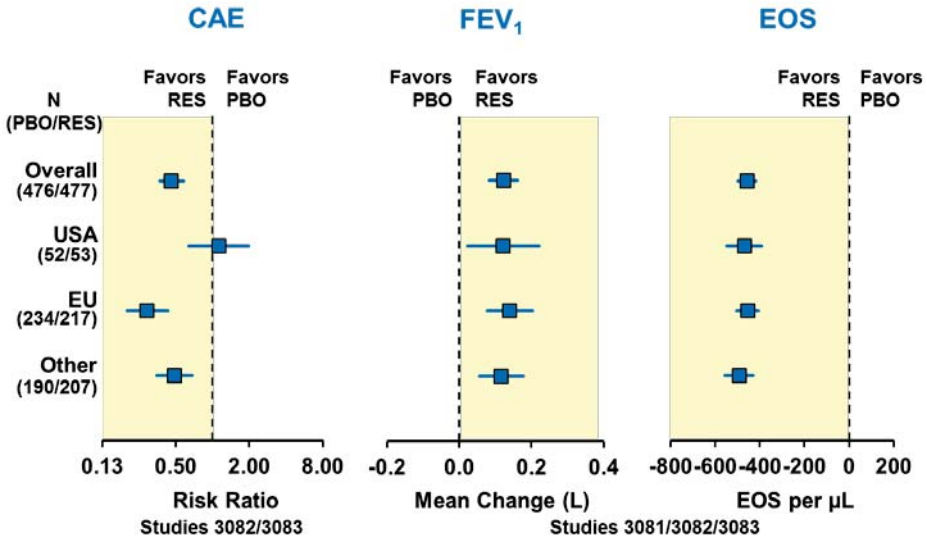
CAE=clinical asthma exacerbation; EOS=eosinophils; FEV_1=forced expiratory volume in 1 second; PBO=placebo; RES=reslizumab.

Figure 25: Reslizumab Effect by Race Subgroup (Integrated Studies)



CAE=clinical asthma exacerbation; EOS=eosinophils; FEV_1=forced expiratory volume in 1 second; PBO=placebo; RES=reslizumab.

Figure 26: Reslizumab Effect by Region Subgroup (Integrated Studies)



CAE=clinical asthma exacerbation; EOS=eosinophils; EU=Europe; FEV_1=forced expiratory volume in 1 second; PBO=placebo; RES=reslizumab; USA=United States of America.

Results of subgroup analyses for adolescents, black race, and US region: Asthma exacerbations are relatively infrequent events for most patients. As such, testing an add-on therapy aimed at treating exacerbations requires an observation period and sample size commensurate with the expected background exacerbation rate and level of asthma control for the population under study; the current studies were not designed to test efficacy in smaller subpopulations. There is no clear reason why the disease state for the subgroups in question

would differ meaningfully from that of the overall population. This is supported by the fact that reslizumab produced the expected changes in blood eosinophil levels and lung function (FEV_1) in the 3 subgroups in question, indicative of a therapeutic response. Given the consistent efficacy across multiple measures of asthma control (including exacerbation reduction) for the overall randomized population, we believe that the apparent lack of effect on exacerbation events in adolescent, US region, and black subgroups is likely due to chance imbalances in baseline asthma control in the small subpopulations.

4.4. Efficacy Summary and Conclusions

The reslizumab Phase 3 program evaluated the addition of reslizumab 3.0 mg/kg every 4 weeks in patients with asthma and elevated blood eosinophil levels (≥400 cells/μL) whose symptoms were inadequately controlled (ACQ ≥1.5) on medium to high doses of corticosteroids ± another asthma controller. Efficacy conclusions are based on 3 studies, including one 16-week-long lung function study and 2 replicated 52-week asthma exacerbation studies. For the 2 asthma exacerbation studies, a history of ≥1 prior asthma exacerbation was requisite for study entry and maintenance OCS was allowed.

The baseline characteristics of the randomized patient population were consistent with a symptomatic, exacerbation-prone asthma population. Approximately 80% were using an inhaled LABA as a second controller, and approximately 11% were on maintenance low dose OCS therapy.

The following are the results of key prespecified analyses (benefits observed on top of the patients' preexisting asthma medications):

- Primary efficacy for asthma exacerbation reduction was met for both 52 week asthma exacerbation trials (50% and 59%, respectively, $p < 0.0001$). The secondary assessment of time to first CAE was longer for reslizumab treated patients, with statistically significant hazard ratio for experiencing CAE favoring reslizumab over placebo.
- FEV_1 was significantly improved over 16 weeks in all 3 studies (ranging from 0.094 to 0.286 L, $p<0.005$; FEV_1 was the primary efficacy measure for the 16-week lung function study and was a multiplicity-controlled secondary efficacy measure in both 52-week studies).

  Increases in FEV_1 relative to placebo ($p<0.05$) were seen at week 4 (first assessment after the first dose of reslizumab) in all 3 studies and were sustained at week 52 in both exacerbation studies.
- Patient-reported measures of asthma control (ACQ7 score) and symptoms (ASUI) were improved over 16 weeks in all 3 studies ($p<0.05$ in all 3 studies) and were multiplicity-controlled secondary efficacy measures for both of the 52 week studies.

  Increases in ACQ and ASUI relative to placebo ($p<0.05$) were seen at week 4 (first assessment after the first dose of reslizumab) in all 3 studies and were sustained at week 52 in both exacerbation studies.

- AQLQ scores were improved at 16 weeks (first on-treatment assessment for this measure) in all 3 studies ($p<0.05$ in all 3 studies) and were multiplicity-controlled secondary efficacy measures for both 52-week studies. These improvements were sustained at week 52 in both exacerbation studies ($p<0.05$).

These results support that an exacerbation-prone asthma patient who remains symptomatic despite optimization of a medium- to high-dose ICS/LABA-based standard-of-care regimen, and who has evidence of ongoing inflammation based on an elevated blood eosinophil level, is likely to obtain clinically meaningful improvement in his/her asthma control with the addition of reslizumab.

5. SAFETY

Safety analyses were performed on all patients and healthy subjects who received at least 1 dose of study drug (n=2195). Of the 2195, 2072 patients are from studies with treatment utilizing multiple doses of reslizumab (regardless of dose).

The asthma studies represent the largest proportion of patients treated with at least 1 dose of reslizumab (1781 patients regardless of dose and regimen out of 2195 total patients [81%] and 1596 asthma patients in the PCTs and OLE study were treated with iv reslizumab 3.0 mg/kg every 4 weeks). In this section, the following integrated data are presented with a cut-off date of 01 September 2014 as submitted in the BLA, using 3 different cohorts:

1. randomized asthma PCTs: Studies Res-5-0010, 3081, 3082, 3083, and 3084 (placebo, n=730; reslizumab 3.0 mg/kg, n=1028; reslizumab 0.3 mg/kg, n=103)
2. PCTs + OLE study (reslizumab 3.0 mg/kg, n=1596)
3. all reslizumab studies (any indication, all doses and regimens) excluding Study 01-I-0155 (an Investigator-initiated study that enrolled 8 patients) for the assessment of rare adverse events (n=2187)

In addition, the OLE Study 3085 (n=1051) with a cut-off date of 17 February 2015 (final CSR database lock) that was submitted in the 120-Day Safety Update is presented. No new patients were enrolled into the OLE study, but the exposure increased by 17.2 patient-years.

Safety endpoints in the asthma PCT included: adverse events, clinical laboratory tests (including assessment of immunogenicity), vital signs, and 12-lead ECGs (except Study Res-5-0010 where ECG was done only at screening).

5.1. Patient Disposition and Demographics

5.1.1. Overall Extent of Exposure

A total of 2195 subjects have been exposed to reslizumab in the entire clinical development program; of these, 1596 asthma patients were exposed to the reslizumab dose of 3.0 mg/kg (Table 15).

Table 15: Study Drug Exposure (as of Cut-Off Date of 01 September 2014 for the BLA)

	Asthma PCTs		Asthma PCTs + OLE study		All studies except Study 01-I-0155
	All reslizumab doses[a]	Reslizumab 3.0 mg/kg	All reslizumab doses[a]	Reslizumab 3.0 mg/kg	All reslizumab doses[b]
Number of patients (PY)	1131 (644)	1028 (613)	1611 (1625)	1596 (1593)	2187 (2155)
Mean duration of treatment (days) (SD)	207.9 (126.87)	217.6 (128.94)	368.3 (259.98)	364.6 (255.98)	360.0 (310.58)
Duration of treatment phase, n (%)					
≥1 month	1123 (>99)	1021 (>99)	1593 (99)	1578 (99)	2015 (92)
≥2 months	1089 (96)	992 (96)	1538 (95)	1526 (96)	1950 (89)
≥4 months	553 (49)	533 (52)	1120 (70)	1112 (70)	1339 (61)
≥6 months	440 (39)	438 (43)	1006 (62)	994 (62)	1189 (54)
≥12 months	389 (34)	389 (38)	759 (47)	743 (47)	922 (42)
≥24 months			237 (15)	213 (13)	371 (17)
≥30 months			11 (<1)	9 (<1)	128 (6)
≥36 months			0	0	64 (3)

[a] Includes the 3.0 and 0.3 mg/kg iv doses.
[b] Includes the 0.03-3.0 mg/kg doses and subcutaneous 220-mg doses.
iv=intravenous; OLE=open-label extension; PCT=placebo-controlled trial; PY=patient-years; SD=standard deviation.

For the OLE Study 3085 (N=1051) with a cut-off date of 17 February 2015, the mean (standard deviation [SD]) duration of exposure to study drug was 346.8 (185.06) days (range: 36.0 to 863.0 days); 451 patients were treated for more than 12 months, and 53 patients were treated for more than 24 months when including their exposure during the PCTs.

5.1.2. Demographics and Baseline Characteristics

Teva considers the patients included in the safety evaluation to be representative of the population of patients requiring treatment for asthma and elevated blood eosinophils and whose symptoms are inadequately controlled by medium- to high-dose ICS-based standard-of-care therapy.

The studies that comprise the asthma PCTs were global studies (except for Study 3084 [US only]). The demographic characteristics were generally reflective of an asthma population and were similar between the reslizumab 3.0 mg/kg and placebo groups (Table 16). The slightly higher percent of black patients in the reslizumab treatment group were due to study 3084 which had a randomization ratio of 1:4 placebo to reslizumab. While a total of 42% of patients were from the US, most were from Study 3084, which was a US-only study that had a randomization ratio of 1:4 for placebo and reslizumab.

Table 16: Demographics by Treatment Group (Asthma PCTs)

Variable/statistic	Placebo (N=730)	Reslizumab 3.0 mg/kg (N=1028)
Age in years, mean (SD)	46.4 (14.10)	45.5 (13.21)
Age group, n (%)		
12 to 17 years	16 (2)	19 (2)
18 to 64 years	658 (90)	965 (94)
≥65 years	56 (8)	44 (4)
Sex, n (%)		
Male	276 (38)	388 (38)
Female	454 (62)	640 (62)
Race, n (%)		
White	549 (75)	729 (71)
Black/African-American (US only)	61 (8)/45 (6)	145 (14)/133 (13)
Asian	57 (8)	79 (8)
American Indian or Alaskan Native	6 (<1)	10 (<1)
Pacific Islander	4 (<1)	1 (<1)
Other	53 (7)	64 (6)
Ethnicity, n (%)		
Hispanic or Latino	112 (15)	157 (15)
Non-Hispanic and non-Latino	615 (84)	869 (85)
Unknown	3 (<1)	2 (<1)
Geographic region, n (%)		
US	224 (31)	517 (50)
Europe	260 (36)	237 (23)
Other countries[a]	246 (34)	274 (27)
Weight in kg, mean (SD)	78.5 (19.34)	81.6 (21.81)
BMI in kg/m^2, mean (SD)	28.3 (6.09)	29.4 (7.59)

[a] Includes Argentina, Australia, Brazil, Canada, Chile, Columbia, Israel, the Republic of Korea, Mexico, Malaysia, New Zealand, Peru, Philippines, Thailand, Taiwan, and South Africa.

BMI=body mass index; PCT=placebo-controlled trial; SD=standard deviation; US=United States.

5.2. Overall Adverse Events

5.2.1. Overview of Adverse Events

In the asthma PCTs, the overall incidence of adverse events was lower in the reslizumab group compared with the placebo group (67% and 81%, respectively). The overall pattern of adverse events by frequency, severity, seriousness, and relationship to study drug was similar between the placebo and reslizumab 3.0 mg/kg groups (Table 17). The overall incidence of adverse events in the OLE study was similar to that of the reslizumab group in the asthma PCTs. The exposure-adjusted incidence of all adverse events in the reslizumab 3.0 mg/kg group was less than the exposure-adjusted incidence of all adverse events in the placebo group (433.9 events per

100 patient-years vs 587.7 events per 100 patient-years, respectively). In the OLE study, the exposure-adjusted incidence of all adverse events was similar to that observed in the reslizumab 3.0 mg/kg group (359.1 events per 100 patient-years) in the asthma PCTs.

Table 17: Overview of Adverse Events in the Asthma PCTs and OLE Study

	Number (%) of patients		
	Asthma PCTs		OLE study
	Placebo (N=730) (PY=517)	Reslizumab 3.0 mg/kg (N=1028) (PY=613)	Reslizumab 3.0 mg/kg (N=1051) (PY=998)
Patients with at least 1 adverse event	589 (81)	690 (67)	744 (71)
Severe adverse events	76 (10)	70 (7)	77 (7)
Treatment-related adverse events	95 (13)	122 (12)	89 (8)
Adverse events leading to discontinuation	40 (5)	48 (5)	16 (2)
Serious adverse events	66 (9)	65 (6)	77 (7)
Deaths[a]	1 (<1)	0	3 (<1)

[a] None of the events were assessed as treatment related. Details are provided in Section 5.2.5.
OLE=open-label extension; PCT=placebo-controlled trial; PY=patient-years.

The clinical development program included studies in various indications (eg, asthma, EoE, nasal polyposis, and healthy subjects) examining reslizumab at various regimens and doses, including doses lower than 3.0 mg/kg (from 0.03 through 3.0 mg/kg). The results of these studies showed that the safety profile for the lower dose was comparable to that of the placebo and the 3.0 mg/kg dose, both in the overall adverse events and in adverse events of special interest (eg, infections, malignancy, immunogenicity, myalgia/creatine phosphokinase [CPK] elevation). Anaphylactic reactions related to reslizumab infusion occurred only in the asthma studies with 3.0 mg/kg; however, anaphylactic reactions to a biologic product are unlikely to be dose related.

5.2.2. Common Adverse Events

Asthma PCTs

The overall frequency of adverse events for any Medical Dictionary for Regulatory Activities system organ class (SOC) in the asthma PCTs was similar or lower for reslizumab than for placebo, and there was no adverse event preferred term (PT) reported for reslizumab that occurred with a frequency greater than 1 percentage point higher than that of the corresponding placebo frequency. The most commonly reported adverse events in the reslizumab 3.0 mg/kg group (reported in >5% of patients in this group) were asthma (of note, asthma worsening was to be reported as an adverse event, per protocol), nasopharyngitis, upper respiratory tract infection (URTI), headache, and sinusitis (Table 18). Overall, respiratory infections and symptoms were the most commonly reported adverse events, and they were more frequent in the placebo group, reflecting the therapeutic effect of reslizumab.

Adverse events considered by the Investigator as treatment related were generally low and similar in the groups (reslizumab, 12%; placebo, 13%). The most frequently reported treatment-related adverse event was headache (2% in both groups).

OLE Study

The adverse event profile in the OLE study was similar to the asthma PCTs, even though the patient exposure to drug during the OLE study was longer (Table 18).

Table 18: Common Adverse Events (at Least 2%) in Descending Order in the Reslizumab 3.0 mg/kg Treatment Group by Preferred Term and Treatment Group (Asthma PCTs and OLE Study)

MedDRA preferred term	Number (%) of patients		
	Asthma PCTs		OLE Study
	Placebo (N=730) (PY=517)	Reslizumab 3.0 mg/kg (N=1028) (PY=613)	Reslizumab 3.0 mg/kg (N=1051) (PY=998)
Patients with at least 1 adverse event	589 (81)	690 (67)	744 (71)
Asthma	289 (40)	232 (23)	304 (29)
Nasopharyngitis	103 (14)	103 (10)	150 (14)
Upper respiratory tract infection	69 (9)	96 (9)	108 (10)
Headache	62 (8)	78 (8)	73 (7)
Sinusitis	51 (7)	57 (6)	78 (7)
Bronchitis	52 (7)	34 (3)	62 (6)
Urinary tract infection	24 (3)	34 (3)	44 (4)
Back pain	25 (3)	33 (3)	37 (4)
Influenza	37 (5)	33 (3)	45 (4)
Rhinitis allergic	22 (3)	28 (3)	50 (5)
Oropharyngeal pain	16 (2)	27 (3)	28 (3)
Pharyngitis	25 (3)	23 (2)	40 (4)
Cough	23 (3)	22 (2)	30 (3)
Dyspnoea	20 (3)	22 (2)	20 (2)
Acute sinusitis	19 (3)	17 (2)	38 (4)
Rhinitis	22 (3)	15 (1)	32 (3)
Arthralgia	21 (3)	16 (2)	29 (3)
Gastroenteritis	15 (2)	7 (<1)	28 (3)
Hypertension	11 (2)	14 (1)	29 (3)
Diarrhoea	21 (3)	14 (1)	23 (2)
Lower respiratory tract infection	10 (1)	8 (<1)	24 (2)
Nasal congestion	7 (<1)	13 (1)	19 (2)
Nausea	19 (3)	20 (2)	18 (2)

MedDRA=Medical Dictionary for Regulatory Activities; OLE=open-label extension; PCT=placebo-controlled trial; PY=patient-years.

5.2.3. Serious Adverse Events

Asthma PCTs

The incidence of serious adverse events in the asthma PCTs was similar in both groups (reslizumab 3.0 mg/kg, 6%; placebo, 9%). Asthma was the most common serious adverse event reported followed by pneumonia; both events were reported with a similar incidence compared to placebo (Table 19). Serious adverse events that were reported by more than 1 patient in the reslizumab group and were not reported in the placebo group included chest pain (4 patients [<1%] with PT of chest pain, non-cardiac pain, and musculoskeletal chest pain), anaphylactic reactions (4 patients [<1%], thoroughly discussed in Section 5.7.1), and falls (2 patients [<1%]). Three of the 4 anaphylaxis events were assessed as related to reslizumab treatment (1 case was an anaphylactic reaction to walnuts). All chest pain cases were assessed as non-cardiac origin, were not temporally linked to reslizumab infusion (occurred on days 6 to 16 after infusion), fully resolved, and were evaluated as not related to reslizumab by both Investigators and Teva. Moreover, the overall incidence (including serious and non-serious events) of fall (2 patients [<1%] in each group) and chest pain (17 patients (2%) in the placebo group and 16 patients (2%) in the reslizumab 3.0 mg/kg group) was similar across groups.

OLE Study

The overall incidence of serious adverse events in the OLE study was 7% (Table 19). Except for asthma, serious adverse event PTs were generally single-patient events distributed across multiple SOCs with no clinically meaningful trend evident or significant difference than the serious adverse events reported in the asthma PCTs.

Table 19: Serious Adverse Events (≥2 Patients in Any Treatment Group) in Descending Order of Total Incidence by Preferred Term and Treatment Group (Asthma PCTs and OLE Study)

MedDRA preferred term	Number (%) of patients		
	Asthma PCTs		OLE study
	Placebo (N=730) (PY=517)	Reslizumab 3.0 mg/kg (N=1028) (PY=613)	Reslizumab 3.0 mg/kg (N=1051) (PY=998)
Patients with at least 1 serious adverse event	66 (9)	65 (6)	78 (7)
Asthma	23 (3)	23 (2)	18 (2)
Pneumonia	7 (<1)	7 (<1)	1 (<1)
Anaphylactic reaction	0	4[a] (<1)	0
Chest pain	0	4 (<1)	1 (<1)
Fall	0	2 (<1)	0
Road traffic accident	3 (<1)	2 (<1)	0
Sinusitis	2 (<1)	2 (<1)	1 (<1)
Urinary tract infection	2 (<1)	0	2 (<1)
Nasal polyps	1 (<1)	0	2 (<1)
Contusion	2 (<1)	0	1 (<1)
Breast cancer	0	0	3 (<1)
Malignant melanoma	0	0	2[b] (<1)
Acute myocardial infarction/myocardial infarction	1 (<1)	0	3 (<1)
Cholelithiasis	0	0	2 (<1)
Suicide attempt	0	0	2 (<1)
Hypovolaemic shock	0	0	2 (<1)
Bronchitis	2 (<1)	0	0

[a] One case was an anaphylaxis reaction related to walnut exposure.
[b] One case had a medical history of malignant melanoma.
MedDRA=Medical Dictionary for Regulatory activities; OLE=open-label extension; PCT=placebo-controlled trial; PY=patient-years.

5.2.4. Discontinuations Due to Adverse Events

Asthma PCTs

Adverse events leading to discontinuation were infrequent (5% for both reslizumab 3.0 mg/kg and placebo), derived from disparate SOCs, and often manifested from an individual patient's medical history, with no apparent trends observed between the reslizumab-treated patients and their placebo comparators. The most common PTs in all groups were asthma (3% for both reslizumab 3.0 mg/kg and placebo) and anaphylactic reaction (3 patients [<1%] and none in the reslizumab 3.0 mg/kg and placebo groups, respectively). There were no additional adverse events reported in ≥2 patients in the reslizumab 3.0 mg/kg group.

OLE Study

Similar to asthma PCTs, discontinuations due to adverse events occurred at a low incidence in the OLE study (18 patients [2%]). The adverse events that led to discontinuation by more than 1 patient were breast cancer (3 patients [<1%]) and cardiac/cardio-respiratory arrest (2 patients [<1%]). Of these, 1 of the breast cancer cases was assessed as related to study drug, and the other 2 breast cancer cases and the 2 cardiac/cardio-respiratory arrest cases were not assessed as related to study drug.

5.2.5. Deaths

Four deaths were reported during the clinical studies; none of the events were considered related to the study drug or due to asthma worsening. In the asthma PCTs, there was 1 death in the placebo group, which was probably due to accidental combined drug intoxication with fentanyl and diphenhydramine. In the OLE study, there were 3 deaths: 1 patient died due to disseminated anal cancer; 1 patient died due to hemoptysis, aspiration pneumonia, and cardio-respiratory arrest; and 1 patient died due to cardiac arrest. Brief descriptions of these deaths are as follows:

- Asthma PCTs
  - A 26-year-old male in the placebo group died due to accidental combined drug intoxication with fentanyl and diphenhydramine (toxicology studies revealed an elevated, potentially toxic level of fentanyl and its metabolite). The death occurred on day 56 of treatment, 1 month after the 2nd placebo infusion.
- OLE Study
  - A 58-year-old white female, who had a family history of cancer but no personal history of cancer, was diagnosed with disseminated anal cancer after 15 total doses of reslizumab and 75 days after the last reslizumab dose in the OLE study. She died approximately 4 months later.
  - A 67-year-old Peruvian male, who had a history of pulmonary tuberculosis, an infective exacerbation of bronchiectasis, and several episodes of massive hemoptysis, died due to massive hemoptysis and aspiration pneumonia that resulted in cardiopulmonary arrest after 28 total doses of reslizumab and 133 days after the last reslizumab infusion.
  - A 60-year-old white female, who had a past medical history of hypertension, obstructive sleep apnea, and craniotomy due to tumor, was found dead at home after 163 total days of exposure to reslizumab (4 weeks after her last infusion). No autopsy was performed. The cause of death in the death certificated was cardiac arrest.

5.3. Long-Term Safety Data

As of the cut-off date for the BLA (01 September 2014), 756 asthma patients were exposed to reslizumab for >12 months, and 237 asthma patients were exposed for >24 months. In the overall clinical studies (regardless of dose, route, and indication), 64 patients were exposed to 3 or more years of treatment.

The evaluation of adverse events by time to onset for the asthma PCTs and OLE study showed no increase in the overall incidence of adverse events, including adverse events of special interest, as treatment exposure increased (Table 20).

Table 20: Select Adverse Events by Time to Adverse Event Onset for Reslizumab-Treated Patients with Exposure ≥12 Months (Asthma PCTs + OLE Study)

	Time to adverse event onset (months)					
	12 to <18 (N=756)		18 to <24 (N=472)		24 to <30 (N=237)	
	n (%)	Event rate per 100 PY	n (%)	Event rate per 100 PY	n (%)	Event rate per 100 PY
Patients with at least 1 adverse event	237 (31)	41.907	72 (15)	16.295	19 (8)	7.930
Infections and Infestations SOC	140 (19)	14.735	42 (9)	5.720	11 (5)	3.095
Malignancy	4 (<1)	0.555	2 (<1)	0.216	0	0
Myalgia PT	0	0	1 (<1)	0.108	0	0

OLE=open-label extension; PCT=placebo-controlled trial; PT=preferred term; PY=patient years; SOC=system organ class.
Note: No anaphylactic reactions occurred after 12 months of treatment.

An analysis of adverse events in the subgroup of patients with more than 12 months of reslizumab exposure was conducted on the asthma PCTs + OLE study. The incidence and nature of events were similar and consistent with what was observed in the asthma PCTs with exposure up to 52 weeks (Table 21).

Table 21: Adverse Events Summary for Patients with Exposure >12 Months (Asthma PCTs + OLE Study)

MedDRA preferred term	Asthma PCTs				Reslizumab 3.0 mg/kg with exposure >12 months (N=756) (PY=1262)	
	Placebo (N=730) (PY=517)		Reslizumab 3.0 mg/kg (N=1028) (PY=613)			
	n (%)	event rate per 100 PY	n (%)	event rate per 100 PY	n (%)	event rate per 100 PY
Patients with at least 1 AE	589 (81)	587.734	690 (67)	433.931	651 (86)	367.336
Common adverse events (>5% incidence)						
Asthma	289 (40)	147.466	232 (23)	69.873	320 (42)	58.067
Nasopharyngitis	103 (14)	29.222	103 (10)	24.978	169 (22)	24.399
Upper respiratory tract infection	69 (9)	19.546	96 (9)	20.897	123 (16)	14.576
Headache	62 (8)	17.224	78 (8)	18.938	104 (14)	12.833
Sinusitis	51 (7)	15.869	57 (6)	12.734	78 (10)	11.407
Bronchitis	52 (7)	12.773	34 (3)	6.204	64 (8)	6.417
Influenza	37 (5)	9.870	33 (3)	6.857	54 (7)	6.100
Patients with at least 1 serious AE	66 (9)	ND	65 (6)	ND	87 (12)	11.804
AEs leading to discontinuation	40 (5)	ND	48 (5)	ND	8 (1)	0.871
Adverse events of special interest						
Infections (SOC)	386 (53)	162.561	420 (41)	130.277	506 (67)	120.650
Anaphylactic reaction[a] (PT)	0	0	5 (<1)	0.816	1 (<1)	0.079
Malignancy[b]	2 (<1)	0.387	6 (<1)	1.143	12 (2)	1.188
Myalgia (PT)	4 (<1)	1.161	10 (<1)	1.633	10 (1)	0.792

[a] Note: Of the 5 anaphylactic reactions reported in the asthma PCTs, 3 were temporally linked to reslizumab infusion and resulted in permanent discontinuation of reslizumab treatment. Two cases (one reported as non-serious) occurred after exposure to nuts and allergy shots, were not associated to reslizumab infusion, and did not reoccur with subsequent reslizumab infusions.

[b] The PTs excluded from the analysis of malignancy cases (after reviewing the verbatim terms) included benign lung neoplasm, lipoma, uterine leiomyoma, adrenal adenoma, fibroadenoma of breast, fibrous histiocytoma, melanocytic naevus, haemangioma, seborrhoeic keratosis, glomus tumor, pituitary tumor benign, skin papilloma, and thyroid neoplasm.

AE=adverse event; ND=not done; OLE=open-label extension; PCT=placebo-controlled trial; PT=preferred term; PY=patient years; SOC=system organ class.

Note: The populations of patients treated with reslizumab (3.0 mg/kg) from the asthma PCTs and those with exposure >12 months overlap and are not mutually exclusive.

5.4. Pediatric Safety

A total of 253 pediatric patients have been treated with multiple doses of reslizumab at doses ranging from 0.3 to 3.0 mg/kg: 38 asthma patients (12 to 17 years of age) and 215 EoE patients (5 to 19 years of age). The majority of patients were treated for more than 2 years, and nearly

one-third of the EoE patients were treated for more than 3 years (Table 22). Approximately 50% of the EoE patients also had asthma.

Table 22: Study Drug Exposure in the Pediatric Population

Exposure to reslizumab	Asthma studies (12 to 17 years of age) (N=38)	Eosinophilic esophagitis studies (5 to 19 years of age)[a] (N=215)	Total (N=253)
≥1 year	23 (61)	179 (83)	202 (80)
≥2 years	9 (24)	158 (73)	167 (66)
≥3 years	0	64 (30)	64 (25)

[a] A total of 127 patients (56%) was 12 to <19 years of age.

The pediatric population had a similar safety profile compared with placebo (Table 23) as well as with the overall population. All serious adverse events and events leading to discontinuation were assessed as unrelated to reslizumab. There were 6 reslizumab-treated pediatric patients (4 patients during the long-term EoE OLE Study Res-5-0004) and 1 placebo-treated patient in the EoE studies that experienced anaphylactic reactions. All events were related to food allergies/allergy shots; none was associated to reslizumab or lead to discontinuation. No malignancies were reported for any of the patients in the pediatric population.

Table 23: Overview of Adverse Events in the Pediatric and Adolescent Population

	Asthma PCTs (12 to 17 years of age)		Eosinophilic esophagitis (5 to 19 years of age) (Study Res-5-0002)	
Pediatric population AEs	Placebo (N=16)	Reslizumab 3.0 mg/kg (N=19)	Placebo (N=57)	Reslizumab 1.0 to 3.0 mg/kg (N=169)
Overall adverse events	13 (81)	16 (84)	47 (82)	133 (79)
Serious adverse events	2 (13)	2 (11)	2 (4)	3 (2)
Adverse events leading to discontinuation	0	0	0	1 (<1)

AE=adverse event; PCT=placebo-controlled trial.

5.5. Clinical Laboratory Evaluations

Except for the pharmacological effect of reslizumab in reducing the eosinophil count and the reflection in the overall white blood cell count, there were no clinically relevant trends or unexpected abnormalities observed in the clinical laboratory tests, serum chemistry, hematology, or urinalysis parameters in the clinical program.

In the integrated laboratory analyses (asthma PCTs excluding Study Res-5-0010), laboratory parameters were generally similar at baseline between the placebo and reslizumab 3.0 mg/kg groups, with the exception of mean CPK value that was higher in the reslizumab group (143 vs 132 U/L) with less patients with normal CPK in the reslizumab group (974 patients [86%]) compared to the placebo group (661 patients [91%]) at baseline. This imbalance resulted

in a higher incidence of elevated CPK post-baseline in the reslizumab group. When a CPK analysis that included only patients with normal CPK at baseline was performed, the incidence of elevated CPK during treatment (overall and across grades) was similar to placebo (additional discussion of CPK values is found in Section 5.7.4).

Overall, there were no significant changes in the laboratory parameter means at endpoint. Shifts in variable values from the normal range at baseline to outside the normal range occurred infrequently, were similar in each group, and were not considered to be clinically meaningful.

IgG measurements (IgG, IgE, and IgM) that were performed in 2 Phase 1 PK/PD studies (Studies 1102 and 1107) did not show meaningful differences between baseline and post-baseline measurements.

5.6. Electrocardiograms and Vital Signs

The nonclinical and clinical data from the overall reslizumab program did not show a risk of cardiovascular toxicity or adverse effects.

Reslizumab is a large molecule; thus, cardiotoxicity resulting from direct human ether-à-go-go-related gene (hERG) channel blockade is generally not a concern. In the clinical program, there has been no evidence of increase ECG abnormalities or in QTc prolongation with reslizumab. In addition, the cardiovascular adverse event profile did not suggest an effect on the cardiovascular system (see Section 5.7.5).

In the asthma PCTs (excluding Study Res-5-0010, where a 12-lead ECG was done only at screening), ECG values in the reslizumab and placebo groups were similar for mean heart rate, PR, QRS, RR, QT, and QTc (Bazett and Fridericia) interval measurements at baseline and post-baseline. ECG results were assessed by the Investigator as either normal or abnormal; abnormal ECG results were further assessed for clinical significance. The incidence of abnormal ECG findings post-baseline was similar across the placebo and reslizumab groups (10% and 12%, respectively), and none of the abnormalities were assessed as clinically significant.

Most patients in the placebo and reslizumab groups in the asthma PCTs (96% to 97%) had post-QTcF interval values <450 msec at end point, and there was no evidence for QTc prolongation. Data from Study 1102, a PK/PD study, showed no evidence for an increase in QTcF with increasing serum concentration of reslizumab.

No treatment effect on vital signs (pulse, blood pressure, respiratory rate, and body temperature) was observed in the asthma PCTs; mean changes from baseline were similar across the placebo and reslizumab groups as well as the incidence of abnormal measures.

5.7. Adverse Events of Special Interest

Given that reslizumab is a biologic therapy to be administered via iv infusion, with a mechanism of action leading to eosinophil suppression, the evaluation of systemic hypersensitivity reactions, immunogenicity, infections, and malignancies was of special interest in the evaluation of the safety profile. Additionally, in light of an imbalance of myalgia events in the integrated safety analysis, further analyses were performed including an analysis of CPK levels. Cardiovascular

events have been raised as an area of special interest for some biologics and other asthma treatments and are therefore summarized as well.

5.7.1. Systemic Hypersensitivity and Anaphylactic Reactions

In the entire clinical development program, 3 patients reported anaphylactic reactions that were considered related to reslizumab. All other anaphylactic reactions were related to other allergen exposure. Except for these 3 cases, there was no evidence of additional systemic hypersensitivity reactions, including anaphylactic reactions.

In contrast to chemical drugs, biological drugs are much larger and structurally complicated, and hypersensitivity reactions, including anaphylaxis can occur. Reslizumab, being a humanized mAb, has a smaller murine fraction in the hypervariable regions of the Fab fragment to reduce the risk of immunogenicity. A thorough evaluation was performed in order to detect and assess possible hypersensitivity reactions. Of note, in the clinical study setting, premedication (eg, with corticosteroids or antihistamines) was not mandated by the study protocols.

Of the 2195 patients exposed to reslizumab in all studies, 2072 patients were from studies with treatment utilizing multiple doses of reslizumab (ie, not single-dose studies). This population is considered the most appropriate to assess this risk since more than 1 infusion is required for drug sensitization. Of note, no anaphylactic reactions were reported in any of the single dose studies.

Of these 2072 reslizumab-treated patients, 11 patients (0.53%) reported at least 1 anaphylactic reaction: 3 cases (0.14%) were temporally linked to reslizumab infusion and 8 cases (0.39%) were related to other allergens (eg, food or allergy shots) (Table 24). Of the 852 placebo patients within these studies, 1 patient reported at least 1 anaphylactic reaction (0.12%), which was related to other allergens. All of the 11 anaphylactic reactions (regardless of causality to reslizumab infusion) occurred in the asthma PCTs and the pediatric EoE studies and are summarized in Table 24. Of note, the reslizumab-treated asthma patients had over 20,000 completed infusions.

Table 24: Anaphylactic Reactions by Association

	Asthma studies			Pediatric EoE studies		
	Asthma PCTs			PCT Study Res-5-0002		
	Placebo (N=730)	Reslizumab 0.3 and 3.0 mg/kg (N=1131)	OLE study Reslizumab 3.0 mg/kg (N=1051)	Placebo (N=57)	Reslizumab (N=169)	OLE study Res-5-0004 (N=190)
Associated with other allergens	0	2 (0.1)	0	1 (1.7)	2 (1.2)	4 (2.1)
Associated with reslizumab	0	3 (0.3)	0	0	0	0

EoE=eosinophilic esophagitis; OLE=open-label extension; PCT=placebo-controlled trial.

Of the 8 cases not related to reslizumab (as considered by the Investigator), 6 cases were from the pediatric EoE studies (2 in the placebo-controlled Study Res-5-0002 and 4 during the OLE Study Res-5-0004) and 2 cases were from the asthma PCTs (Studies 3082 and 3084). For these 8 cases, the events were not temporally linked to reslizumab infusion or considered related to reslizumab. These cases were related to exposure to other previously known allergens. Reslizumab treatment was continued in all cases with no subsequent reactions following repeated exposure (with the exception of 1 food allergy event in an EoE patient who did not continue treatment due to lack of therapeutic effect in EoE). These events are not unexpected in an asthma, pediatric, or EoE population that are known to have higher incidence rates of allergy and anaphylactic reaction compared to the general population (Gonzalez-Perez et al 2010, Boros et al 2000, Ridolo et al 2012). Of note, in the OLE EoE Study Res-5-0004 (in which 4 patients reported anaphylactic reactions to other allergens), dietary advancement was not prohibited as opposed to the EoE placebo-controlled Study Res-5-0002. Narratives for these 8 cases are in Section 5.7.1.2.

All 3 cases causally related to reslizumab as assessed by the Investigator were reported in the asthma PCT Phase 3 studies. The events were observed during or within 20 minutes after the completion of an infusion. These events occurred on the 2nd or 12th infusion (2 and 1 cases, respectively) and were from 3 different batches of drug product. None of the cases occurred on the first infusion, suggesting that patients were not pre-sensitized (ie, alpha gal). The events included symptoms of skin or mucosal involvement, dyspnea, wheezing, gastrointestinal symptoms, and chills. In all cases, treatment was permanently discontinued after the event and no re-challenge was performed. All cases fully resolved within 2 to 4 hours after medical treatment at the investigational center. One of the 3 cases was treated with epinephrine. Two of the cases (from the same investigational site) were treated with iv fluids, although no hypotension was present. None of the cases required hospitalization. Of note, all 3 cases were atopic patients; 2 had previous drug hypersensitivity reactions, including aspirin anaphylactoid reactions. Narratives for these 3 cases are provided in Section 5.7.1.1.

All patients who reported anaphylactic reaction were negative for anti-reslizumab antibodies. The anti-drug antibody (ADA) assay provides sensitive (22 ng/mL) detection of all ADA Ig isoforms. However, this observation does not rule out the possibility of involvement of very low levels of IgE anti-reslizumab antibodies.

The event of anaphylaxis was assessed based on Investigator's clinical judgement. However, in the absence of confirmatory tests (eg, IgE testing, rechallenge), the exact immune mechanism leading to these reactions is unknown.

5.7.1.1. Narratives of Patients with Reslizumab-Related Anaphylactic Reactions

- A 45-year-old white female with a history of drug hypersensitivity (novaminsulfon allergy and aspirin sensitivity, including anaphylactoid reactions) reported an anaphylactic reaction 14 minutes after initiation of the 2nd reslizumab 3.0 mg/kg infusion, characterized by dyspnea, shivering, vomiting, and flushing. The reaction was serious and considered to be related to study treatment by both the Investigator and Teva. The patient was treated with systemic corticosteroids, antihistamines, and iv fluids and was withdrawn from the study.

- A 47-year-old white female with a history of allergies (mold and dog hair) and drug hypersensitivities (penicillin and aspirin, including anaphylactoid reactions), 20 minutes after completing the 12th reslizumab 3.0 mg/kg infusion, experienced skin reactions (pruritus and wheal), severe lower abdominal pain, and severe burning and itching in the genital area with no evidence of circulatory collapse/shock. The reaction was serious and considered related to study treatment by both the Investigator and Teva. The patient was treated with systemic corticosteroids, antihistamines, and iv fluids and withdrew from the study.
- A 52-year-old black female with a history of allergic rhinitis, within 10 minutes after initiation of the 2nd reslizumab 3.0 mg/kg infusion, reported an anaphylactic reaction to the infusion (shortness of breath, wheezing, could not speak, swollen eyes, flushing, and oxygen saturation of 89%). The patient had eaten shortly before the infusion began and was therefore evaluated at the investigational center for common food allergies, but the evaluation was negative. The reaction was serious and considered to be related to study treatment by both the Investigator and Teva. The patient was treated with epinephrine, prednisone, albuterol, and montelukast and withdrew from the study.

5.7.1.2. Narratives of Patients with Anaphylactic Reactions Considered Not Causally Related to Reslizumab

Asthma Patients

- A 21-year-old white female with a history of latex and food allergies (including nut allergy) experienced anaphylaxis to walnut exposure on day 186 (4 days after the 7th reslizumab infusion). The patient was treated with epinephrine and methylprednisolone. The event was non-serious, assessed as not related to study drug, and resolved with no residual effect; the patient continued in the study on reslizumab 3.0 mg/kg.
- A 38-year-old white female with a history of nickel allergy and allergic rhinitis experienced an anaphylactic reaction 1 hour 15 minutes after receiving an allergy immunotherapy injection on day 137 of the study (45 days after the last reslizumab infusion). The event was serious and considered not related to reslizumab 3.0 mg/kg. The patient was treated with an Epi-Pen injection and prednisone; the event resolved with no residual effect, and the patient remained in the study and continued on reslizumab 3.0 mg/kg.

Pediatric EoE Patients

- A 7-year-old female with EoE and a history of food allergies (nuts, eggs, seafood, and peanuts) had an anaphylactic allergic reaction associated with eating a cookie containing peanuts 7 days after her 3rd administration of reslizumab 3.0 mg/kg. The event was considered mild and unlikely related to study drug administration. The subject received 1 dose of oral prednisone, and the event resolved the same day. Reslizumab administration was continued with no adversity related to reslizumab infusion.

- A 17-year-old white male with EoE and a history of allergies to bananas and nuts had a "near anaphylaxis" reaction associated with peanut ingestion 15 days after his first dose of reslizumab 3.0 mg/kg. The subject was given a single dose of epinephrine iv; the event resolved on the same day. The event was considered moderate and unrelated to study drug administration. Reslizumab administration was continued with no adversity related to reslizumab infusion.
- A 6-year-old white male with EoE and a history of environmental allergies had 3 events of anaphylactic reaction on days 580, 858, and 1106 of the study (ranging from 11 to 15 days after administration of reslizumab 2.0 mg/kg). The 1st event was described as having an unknown etiology (treated with epinephrine, corticosteroids, and antihistamines), the 2nd event was due to almonds (treated with antihistamines), and the 3rd event was due to pizza (treated with antihistamines). Each event was considered as mild or moderate in severity, not related to study drug administration, and recovered by either the same day or within 6 days. After each occurrence, reslizumab administration was continued with no adversity related to reslizumab infusion.
- A 6-year-old white male with EoE and a known allergy to wheat had an anaphylactic reaction described as a food allergy (after consuming wheat products) on day 404 of the study, 2 days after administration of reslizumab 1.0 mg/kg. The event was considered severe yet not related to study drug administration. The event resolved after 1 day. Reslizumab administration was discontinued as the patient withdrew from the study because of lack of efficacy/worsening of the disease.
- A 10-year-old white male with EoE and a history of food and environmental allergies had 6 events of anaphylactic reaction or allergic reaction on days 118, 240, 419, 537, 580, and 771 of the study (ranging from 6 to 22 days after administration of reslizumab at 2.0 mg/kg). Events 1, 3, 4, and 5 were described as due to allergy shots and were each considered severe, not related to study drug administration, and recovered on the same day. The second event was described as due to exposure to a cat, and the 6th event was due to an allergic reaction to eggs. Both of these events were moderate in severity and considered not related or unlikely to be related to the study drug. Treatments of the events included epinephrine, corticosteroids, antihistamines, and bronchodilators, and the events resolved on the next day. Additionally, the patient had an event of infusion-related reaction on day 342, which was described as fever after start of study infusion; considered as not serious, mild in severity, and unlikely to be related to study drug administration; treated with paracetamol; and recovered on the same day. After each occurrence, reslizumab administration was continued with no adversity related to reslizumab infusion.
- An 11-year-old male of "other" race with EoE and a history of allergies to eggs, many other foods, and nuts had 3 events of anaphylactic reaction on days 682, 756, and 896 of the study (ranging from 13 to 16 days after administration of reslizumab at 1.0 mg/kg). Each event was described as due to nuts, considered moderate in severity and not related to study drug administration, and recovered on the same day. After

each occurrence, reslizumab administration was continued with no adversity related to reslizumab infusion.

5.7.1.3. Additional Analyses

Additional analyses were performed in order to detect unrecognized anaphylactic reactions and to assess other potential hypersensitivity reactions/infusion reactions related to reslizumab. These are summarized in Table 25.

1. Searches in the safety analysis set for the Anaphylactic Reaction and Angioedema standardized Medical Dictionary for Regulatory Activities query (SMQ) (broad) were performed as follows:
   - All cases in the asthma studies under the broad anaphylactic reaction and Angioedema SMQs (regardless time of event) are summarized in Table 25. In the broad anaphylactic reaction SMQ search, which includes a broad list of terms that might be associated with anaphylactic reactions (including some terms that overlap with asthma, eg, asthma, wheezing, dyspnea, cough), the incidence of events was higher in the placebo group. A similar search was done also for the angioedema SMQ, which revealed a similar incidence in both groups.
   - Additionally, all cases in the asthma studies under the broad anaphylactic reaction SMQs that occurred on the day or the day after of infusion are summarized in Table 25. In the asthma PCTs, the incidence was higher in the placebo group (120 [16%]) than in the reslizumab 3.0 mg/kg group (87 [8%]). Also, when this analysis was done with excluding events of "asthma" and "cough" (in order to eliminate the possible therapeutic effect of reslizumab), the overall incidence of broad anaphylactic reaction SMQ that occurred on the day or the day after of infusion was higher in placebo-treated patients (19 [3%]) than in reslizumab-treated patients (20 [2%]).
   - All cases in the asthma studies under the broad anaphylactic reaction SMQ that occurred during the day and day after of infusion were narrated and reviewed by Teva. Except for the cases that were reported as anaphylactic reactions, no additional cases were found to meet the criteria of anaphylactic reactions. These cases (blinded to treatment, eosinophil count and ADA status) are being evaluated by an independent committee to identify cases that follow anaphylactic reaction according to the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network criteria (Sampson et al 2006). The results of this evaluation are not available for this briefing document but will be available for the Advisory Committee meeting.
2. The incidence of the PTs of hypersensitivity and drug hypersensitivity was similar in both groups. All these cases were related to other allergens (medications, environmental allergies), except for 1 case in the reslizumab group that was also reported as drug eruption with negative rechallenge. None of the cases led to discontinuation. Infusion reactions were reported in both groups; none of the cases had a recurrence with subsequent infusions.

These additional analyses and reviews did not reveal additional cases suggestive of hypersensitivity or anaphylactic reactions to reslizumab.

Table 25: Anaphylactic Reactions, Angioedema, and Hypersensitivity by Treatment Group (Asthma PCTs and OLE Study)

	Asthma PCTs		PCTs + OLE Study
	Placebo (N=730) n (%)	All reslizumab (N=1131) n (%)	All reslizumab (N=1611) n (%)
Broad Anaphylactic reaction SMQ			
All	326 (45)	294 (26)	555 (34)
On day or day after of infusion[a]	120 (16)	87 (8)	165 (10)
On day or day after of infusion[a] excluding asthma and cough	19 (3)	20 (2)	31 (2)
Broad Angioedema SMQ	38 (5)	36 (3)	5.232
Hypersensitivity			
Drug hypersensitivity	2 (<1)	4 (<1)	6 (<1)
Hypersensitivity	1 (<1)	2 (<1)	2 (<1)
Infusion reactions	1 (<1)	2 (<1)	2 (<1)
Anaphylactic reaction meeting NIAID/FAAN criteria[b]			
All	0	5 (<1)	5 (<1)
Related to reslizumab infusion	0	3 (<1)	3 (<1)

[a] Since the exact time of event was not collected in the studies, for events that occurred on the same day of infusion, we cannot differentiate whether occurred before or after the infusion.

[b] Sampson et al 2006.

FAAN=Food Allergy and Anaphylaxis Network; NIAID=National Institute of Allergy and Infectious Disease; OLE=open-label extension; PCT=placebo-controlled trial; SMQ=standardized Medical Dictionary for Regulatory Activities query.

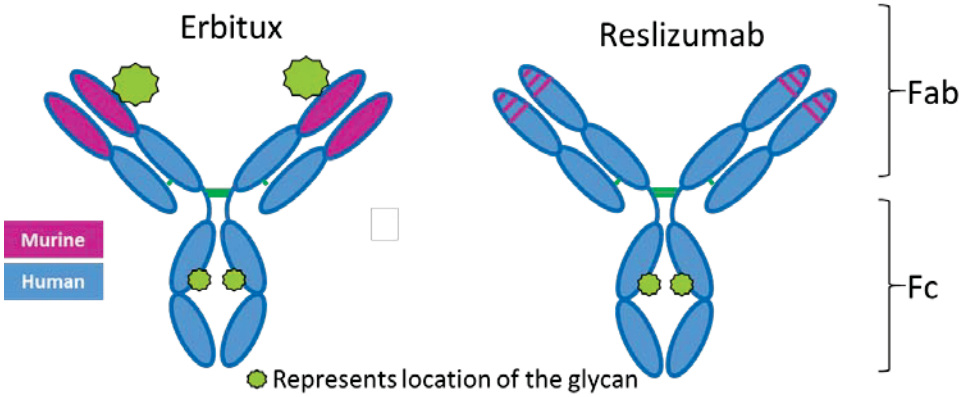
Note: This table includes patients treated with reslizumab 0.3 mg/kg in the "all reslizumab" columns.

5.7.1.4. Assessment of Alpha Gal as the Cause of Anaphylaxis with Reslizumab Treatment

Since reslizumab contains low levels of alpha gal epitopes, the FDA has raised a question if the anaphylaxis cases diagnosed based on clinical criteria could be due to its presence. At present, the immune mechanisms responsible for the clinical anaphylaxis cases are not known. In order to evaluate if the alpha gal present on reslizumab could lead to anaphylaxis, the levels of alpha gal and location of the glycan within the reslizumab antibody structure were compared to other marketed antibodies studied in literature known to contain alpha gal glycosylation. In the case of reslizumab, the alpha gal levels and location indicate that reslizumab is unlikely to interact with pre-existing alpha gal IgE antibodies and therefore should not result in anaphylaxis in alpha gal sensitized patients.

In contrast to the 30% alpha gal contained in cetuximab, the levels of glycan species G2F+αGal and G2F+2αGal in reslizumab have been detected at low and consistent levels throughout development, ranging from 0.5 to 1.7% and 0.1 to 0.3%, respectively, in reslizumab (Figure 27). Importantly, reslizumab has no Fab glycosylation, and hence, the alpha gal on reslizumab is limited to the Fc region, making it less accessible to interact with IgE.

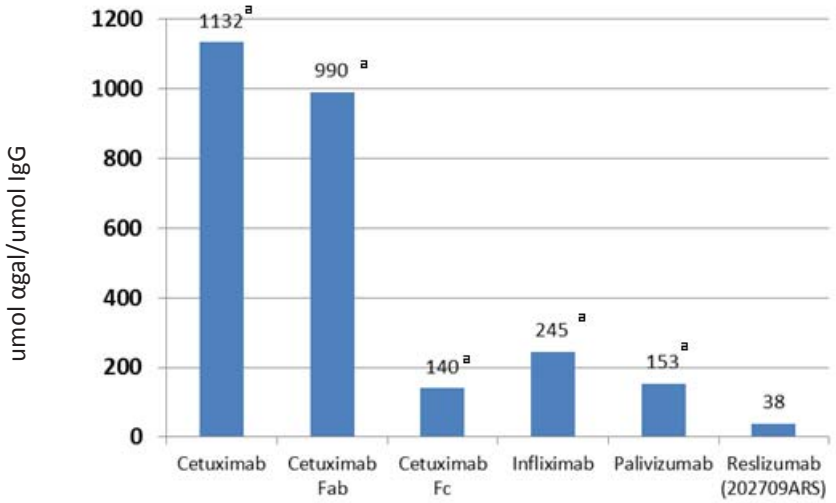
Figure 27: Levels of Alpha Gal and Location of the Glycan within the Reslizumab Antibody Structure



Source: Adapted from the original to show potential location of the glycan (Qian et al 2007).
Fab= fragment antigen-binding; Fc= fragment crystallizable.

Other monoclonal antibodies known to contain alpha gal glycosylation have been evaluated for their propensity to bind alpha gal IgE in alpha gal sensitized patients. Teva has summarized the results of these published data in Figure 28, which shows the levels and location of alpha gal for cetuximab, infliximab and palivizumab. Both infliximab and palivizumab reportedly have alpha gal present only on the Fc domain (similar to reslizumab) at levels of 10% and 7%, respectively (Qian et al 2007, Lammerts van Bueren et al 2011). Notably, reslizumab has approximately 4 to 6 times lower levels of alpha gal when compared to these 2 products. In the study published by Lammerts van Bueren et al, anti-alpha gal IgE Ab from sensitized patients did not bind to either infliximab or palivizumab, suggesting that the low levels of alpha gal glycans within the Fc domains of reslizumab would not lead to the binding of reslizumab to anti-alpha gal IgE and the cross-linking of IgE on mast cells in alpha gal sensitized patients (Lammerts van Bueren et al 2011).

Figure 28: Alpha Gal Content in Monoclonal Antibody Therapies



[a] Lammerts van Bueren et al 2011.
Fab=fragment antigen-binding; Fc=fragment crystallizable; Ig=immuglobulin.

In summary, the low levels of alpha gal solely expressed on the Fc portion of reslizumab are unlikely to bind alpha gal IgE antibodies in alpha gal sensitized individuals and should not contribute to the IgE-mediated anaphylactic reactions due to this reason. Moreover, the 3 cases of anaphylaxis related to reslizumab observed in the clinical program differed from the cetuximab-reported cases in that the reactions did not occur with the first reslizumab infusion, and patients were not located in the southeastern US (1 in Brooklyn, NY, and 2 in Germany). Additionally, none of the patients had a history of allergy to red meat, suggesting that these reactions were unlikely due to a pre-sensitization to alpha gal.

5.7.1.5. Summary

In conclusion, of the 2072 patients from studies with treatment utilizing multiple doses of reslizumab, 3 patients (0.14%) reported anaphylactic reaction that was considered related to reslizumab. All other anaphylactic reactions were related to other allergen exposure. Except for these 3 cases, there was no evidence of additional systemic hypersensitivity reactions, including anaphylactic reactions. The 3 events occurred either during the infusion or within 20 minutes of cessation of the infusion and were managed in the clinic with standard therapies for these types of reactions with no untoward complications or sequelae. The immune mechanism of the 3 treatment-related anaphylaxis cases is unknown. The presence of alpha gal on reslizumab is unlikely to be the cause for these reactions based on the low level of alpha gal present on the Fc portion of the molecule and the absence of reactions with the first infusion.

Anaphylactic reactions are designated as an adverse drug reaction of reslizumab. These are important events and both patients and prescribers should be made aware of this risk by way of appropriate labeling. Reslizumab is an iv infusion and will be administered under the supervision of a health care professional capable of managing the risk of anaphylaxis as is done with other currently available therapies used in the treatment of asthma. Teva is committed to ensuring that

patients and health care providers are properly informed about the risk of anaphylaxis via the Prescribing Information and Patient Information. Additionally, Teva intends to make nurse trainers available to patients and health care professionals to help ensure the appropriate use of reslizumab.

5.7.2. Infections

Overall Infections

Overall, the events reported are consistent with what is expected in a patient population with an underlying condition of asthma and were lower in the reslizumab group. There was no increase of infections or incidence over time, and no helminth infections or potential opportunistic infections were reported.

Asthma PCTs

The overall incidence of infections in the asthma PCTs were higher in the placebo group (386 patients [53%]) than in the reslizumab 3.0 mg/kg group (420 patients [41%]). The most common events (>5%) of nasopharyngitis, URTI, sinusitis, and bronchitis were reported at a similar or lower incidence in the reslizumab group relative to the placebo group and are commonly reported in the asthma population. There was no increase in the incidence of infections over time, and no potential opportunistic or atypical infections were reported. The incidence of serious adverse events due to infections was low, with only pneumonia and sinusitis reported by more than 1 patient in the reslizumab group and with a similar to that observed in the placebo group (Table 26).

Table 26: Incidence of Infections and Infestations (Asthma PCTs)

Infections and Infestations System Organ Class	**Placebo (N=730) n (%)**	**Reslizumab 3.0 mg/kg (N=1028) n (%)**
Any adverse event	386 (53)	420 (41)
Most common (>5%) adverse events		
Nasopharyngitis	103 (14)	103 (10)
Upper respiratory tract infection	69 (9)	96 (9)
Sinusitis	51 (7)	57 (6)
Bronchitis	52 (7)	34 (3)
Influenza	37 (5)	33 (3)
Any serious adverse event	22 (3)	18 (2)
Most common (>1 patient) serious adverse events		
Pneumonia	7 (<1)	7 (<1)
Sinusitis	2 (<1)	2 (<1)
Bronchitis	2 (<1)	0
Urinary tract infection	2 (<1)	0

PCT=placebo-controlled trial.

OLE Study

In the OLE study, 512 patients (49%) had adverse events in the Infections and Infestations SOC. The most common infections (≥5%) reported were nasopharyngitis, URTI, sinusitis, and bronchitis. Fourteen patients had serious infection adverse events, which were single events except for a UTI reported by 2 patients. There was no specific pattern of infections (serious, severe, or otherwise) to suggest a risk due to reslizumab treatment.

Helminth Infections

Eosinophils are considered to play a role in protective immunity against helminth parasites. Since IL-5 is responsible for the maturation, recruitment, and activation of eosinophils, there is concern that therapeutic antibodies that neutralize IL-5 (eg, reslizumab) may affect the immune response to helminth infection. Patients with recent parasitic infections per medical history were excluded from participation in the reslizumab clinical studies. There were no reports of helminthic infections in the entire clinical program (all indications), which enrolled 392 asthma patients (219 in the reslizumab group and 173 in the placebo group) from regions known to be endemic for helminthic parasites (ie, from South and Central America, Africa, and Asia, with a helminth infection prevalence of 20% to 50%). Moreover, review of adverse events that could be associated with helminth infections (ie, low hemoglobin, eosinophilia, elevated liver function tests, and gastrointestinal infections and disorders) did not reveal any difference between placebo- and reslizumab-treated patients.

5.7.3. Malignancies

Reslizumab was not mutagenic or carcinogenic and did not show an increased tumor rate in a pharmacologically relevant transgenic mouse model (see Section 9.7).

In the asthma PCTs, there was a numerical imbalance in reported malignancies in the reslizumab group compared with the placebo group. Of note, patients with previous malignancies were not excluded from the clinical studies. The observed malignancies in the reslizumab clinical development program, considering both asthma PCTs and the OLE study presented a diverse range of common tissue types that would not be unexpected in a primarily adult population. There were no clusters of specific types of malignancies that would suggest an immunosuppressive mechanism. No malignancies occurred in children or adolescent patients in any reslizumab study. Most of the malignancies were diagnosed within less than 12 months from starting reslizumab treatment.

Asthma PCTs

Malignant neoplasms were reported by 6 patients (0.58%; event rate: 1.14 per 100 patient-years) in the reslizumab 3.0 mg/kg group and 2 patients (0.27%; event rate: 0.39 per 100 patient-years) in the placebo group; 2 of the malignancies in the reslizumab group were non-melanoma skin cancer (NMSC). All malignancies except 1 skin squamous cell carcinoma were diagnosed within less than 6 months after starting study treatment, suggesting that these were pre-existing conditions.

OLE Study

In the OLE study, there were an additional 15 patients (1.4%; event rate: 1.17 per 100 patient-years) diagnosed with malignancy.

The overall list of all reported malignancies in asthma patients treated with reslizumab is shown in Table 27. There were no additional malignancies diagnosed in reslizumab-treated patients in other studies. These observations illustrate a diverse array of tissue types that do not suggest a common mechanism of carcinogenicity. Of the overall malignancies reported, 5 patients had previous malignancy history, 2 of which were the same malignancies diagnosed before reslizumab exposure. The most common malignancies diagnosed were NSMCs (5 patients).

Table 27: All Reported Malignancies in Patients Treated with Reslizumab 3.0 mg/kg (Asthma PCTs + OLE Study)

	Reslizumab 3.0 mg/kg (N=1596)		
	Events, n	**Patients, n (%)**	**Latent period[a] (days)**
Overall malignancies	**24**	**21 (1)**	
Basal cell carcinoma	5	3 (<1)	132, 256, 496 (2 events), 721
Breast cancer	3	3 (<1)	169, 194, 500
Malignant melanoma[b]	3	3 (<1)	202, 342, 673
Prostate cancer	2	2 (<1)	35, 624
Lung cancer[c]	2	2 (<1)	45, 169
Ovarian cancer[d]	2	2 (<1)	770, 887
Anal cancer	1	1 (<1)	475
Colon cancer	1	1 (<1)	64
Keratoacanthoma	1	1 (<1)	<13
Lymphoma	1	1 (<1)	673
GI metastases to lung	1	1 (<1)	482
Plasmacytoma	1	1 (<1)	147
Squamous cell carcinoma (skin)	1	1 (<1)	231

[a.] Number of days on reslizumab treatment until diagnosis of malignancy.
[b.] One melanoma in-situ, one malignant melanoma in a patient with previous melanoma.
[c.] Adenocarcinoma and small cell lung cancer.
[d.] Adenocarcinoma and borderline ovarian tumor.
GI=gastrointestinal; n=number; OLE=open-label extension; PCT=placebo-controlled trial.
Note: The PTs excluded from the analysis of malignancy cases (after reviewing the verbatim terms) included benign lung neoplasm, lipoma, uterine leiomyoma, adrenal adenoma, fibroadenoma of breast, fibrous histiocytoma, melanocytic naevus, haemangioma, seborrhoeic keratosis, glomus tumor, pituitary tumor benign, skin papilloma, and thyroid neoplasm.

Comparison of Reslizumab Malignancy Rate to External Data Source

Most of the malignancies in the reslizumab-treated patients were diagnosed during the OLE study that was not controlled, so Teva compared the malignancy rate in the clinical program to the published malignancy rates. Since all the malignancies that were diagnosed in reslizumab-treated patients were asthma patients treated with 3.0 mg/kg every 4 weeks, Teva

used a conservative approach and calculated the malignancy rates with a dominator (ie, 1596 patients) of only asthma patients treated with 3.0 mg/kg and not all patients exposed to reslizumab. The comparison of malignancy rates between the reslizumab asthma PCTs + OLE study and the external database Surveillance Epidemiology and End Results (SEER) suggested a higher rate in the reslizumab studies (standardized incidence ratio [SIR] >1) (Table 28) though the CI included unity. It is noteworthy that these comparisons to external databases have several limitations, such as a high probability of detection bias (ie, clinical study setting with frequent clinical visits and evaluations vs population-based data collection) and differences in the demographic and clinical composition of the compared populations.

The latent period between a causative agent exposure and development of malignant tumors is generally on the order of years based on published data. Minimal latent periods for hematologic malignancies (Hayes et al 1997) and solid tumors (Ivanov et al 2009) have been reported as 1.5 and 4 years, respectively. Given this evidence, the reslizumab mechanism of action, and employing the most stringent assumptions, Teva is of the opinion that malignancies developing within 6 months of study drug treatment are unlikely to be related to reslizumab exposure. Therefore, a supplemental analysis that excluded malignancies diagnosed within 6 months of reslizumab exposure is also provided. When the malignancy rates were compared after excluding malignancies that were diagnosed within less than 6 months after initiating reslizumab, the SIR values fell below 1, indicating that the reslizumab malignancy rates were consistent with the expected rates.

Table 28: Overall Malignancy Rates in Patients Treated with Reslizumab 3.0 mg/kg (Asthma PCTs + OLE Study; N=1596) Compared with the SEER Malignancy Rate

Malignancies	Observed	Expected[b]	SIR	Lower CI	Upper CI	P value
All malignancies[a]	12	9.022	1.330	0.69	2.32	0.199
Malignancies excluding those diagnosed within <6 months of treatment	6	9.022	0.665	0.24	1.45	0.8856

[a] NMSCs, melanoma in-situ and GI metastasis were excluded since they are not included in the SEER database.
[b] Expected values are age adjusted.
CI=confidence interval; GI=gastrointestinal; NMSC=non-melanoma skin cancer; OLE=open-label extension; PCT=placebo-controlled trial; SIR=standardized incidence ratio.
Note: Data as of the cut-off date of 01 September 2014.

Conclusion

In summary, based on nonclinical and clinical studies, there was no evidence of an association between reslizumab treatment and the potential for an increased risk of malignancy.

Patients with previous malignancies were not excluded from the clinical studies, and in 2 patients, the malignancy reported was a recurrence of a previously diagnosed malignancy. Additionally, the malignancies that were diagnosed were of diverse origins and tissue types, not

suggesting a common mechanism of carcinogenicity. The most commonly reported malignancies were NMSCs.

All malignancies in the asthma PCTs except 1 skin squamous cell carcinoma were diagnosed within less than 6 months after starting study treatment; this short latent period suggests that these were pre-existing conditions.

The malignancy rate for the reslizumab program was comparable to the rates published in other data sources, such as SEER.

5.7.4. Musculoskeletal/Creatine Phosphokinase Analyses

Reslizumab exposure was associated with a higher frequency of uncommon, transient, mild to moderate myalgia events compared with placebo (0.97% vs 0.55%). One patient each withdrew from the study for myalgia in the reslizumab and placebo groups, and none of the myalgia cases were associated with myositis or rhabdomyolysis.

CPK elevations that achieved a Teva's potentially clinically significant definition (>5 × upper limit of normal range) during the treatment period were more frequent in the reslizumab 3.0 mg/kg group (2%) than in the placebo group (1%).

These initial observations lead to a thorough evaluation of the clinical and laboratory data to determine if reslizumab treatment is associated with muscle injuries/myositis/ rhabdomyolysis. Since baseline differences in the incidence of events could bias these assessments, clinical and laboratory events were compared at baseline and during treatment to minimize risk of bias due to baseline differences.

Baseline evaluation:

- An ongoing medical history of abnormalities under the Musculoskeletal and Connective Tissue Disorders SOC was reported slightly more in the reslizumab group (169 [23%] in placebo group and 278 [27%] in the reslizumab 3.0 mg/kg group).
- There were more patients in the reslizumab group treated prior to the study with lipid-modifying agents (including statins) and drugs commonly used for musculoskeletal complaints (eg, inflammatory and antirheumatic products and analgesics).
- Mean baseline CPK value was greater in the reslizumab 3.0 mg/kg group (142.8 U/L) compared with the placebo group (132.5 U/L), and there were more patients in the reslizumab 3.0 mg/kg group with elevated CPK before or at baseline than the placebo group (14% vs 9%, respectively). This was most notable for Grade 4 pre-dosing CPK elevations (seen in 3 patients in the reslizumab 3.0 mg/kg group and no patients in the placebo group).

CPK Analysis

The imbalance in the pre-dosing CPK values between the treatment groups led Teva to conduct an analysis of patients with normal CPK values at baseline and their respective shifts to their highest abnormal post-baseline CPK values.

The majority of patients in both treatment groups with normal CPK values at baseline maintained normal values throughout the study. The overall incidence of shifts was similar across treatment groups when considering baseline/pre-dosing elevated CPK values (Table 29), both in the overall shifts and in the specific grades of elevations, suggesting no effect of reslizumab on CPK elevation. When increased CPK values were observed, they were frequently transient and did not result in discontinuation of reslizumab treatment.

Table 29: Shift from Normal at Baseline to Highest Post-Baseline Abnormal Creatine Phosphokinase Grade Level (Asthma PCTs)

CPK Category[a]	Placebo (N=730) n (%)	All reslizumab (N=1131) n (%)	Reslizumab 0.3 mg/kg (N=103) n (%)	Reslizumab 3.0 mg/kg (N=1028) n (%)
Patients with normal test (<1.25 × ULN) at Baseline	663 (91)	982 (87)	88 (85)	894 (87)
Mild (Grade 1: 1.25 × ULN to 1.5 × ULN)	52 (8)	68 (7)	3 (3)	65 (7)
Moderate (Grade 2: 1.6 × ULN to 3 × ULN)	49 (7)	92 (9)	3 (3)	89 (10)
Severe (Grade 3: 3.1 × ULN to 10 × ULN)	17 (3)	20 (2)	0	20 (2)
Potentially life threatening (Grade 4: >10 × ULN)	3 (<1)	6 (<1)	1 (1)	5 (<1)

[a] Categories are based on "Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials."

CPK=creatine phosphokinase; n=number of patients; PCT=placebo-controlled trial; ULN=upper limit of normal.

Note: The denominator for calculating percentages is the number of patients with a normal baseline CPK value. Subjects are counted at the highest post-baseline toxicity grade level.

Muscle-related Adverse Event Analysis

All 168 cases of muscle-related adverse events from the primary integrated safety asthma PCTs that fulfilled the below categories were tabulated (Table 30) and individual narratives were medically reviewed and evaluated. These categories were defined in order to detect cases that might be associated with myositis/rhabdomyolysis and are summarized in Table 30.

Table 30: Summary of CPK Narrative Criteria by Treatment Group

Category[a]	Placebo (N=730) n (%)	All reslizumab (N=1131) n (%)	Reslizumab 0.3 mg/kg (N=103) n (%)	Reslizumab 3.0 mg/kg (N=1028) n (%)
Patients fall into at least 1 category[b]	65 (9)	103 (9)	4 (4)	99 (10)
A	3 (<1)	8 (<1)	0	8 (<1)
B	3 (<1)	9 (<1)	1 (<1)	8 (<1)
C	0	2 (<1)	0	2 (<1)
D	57 (8)	86 (8)	3 (3)	83 (8)
E	11 (2)	23 (2)	0	23 (2)

[a] Categories are based on FDA Question 2 from Information Request on 24 September 2015.
[b] Some patients fall into more than 1 category.
CPK=creatine phosphokinase; FDA=Food and Drug Administration; HLGT=high level group term; HLT=high level term; n=number of patients; PT=preferred term; SOC=system organ class; ULN=upper limit of normal.
A: Serious adverse events, discontinuations, or temporary interruptions in study drug for adverse event from Musculoskeletal and Connective Tissue Disorders SOC or CPK elevations.
B: All Grade 4 CPK elevations >10 × ULN postbaseline (regardless of CPK values at baseline).
C: HLT for myopathy.
D: Identified via Teva-generated customized post-hoc analysis of myopathy adverse events:

- PTs under the HLT of Skeletal and cardiac muscle analyses
- PTs under HLGT of Muscle disorders
- Additional PTs: biopsy muscle, biopsy muscle abnormal, myoglobin blood increased, myoglobin urine, myoglobin urine present, musculoskeletal pain, neck pain, and back pain

E: Adverse events occurring within 24 hours after infusion in the Musculoskeletal and Connective Tissue Disorders SOC.

The results of these analyses showed that there is no pattern or trend suggesting a risk of myositis (including rhabdomyolysis) or myopathy related to reslizumab. This conclusion is based on the following:

- The overall incidence of these cases was similar in both treatment groups (65 [9%] in the placebo group and 99 [10%] in the reslizumab 3.0 mg/kg group). The incidence in each category was balanced for placebo and reslizumab, except in the myopathy HLT where there were 2 events in the reslizumab group and none in the placebo group. Both non-serious cases were not consistent with myositis/rhabdomyolysis related to reslizumab (ie, 1 case of mild toxic myocardiopathy of unknown etiology with normal CPK and no ECG changes, 1 case of asymptomatic CPK elevation which normalized in subsequent test).
- The review of serious adverse events and events leading to discontinuation under the Musculoskeletal and Connective Tissue Disorders SOC or PT of blood CPK increased did not detect events consistent with myositis (ie, the serious events included back pain, musculoskeletal chest pain, spinal osteoarthritis, osteoarthritis,

and foot deformity; none were with elevation of CPK. Events leading to discontinuation included back pain and myalgia with normal CPK values and 1 case of transient elevated CPK in a patient with liver abscess.).

- All patients with significant elevated CPK (Grade 4) postbaseline were asymptomatic. Five of them had elevated CPK at baseline. Most of the patients had transient elevations from baseline with no interruption of reslizumab treatment.
- There were more patients in the placebo group with muscle adverse events (Category D) accompanied by CPK elevation Grade 3 (6/57 placebo patients [10.5%] and 2/83 reslizumab 3.0 mg/kg patients [2.4%]). Both cases in the reslizumab group were not consistent with myositis; the muscle events (1 case of myalgia and 1 case of muscle spasm accompanied by nephrolithiasis) were transient and CPK values returned to baseline values with no interruption of reslizumab treatment.
- In conclusion, myalgia was reported in a slightly higher incidence in the reslizumab group compared to the placebo group. The review of the safety data did not reveal any cases associated with myositis and/or rhabdomyolysis related to reslizumab treatment.

5.7.5. Cardiovascular Events

Cardiovascular events have been raised as an area of interest for some biologics and other asthma treatments. No specific cardiovascular outcomes study was necessary based on the molecular structure, mechanism of action, or data observed in early clinical studies. No formal QTc study was conducted in the reslizumab clinical program; however, a Phase 1 study showed no impact of reslizumab on QTc in the PK/PD analysis, and the integrated ECG analyses did not show differences between treatment groups or evidence of increase ECG abnormalities or QTc prolongation with reslizumab. Observed ECG parameters are discussed in Section 5.6.

The incidence of individual cardiovascular events (PTs) reported in patients treated with reslizumab was low (<1%) (Table 31). In the asthma PCTs, the events were similar or lower for reslizumab than for placebo. In summary, based on the clinical data in the overall development program, there is no evidence for a risk of cardiovascular toxicity.

Table 31: Cardiovascular Events Reported in Reslizumab Clinical Studies

MedDRA preferred term	Asthma PCTs		All studies except Study 01-I-0155
	Placebo (N=730) n (%)	Reslizumab 3.0 mg/kg (N=1028) n (%)	All reslizumab doses[a] (N=2187) n (%)
Angina pectoris	3 (<1)	1 (<1)	4 (<1)
Coronary artery disease	3 (<1)	1 (<1)	1 (<1)
Acute myocardial infarction	1 (<1)	0	1 (<1)
Myocardial infarction	0	0	2 (<1)
Myocardial ischaemia	1 (<1)	0	2 (<1)
Carotid artery occlusion	0	1 (<1)	1 (<1)
Cerebrovascular accident	0	0	1 (<1)
Carotid artery stenosis	1 (<1)	0	0
Transient ischaemic attack	0	0	1 (<1)
Deep vein thrombosis	0	1 (<1)	1 (<1)

[a] Includes the 0.03 to 3.0mg/kg doses and subcutaneous 220 mg doses.
PCT=placebo-controlled trial.

5.8. Safety in Subgroups

Overall, the safety profile of reslizumab was generally similar in the patient subgroups analyzed and similar or lower than placebo (of note, there were insufficient data to fully assess the impact of moderate to severe renal or hepatic impairment; Table 32). Moreover, the safety profile in the subset population was consistent with that of the overall population. These findings are consistent with the lack of noteworthy impact of age, sex, race, ADA status, concomitant medication use, or renal or abnormal liver function tests on the PK of reslizumab.

Table 32: Overall Adverse Events in Subgroup Populations (Asthma PCTs)

Any adverse event	**Placebo n/N (%)**	**Reslizumab 3.0 mg/kg n/N (%)**
Age		
12-17 years	13/16 (81)	16/19 (84)
18-64 years	528/658 (80)	652/965 (68)
≥65 years	48/56 (86)	22/44 (50)
Sex		
Male	213/276 (77)	252/388 (65)
Female	376/454 (83)	438/640 (68)
Race		
White	449/549 (82)	487/729 (67)
Black	46/61 (75)	84/145 (58)
Asian	44/57 (77)	60/79 (76)
Other	50/63 (79)	59/75 (79)
Post-baseline ADA status		
ADA positive	NA	45/69 (65)
ADA negative	NA	645/959 (67)
Baseline eosinophil count		
<400 cells/μL	177/248 (71)	269/478 (56)
≥400 cells/μL	329/480 (69)	331/549 (60)
Geographic region		
US	173/224 (77)	301/517 (58)
Europe	209/260 (80)	163/237 (69)
Other countries	207/246 (84)	226/274 (82)
OCS use at baseline (per CRF)		
Yes	57/58 (98)	38/48 (79)
No	532/672 (79)	652/980 (67)
LABA use at baseline		
Yes	450/546 (82)	531/782 (68)
No	139/184 (76)	159/246 (65)
LTRA use at baseline		
Yes	132/155 (85)	149/202 (74)
No	457/575 (79)	541/826 (65)
ICS dose at baseline		
High	187/208 (90)	163/203 (80)
Moderate	220/267 (82)	211/274 (77)

Table 32: Overall Adverse Events in Subgroup Populations (Asthma PCTs) (Continued)

Any adverse event	Placebo n/N (%)	Reslizumab 3.0 mg/kg n/N (%)
Renal impairment		
Normal or high (G1)	396/499 (79)	488/735 (66)
Mildly decreased (G2)	171/207 (83)	178/266 (67)
Mildly to moderately decreased (G3a)	19/20 (95)	24/27 (89)
Moderately to severely decreased (G3b)	2/2 (100)	0
Severely decreased (G4)	0	0
Hepatic impairment: AST		
Normal	569/702 (81)	672/1003 (67)
>ULN - 3.0 x ULN	18/26 (69)	18/24 (75)
>3.0 - 5.0 x ULN	0	0
Hepatic impairment: ALT		
Normal	534/657 (81)	637/938 (68)
>ULN - 3.0 x ULN	52/68 (76)	53/88 (60)
>3.0 - 5.0 x ULN	2/4 (50)	0
Hepatic impairment: bilirubin		
Normal	574/713 (81)	676/1003 (67)
>ULN - 1.5 x ULN	12/14 (86)	10/21 (48)
>1.5 - 3.0 x ULN	2/2 (100)	4/4 (100)

ADA=anti-drug antibody; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CRF=case report form; ICS=inhaled corticosteroids; IVRS=interactive voice response system; LABA= long-acting beta-agonist; LTRA=leukotriene receptor antagonists; OCS=oral corticosteroids; ULN=upper limit of normal; US=United States.

Note: The ADA assay provides sensitive (22 ng/mL) detection of all ADA Ig isoforms.

5.9. Concomitant Medications

Review of the common concomitant medications (>5% of patients in any group) revealed that the use of certain therapeutic classes of medications commonly used to treat worsening asthma and/or allergic and infectious comorbidities was notably higher in incidence in the placebo group than in the reslizumab group (Table 33). These included antibacterials for systemic use, antihistamines for systemic use, corticosteroids for systemic use, and nasal preparations. Fewer patients in the reslizumab group (57%) started new medications while in the studies compared to the placebo group (74%) mainly due to less medications commonly used to treat asthma and its complications. These differences would bias the efficacy towards placebo making the benefits associated with reslizumab treatment even more compelling.

Table 33: Concomitant Medications Reported by >5% of Patients in Any Treatment Group by Therapeutic Class

Measure	Placebo (N=730)	Reslizumab 3.0 mg/kg (N=1028)
Patients receiving concomitant medications	729 (>99)	1028 (100)
Drugs for obstructive airway diseases[a]	675 (92)	970 (94)
Antihistamines for systemic use	321 (44)	375 (36)
Nasal preparations	268 (37)	325 (32)
Analgesics	196 (27)	272 (26)
Antibacterials for systemic use	290 (40)	270 (26)
Corticosteroids for systemic use	288 (39)	246 (24)
Anti-inflammatory and antirheumatic products	135 (18)	206 (20)
Drugs for acid-related disorders	141 (19)	191 (19)
Vitamins	80 (11)	150 (15)
Lipid-modifying agents	73 (10)	123 (12)
Adrenergics, inhalants	53 (7)	53 (5)

[a] Drugs for obstructive airway diseases were kept stable during the studies per protocols.

5.10. Overdose and Abuse Potential

The highest iv dose of reslizumab studied in clinical studies was 3.0 mg/kg. There have been no cases of reslizumab overdose reported as an adverse event and no adverse events associated with a reslizumab overdose were observed in any of the clinical studies conducted with reslizumab.

Overall, there were 56 occurrences of infusion dose >3.5 mg/kg in 21 patients in the asthma studies. The maximal overdose was 12.1 mg/kg. A review of adverse events reported within 1 month after administration of these doses did not reveal any safety concerns. The maximum tolerated dose of reslizumab has not been determined.

The potential for abuse of reslizumab is low given its route of administration, mechanism of action (IL-5 neutralization with resultant eosinophil depletion), and lack of penetration of the blood-brain barrier owing to the large size of its molecule.

5.11. Rebound

Clinical withdrawal or rebound effects have not been observed in clinical studies in the follow-up period (90-day follow-up after the end-of-treatment visit; see Section 4.3.2). Adverse event data from the follow-up period did not support an exaggerated return of symptoms after cessation of treatment; the adverse event profile during the follow-up period was not meaningfully different from that observed during the treatment period, and there was no significant difference between the placebo- and reslizumab-treated patients during the follow-up period. Additionally, the effect of blood eosinophil reduction was reversible. Blood eosinophils that were tested 90 days after the end of the treatment period were near pretreatment counts, which is an expected physiological response.

5.12. Pregnancy

Based on nonclinical data, reslizumab is not genotoxic and did not affect reproductive parameters, and therefore, the risk of pregnancy complications and offspring abnormalities appears to be low. In all clinical studies, females of child-bearing potential must have had a negative pregnancy test at screening and before each study drug administration and agree to use a protocol-specified acceptable contraceptive method consistently and correctly. Few pregnancies (8 patients) have been reported in the clinical program in patients treated with reslizumab, and all cases resulted in discontinuation of treatment. Outcomes are known for 7 patients: 2 ended in elective abortions and 5 concluded with live births of infants with no malformations (1 male baby had neonatal jaundice that was reported as an unrelated adverse event and was assessed as a physiological jaundice). Information about 1 pregnancy case was not available.

5.13. Safety Conclusions

In summary, the safety profile of reslizumab is well characterized based on 2155 patient-years of exposure from 2187 patients and subjects enrolled in Sponsor-initiated trials who received at least 1 dose of reslizumab. A total of 1596 asthma patients were exposed to the reslizumab dose of 3.0 mg/kg, including 743 patients exposed for ≥1 year and 213 patients exposed for ≥2 years.

- Reslizumab, administered as an iv infusion 3.0 mg/kg every 4 weeks, demonstrated an acceptable safety profile. The overall incidence of adverse events was lower in the reslizumab group than that in the placebo group (67% and 81%, respectively). The most frequently observed adverse events (≥5% observed for reslizumab) were of the types expected for the study population (ie, asthma, nasopharyngitis, upper respiratory tract infection, headache, and sinusitis). There were no adverse event types in the reslizumab-treated patients that had an incidence that exceeded by more than 1% the incidence in the placebo-treated patients. There were no deaths related to reslizumab or asthma worsening in the reslizumab program. Serious adverse events occurred more frequently overall in the placebo treated patients than in the reslizumab-treated patients (9% versus 6%, respectively), and the incidence of discontinuation due to adverse events was similar in the 2 groups (5% for each group).
- Anaphylactic reactions were associated with reslizumab infusions in 3 patients (0.14%) in the asthma PCTs. All cases occurred during infusion or within 20 minutes after completion of the infusion and fully resolved within 2 to 4 hours with standard treatment at the study site with no residual effects. The diagnosis of anaphylaxis was based on clinical judgement of the investigator, and the immune mechanism of the reactions is unknown. The evidence would suggest that these patients were unlikely to be alpha gal sensitive due to geography and lack of pre-existing meat allergy. The low level of alpha gal present on the Fc domain of reslizumab makes it unlikely to bind pre-existing alpha gal IgE antibodies in sensitized individuals. A thorough evaluation of the safety data did not identify any other hypersensitivity events related to reslizumab treatment.
- Reslizumab is an iv infusion and will be administered under the supervision of a healthcare professional capable of managing the risk of anaphylaxis as is done with other

currently available therapies used in the treatment of asthma. Teva is committed to ensuring that patients and health care providers are properly informed about the anaphylaxis risks via the Prescribing Information and Patient Information. Additionally, Teva intends to make nurse trainers available to patients and health care professionals to help ensure the appropriate use of reslizumab.

- Non–severe/serious reports of myalgia occurred in a higher frequency in reslizumab-treated asthma patients (0.97%) than in placebo-treated patients (0.55%). These adverse events were transient, with no evidence of muscle injury, myositis and rhabdomyolysis (Section 5.7.4).
- The profile of other specific adverse events of special interest (namely malignancies, infections, and cardiovascular events) showed no increased risk following reslizumab treatment.
- Except for the pharmacological effect of reduced eosinophils, there were no clinically meaningful differences or patterns of abnormality for any clinical laboratory tests, and variable value shifts were similar in each group. There were no clinically meaningful differences or potentially clinically important trends in vital signs, ECG intervals, or overall ECG assessments.
- Patients in the reslizumab group had a lower incidence in the overall concomitant medications commonly used to treat worsening asthma and/or allergic and infectious comorbidities (ie, antibacterials for systemic use, antihistamines for systemic use, corticosteroids for systemic use, and nasal preparations).
- The adverse event profile of patients exposed to >12 months of treatment was similar to that of the overall population. There were no increases in overall adverse events over time (including the specific adverse event of special interest), and no new events of concern arose with longer-term use. Of note, there were no anaphylactic reactions reported after 12 months.
- Pediatric Safety Data: A total of 253 pediatric patients from 5 to 19 years of age with EoE or asthma have been treated with reslizumab at doses up to 3.0 mg/kg. The majority of these pediatric patients (167 patients, 66%) were treated with reslizumab for more than 2 years. The reslizumab-treated pediatric population had a similar safety profile as the placebo-treated population as well as with the overall population.

6. IMMUNOGENICITY RESULTS

All therapeutic proteins have the potential to induce an ADA response; ADAs may alter PK/PD, produce adverse reactions, or reduce efficacy. However, in most circumstances, ADAs are of no clinical significance. Immunogenicity was assessed as part of the reslizumab clinical program.

Immunogenicity methods evolved with regard to assay platform and detection technology over the course of reslizumab development to improve assay sensitivity, drug tolerance, and specificity. The method used for ADA assessment in all the Phase 3 clinical studies in patients with asthma was a homogenous bridging ELISA that employed the labeled drug as both the

capture and detection reagents. This assay employs a tiered assay testing strategy, with an adequate level of drug tolerance, and includes a step to eliminate interference due to IL-5. This immunogenicity assay platform provides sensitive and specific detection of ADAs of all Ig subtypes. In the Phase 3 clinical studies, a patient was classified as having a treatment-emergent ADA response if a sample tested positive at any postdose timepoints but not at the predose timepoint, or if postdose ADA titer increased 4-fold or greater from a positive baseline ADA sample. The assay sensitivity was 22 ng/mL, which is well below the FDA required threshold for assay sensitivity of 250 ng/mL.

ADA data from the individual studies suggested that there was a limited level of immune responses to reslizumab treatment. **In Phase 3 placebo-controlled studies with a duration of 16 to 52 weeks (Studies 3081, 3082, 3083 and 3084), low-titer, frequently transient anti-reslizumab antibodies were detected in 53/983 (5%) asthma patients receiving reslizumab treatment at 3.0 mg/kg.**

The adverse event profile was similar for the ADA-positive and -negative patients (64% vs 66% adverse event incidence, respectively). There were no anaphylactic reactions/systemic hypersensitivity adverse events linked to a positive ADA response, and there was no indication of adverse events related to an immune complex disorder (eg, renal dysfunction and rash) in the clinical studies conducted.

There was no obvious indication of reduced exposure in patients who formed ADA versus those who did not, based on PK parameters (see Section 9.5 for an overview).

There was no obvious difference in ADA positive or ADA negative patients in reslizumab clinical activity for blood eosinophil reduction, or clinical efficacy based on FEV_1 improvement.

In the long-term OLE (Study 3085) in patients with asthma receiving 3.0 mg/kg reslizumab for up to 36 months, ADA responses were detected in 49 (5%) of 1014 patients analyzed for immunogenicity response. Similar to the placebo-controlled studies, ADA was frequently transient and of low titer. There was no observed association of ADA response with adverse events. Eosinophil levels in ADA-positive patients were similar to those in ADA-negative patients, implying that the presence of a positive ADA response during treatment with reslizumab did not interfere with reslizumab activity.

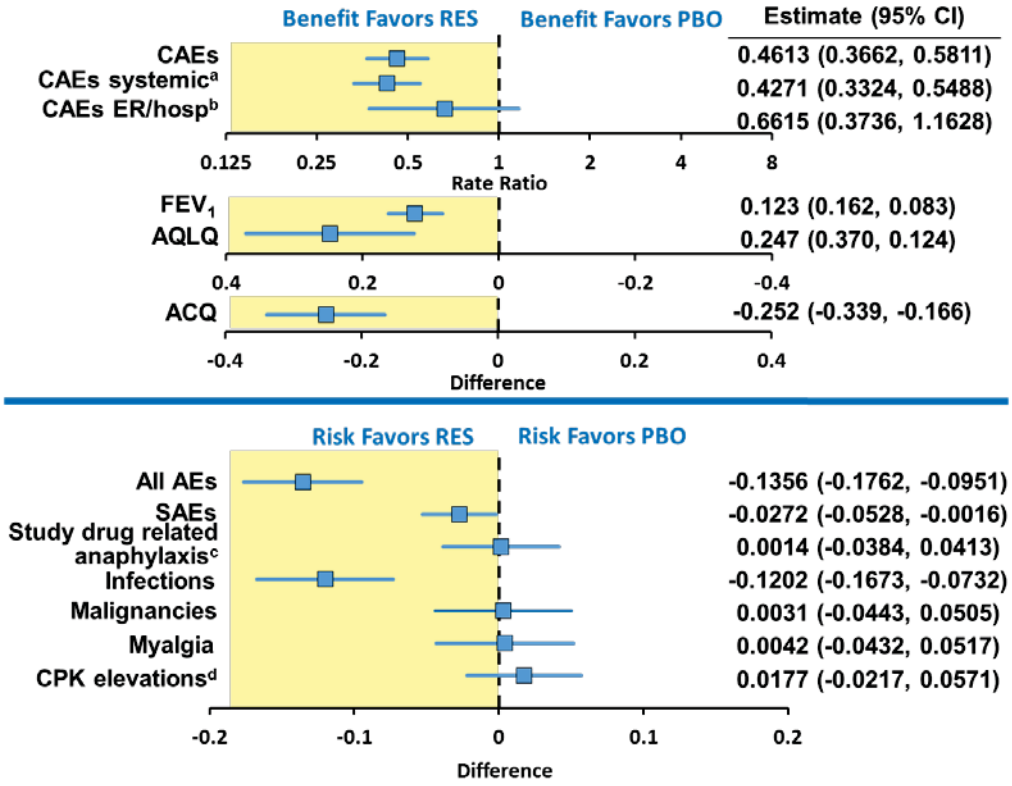
7. BENEFIT-RISK ASSESSMENT AND CONCLUSIONS

Therapeutic Justification: Asthma with elevated blood eosinophils has been recognized as a distinct phenotype associated with an increased risk for exacerbations and lower lung function. Reslizumab was developed as a targeted therapy for this phenotype - specifically, exacerbation prone asthma patients with elevated blood eosinophils whose symptoms remain inadequately controlled by medium- to high-dose ICS-based therapies.

Assessment of Benefits and Risks: An overall positive benefit-risk profile of reslizumab 3.0 mg/kg every 4 weeks has been demonstrated in the target population based on the following (as shown in Figure 29):

- reduction in asthma exacerbations and improvements in lung function, asthma symptoms, and asthma-related quality of life
- a well-characterized and acceptable safety profile based on 2155 patient-years of exposure

Figure 29: Summary of Reslizumab Benefit and Risk



[a] CAEs requiring use of systemic corticosteroids.
[b] CAEs requiring ER or hospitalization.
[c] The patient population utilized for the assessment of drug-related anaphylaxis totaled 2072 patients from studies with treatment using multiple doses of reslizumab (ie, not single-dose studies). See Section 5.7.1 for a more detailed description.
[d] CPK elevations contains data for all patients with normal baseline values. See Section 5.7.4 for a more detailed description.

ACQ=Asthma Control Questionnaire; AE=adverse event; AQLQ=Asthma Quality of Life Questionnaire; CAE=clinical asthma exacerbation; CI=confidence interval; CPK=creatine phosphokinase; ER=emergency room; FEV_1=forced expiratory volume in 1 second; PBO=placebo; RES=reslizumab; SAE=serious adverse event.

The measures of clinical benefit include the CAE assessments (integrated cohort from the two 52-week exacerbation studies [3082 and 3083]) as well as the asthma control and impairment assessments at 16 weeks (integrated cohort from Phase 3 Studies 3081, 3082, and 3083). Full discussions of these efficacy measures are found in Section 4.2. The variables displayed to show the risk profile of reslizumab are based on the patient populations from the randomized asthma PCTs (Studies Res 5 0010, 3081, 3082, 3083, and 3084), except as noted for anaphylaxis. Full discussions of these safety parameters are found in Section 5. Point estimates are provided at the

right side of each parameter and include 95% CIs of the estimate (also displayed as lines within the figure).

Conclusion: Based on the totality of the efficacy and safety data, Teva believes that reslizumab 3.0 mg/kg every 4 weeks demonstrates a positive benefit-risk profile in in exacerbation-prone asthma patients with elevated blood eosinophils who have limited treatment options.

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9. APPENDICES

9.1. Clinical Studies - Design and Key Findings

Table 34 includes the study design and key findings for each of the 8 studies in the reslizumab clinical program not described in Table 3.

Table 34: Description of Additional Clinical Studies

Study number	Dose group (n)	Key endpoints / Objectives	Target population	Design	Key findings
Eosinophilic esophagitis					
Res-5-0002	1.0 mg/kg: (55) 2.0 mg/kg: (57) 3.0 mg/kg: (57) PBO: (57)	Esophageal eosinophil counts, Physician's Global Assessment, Child Health Questionnaire, safety, and tolerability	Pediatric patients with eosinophilic esophagitis Age: 5 to 18 years	Phase 2b/3, 15-week, randomized, double-blind, placebo-controlled, parallel-group study Reslizumab iv infusion every 4 weeks for 4 doses	Highly significant reduction in the mean peak esophageal eosinophil counts; not associated with an improvement in the Physician's Global Assessment; symptom improvement; well tolerated; and number of drug-related adverse events was low and similar to placebo
Res-5-0004	1.0 mg/kg: (11) 2.0 mg/kg: (21) 3.0 mg/kg: (14)	Esophageal eosinophil counts, Physician's Global Assessment, Child Health Questionnaire, safety, and tolerability	Pediatric patients with eosinophilic esophagitis Age: 5 to 18 years	Long-term evaluation of pediatric patients with eosinophilic esophagitis who were previously enrolled in Study Res-5-0002	Maintained beneficial effects on peak esophageal eosinophil counts and symptom assessments; well tolerated
Hypereosinophilic syndrome					
NIH Protocol 01-I-0155	<0.1 mg/kg: (8)	Safety and efficacy	Patients with hypereosinophilic syndrome or eosinophilic gastroenteritis Age: ≥18 years	Uncontrolled, Phase 2, open-label, single- and repeat-dose study	Repeat dosing with reslizumab led to decreased eosinophils and symptomatic improvement; well-tolerated
Nasal polyposis					
P01942	1.0 mg/kg: (8) 3.0 mg/kg: (8) PBO: (8)	Safety, tolerability, and pharmaco-kinetics	Patients with nasal polyposis Age: ≥18 years	Phase 1, reslizumab single-dose, multicenter, randomized, evaluator-blind, parallel-group, placebo-controlled study	Safe at both doses tested; exposure increased in dose-proportional manner; long half-life and low volume of distribution; decreases in blood eosinophil levels

Table 34: Description of Additional Clinical Studies (Continued)

Study number	Dose group (n)	Key endpoints / Objectives	Target population	Design	Key findings
Healthy subjects					
1102	0.3 mg/kg: (18) 1.0 mg/kg: (20) 2.0 mg/kg: (20) 3.0 mg/kg: (42)	Safety, tolerability, and pharmaco-kinetics of reslizumab in Japanese and non-Japanese subjects	Healthy subjects Age: 20 to 45 years	Phase 1, 20-week, repeat-dose, randomized, open-label study Reslizumab iv infusion every 4 weeks for 5 doses	No statistically significant differences or consistent trends toward differences in exposures between Japanese and non-Japanese subjects after either single or multiple doses; C_{max} and AUC increased in an approximately dose-proportional manner; decreased blood eosinophils at all dose levels; no trend toward an increase in QTcF; well tolerated and no new safety signals were identified
1107	220 mg (sc): (45) 3.0 mg/kg: (30)	Pharmaco-kinetics, pharmaco-dynamics, and safety profile after single sc or iv administration in healthy Japanese and non-Japanese subjects	Healthy subjects Age: non-Japanese (18 to 45 years) Japanese (21 to 45 years)	Phase 1, single-dose, open-label study Non-Japanese subjects were randomized to receive a single 220-mg iv or sc dose of reslizumab Japanese subjects received a single 220-mg sc dose of reslizumab	No apparent trends toward differences in exposures between Japanese and non-Japanese subjects; decreased blood eosinophils after both iv and sc administration; well tolerated after both iv and sc administration

AUC=area under the curve; C_{max}=maximum concentration; iv=intravenous; NIH=National Institutes of Health; PBO=placebo; sc=subcutaneous.

9.2. Demographics and Baseline Characteristics

9.2.1. Study Res-5-0010 and Study 3084

Demographics and baseline disease characteristics for Study Res-5-0010 and Study 3084 are shown in Table 35. In the Phase 2 Study Res-5-0010, the groups were similar in terms of demographics and baseline disease characteristics. In Study 3084, the groups were generally similar in terms of demographics and baseline characteristics, and baseline disease state was indicative of asthma that was inadequately controlled. With the exception of blood eosinophils, the baseline disease characteristics for patients in Study 3084 were generally similar to those of patients in each of the adequate and well-controlled Phase 3 studies (Studies 3081, 3082, and 3083) (Section 4.1.2).

Table 35: Demographic and Baseline Characteristics (Study Res-5-0010 and Study 3084)

Demographic/baseline characteristic	Study Res-5-0010		Study 3084	
	Placebo (N=53)	Reslizumab 3.0 mg/kg (N=53)	Placebo (N=98)	Reslizumab 3.0 mg/kg (N=398)
Age (years), mean (SD)	45.8 (11.74)	44.9 (13.94)	45.11 (13.382)	44.90 (11.996)
Age group, n (%)				
12-17 years	0	0		
18-44 years	20 (38)	28 (53)		
45-64 years	32 (60)	19 (36)		
18-64 years			95 (97)	394 (99)
≥65 years	1 (2)	6 (11)	3 (3)	4 (1)
Sex, n (%)				
Male	24 (45)	19 (36)	44 (45)	137 (34)
Female	29 (55)	34 (64)	54 (55)	261 (66)
Race, n (%)				
White	41 (77)	42 (79)	73 (74)	260 (65)
Black	10 (19)	8 (15)	21 (21)	113 (28)
Asian	1 (2)	1 (2)	2 (2)	10 (3)
American Indian or Alaskan Native	1 (2)	0	0	3 (<1)
Pacific Islander			2 (2)	0
Other	0	2 (4)	0	12 (3)
Ethnicity, n (%)				
Hispanic or Latino	1 (2)	1 (2)	90 (92)	354 (89)
Non-Hispanic or non-Latino	52 (98)	52 (98)	8 (8)	44 (11)
BMI (kg/m^2), mean (SD)			31.6 (6.66)	32.3 (8.69)
Geographic region, n (%)				
United States			98 (100)	398 (100)
Other countries			0	0

Table 35: Demographic and Baseline Characteristics (Study Res-5-0010 and Study 3084) (Continued)

Demographic/baseline characteristic	Study Res-5-0010		Study 3084	
	Placebo (N=53)	Reslizumab 3.0 mg/kg (N=53)	Placebo (N=98)	Reslizumab 3.0 mg/kg (N=398)
Baseline disease characteristic				
Asthma duration, mean (SD) in years	26.1 (16.06)	23.3 (11.38)	25.825 (16.7506)	26.166 (15.6895)
Asthma exacerbation within 12 months, n (%)			37 (38)	166 (42)
Number of exacerbation events, mean (SD)			1.973 (1.4811)	1.831 (1.3735)
ACQ score, mean (SD)	2.5 (0.73)	2.8 (0.79)	2.564 (0.6909)	2.558 (0.6992)
Airway reversibility (%), mean (SD)	29.52 (21.297)	23.08 (10.068)	24.159 (13.9742)	25.972 (17.7145)
FEV_1 (L)[a], mean (SD)	2.26 (0.746)	2.08 (0.609)	2.180 (0.6355)	2.101 (0.6950)
FVC (L)[a], mean (SD)	3.43 (1.020)	3.13 (0.830)	3.215 (0.9076)	3.047 (0.9577)
FEV_1/FVC, mean (SD)			0.682 (0.1080)	0.696 (0.1295)
$FEF_{25\%-75\%}$ (L/sec)[a], mean (SD)	1.59 (0.909)	1.45 (0.791)	1.553 (0.6791)	1.650 (0.9037)
% Predicted FEV_1[a], mean (SD)	68.90 (16.33)	66.31 (15.13)	66.466 (15.5310)	66.774 (16.2619)
Blood eosinophil count (10^9 cells/L), mean (SD)	0.5 (0.34)	0.5 (0.32)	0.277 (0.2209)	0.281 (0.2448)
SABA use: daily average number of puffs in past 3 days, mean (SD)			2.0 (1.82)	1.9 (1.84)
Total daily ICS dose (µg), mean (SD)			627.8 (224.08)	615.7 (240.75)
Medium-dose ICS, n (%)			73 (74)	305 (77)
High-dose ICS, n (%)			25 (26)	93 (23)
Non-ICS controller drug[b]			83 (85)	315 (79)
LABA use at baseline, n (%)			80 (82)	307 (77)
Leukotriene inhibitor, n (%)			19 (19)	79 (20)

[a] n=52 for each group

[b] This category includes drugs in addition to moderate to high doses of ICS.

ACQ=Asthma Control Questionnaire; BMI=body mass index; $FEF_{25\%-75\%}$=forced expiratory flow during the middle half of the forced vital capacity; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; ICS=inhaled corticosteroid; LABA=long-acting beta-agonist; % predicted FEV_1=actual FEV_1 divided by standard predicted FEV_1 times 100%; SABA=short-acting beta-agonist.; SD=standard deviation.

9.2.2. Subgroups (US Versus Non-US, Adolescents)

Demographic and baseline disease characteristics for Studies 3081, 3082, and 3083 are provided for adolescents aged 12 to 17 years in Table 36 and for United States (US) versus non-US in Table 37.

Table 36: Demographics and Baseline Characteristics – Subjects 12 to <18 Years of Age (Studies 3081, 3082, and 3083)

Demographic or baseline characteristic	Study 3081	Study 3082	Study 3083
Demographics			
Age, mean in years	14.47	13.85	14.50
Asthma duration, mean in years	11.362	8.280	10.088
Pulmonary function tests			
Pre-bronchodilator FEV_1, mean % predicted	74.014	82.717	91.817
Pre-bronchodilator FEV_1/FVC ratio, mean	0.751	0.712	0.749
Reversibility, mean % ΔFEV_1 post-SABA	21.1%	31.0%	26.9%
Eosinophil counts			
Baseline mean blood eosinophil count/µL	803	583	414
Exacerbation history			
Mean number of exacerbations in previous year	2.636	2.833	2.083
Percentage patients with ≥2 exacerbations in previous year	40%	54%	58%
Percentage patients with ≥3 exacerbation in previous year	40%	31%	25%
Background treatments for asthma (%)[a]			
Moderate-dose ICS	87%	69%	83%
High-dose ICS[b]	13%	31%	17%
Non-ICS controller drug[c]	93%	92%	58%
OCS (IVRS)	NA	8%	0
OCS (CRF)[d]	NA	8%	0

a. All patients had to be on ICS background therapy and could have been receiving any combination of background therapies (ICS with or without another controller [non-ICS and/or OCS]; therefore, some patients may be counted more than once in each category).

b. ICS doses that are considered to be high are based on consideration of comparability tables in the National Asthma Education and Prevention Program (see Figure 4.8b in the guidance; NAEPP 2007) and the Global Initiative for Asthma (see Box 3-6 in the guidance; GINA 2014) and the product labels.

c. This category includes drugs in addition to moderate to high doses of ICS.

d. OCS was a stratification factor only for Studies 3082 and 3083. OCS is not captured as a background treatment for Study 3081 and is therefore not available.

CRF=case report form; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; ICS=inhaled corticosteroid; IVRS=interactive voice response system; NA=not available; OCS=oral corticosteroid; SABA=short-acting beta-agonist. .

Table 37: Demographics and Baseline Characteristics – US versus non-US Subjects (Studies 3081, 3082, and 3083)

Demographic or baseline characteristic	Study 3081		Study 3082		Study 3083	
	US	Non-US	US	Non-US	US	Non-US
Demographics						
Age, mean in years	42.02	44.97	43.24	47.25	42.61	47.29
Asthma duration, mean in years	20.288	20.388	26.077	18.041	24.298	17.983
Pulmonary function tests						
Pre-bronchodilator FEV_1, mean % predicted	71.560	69.317	62.932	64.558	69.477	69.190
Pre-bronchodilator FEV_1/FVC ratio, mean	0.717	0.642	0.649	0.638	0.698	0.669
Reversibility, mean % ΔFEV_1 post-SABA	26.1%	24.8%	23.8%	26.6%	24.7%	28.6%
Eosinophil counts						
Baseline mean blood eosinophil count/µL	604	619	677	657	597	653
Exacerbation history						
Mean number of exacerbations in previous year	2.099	1.990	1.775	2.022	1.633	1.958
Percentage patients with ≥2 exacerbations in previous year	27%	23%	41%	40%	29%	42%
Percentage patients with ≥3 exacerbation in previous year	17%	16%	20%	21%	16%	20%
Background treatments for asthma (%)[a]						
Moderate-dose ICS	72%	64%	61%	55%	68%	58%
High-dose ICS[b]	28%	36%	39%	45%	32%	42%
Non-ICS controller drug[c]	79%	87%	97%	86%	77%	84%
OCS (IVRS)	NA	NA	14%	20%	6%	12%
OCS (CRF)[d]	NA	NA	12%	13%	0	10%

a. All patients had to be on ICS background therapy and could have been receiving any combination of background therapies (ICS with or without another controller [non-ICS and/or OCS]; therefore, some patients may be counted more than once in each category).
b. ICS doses that are considered to be high are based on consideration of comparability tables in the National Asthma Education and Prevention Program (see Figure 4.8b in the guidance; NAEPP 2007) and the Global Initiative for Asthma (see Box 3-6 in the guidance; GINA 2014) and the product labels.
c. This category includes drugs in addition to moderate to high doses of ICS.
d. OCS was a stratification factor only for Studies 3082 and 3083. OCS is not captured as a background treatment for Study 3081 and is therefore not available.

CRF=case report form; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; ICS=inhaled corticosteroid; IVRS=interactive voice response system; NA=not available; OCS=oral corticosteroid; SABA=short-acting beta-agonist; US=United States of America.

9.3. Efficacy and Patient-Reported Outcomes Endpoints

9.3.1.1. Lung Function and Asthma Control

Pulmonary Function Tests

Pulmonary function tests were performed using spirometry, and the parameters of FEV_1, FVC, and $FEF_{25\%-75\%}$ were evaluated. Absolute FEV_1 is considered to be an appropriate measure of asthma control, as endorsed by the guidelines (GINA 2014, NAEPP 2007).

Short-Acting Beta-Agonist Use

Patients reported their SABA use to evaluate their level of asthma control. The number of times SABA therapy was used was recorded. Patients were asked to recall if SABA therapy was used within the last 3 days of the scheduled visit (yes or no), and if so, how many puffs were used.

Blood Eosinophil Counts

The blood eosinophils were measured centrally using a standard complete blood count with differential blood test. The Phase 2 Study Res-5-0010 also formally assessed the percentage of sputum eosinophils at baseline and end of treatment.

9.3.1.2. Patient-Reported Outcomes

Patients completed a battery of questionnaires to evaluate their level of asthma control and quality of life.

Asthma Control Questionnaire

The ACQ was developed and validated by Juniper et al 1999 to measure asthma control. The ACQ has been widely used and consists of 7 items: 6 self-assessment questions and an FEV_1 measurement. Each of the items that comprise the ACQ is scored on a scale of 0 to 6, where higher scores indicate poorer asthma control and lower scores indicate better asthma control. For the purpose of analysis, the overall ACQ score for a visit was presented as the average of the individual item scores. As defined by the NAEPP Expert Panel Report 3 (NAEPP 2007), patients with overall ACQ scores of ≤ 0.75 have asthma that is well controlled, patients with overall ACQ scores of 0.76 to 1.4 have asthma with symptom control that is indeterminate, and patients with overall ACQ scores of ≥ 1.5 have asthma that is not well controlled.

Asthma Quality of Life Questionnaire

The AQLQ (Juniper et al 1999) consists of 32 questions that span 4 domains (symptoms, activity limitations, emotional function, and environmental stimuli) administered as a self-assessment. Patients were asked to recall their experiences during the last 2 weeks and to respond to each question on a 7-point scale (7=no impairment, 1=severe impairment). Five of the activity questions are "patient-specific," which means that each patient identifies and scores 5 activities in which they are limited by their asthma. These 5 activities were identified at the first visit and retained for all subsequent follow-up visits.

Asthma Symptom Utility Index

The ASUI is a validated, 11-item instrument designed to assess the frequency and severity of asthma symptoms (cough, wheezing, dyspnea, and nighttime awakenings) and side effects (ie, of

asthma medication) reported during the preceding 2 weeks, weighted by patient preferences (Revicki et al 1998). Scores range from 0 (worst possible symptoms) to 1 (no symptoms). ASUI scores were calculated according to Revicki et al 1998 and Bime et al 2012.

9.4. Statistical Considerations for Efficacy Analysis

9.4.1. Summary of Analyses by Study

Table 38: Summary of Statistical Analyses for Clinical Asthma Studies Utilizing the 3.0 mg/kg Dose

Study/Phase/ Sample size	Statistical analyses	Multiplicity control
Res-5-0010/ 3.0 mg/kg: (53) PBO: (53)	Primary efficacy analysis: ANCOVA testing the difference between the 2 groups, in the ITT analysis set, with adjustment for baseline ACQ score, treatment group, and stratification factor.	No adjustments for multiple comparisons
3081/ 0.3 mg/kg: (104) 3.0 mg/kg: (106) PBO: (105)	Primary efficacy analysis: MMRM with fixed effects (treatment, stratification factors, sex, visit, interaction of treatment and visit), covariates (height, baseline value), and patient as the random effect. An unstructured covariance matrix was used for the within-patient correlation modeling. Secondary efficacy endpoints: change from baseline in AQLQ score, ACQ score, ASUI score, SABA use, blood EOS count, and other measures of lung function (% predicted FEV_1, FVC, and $FEF_{25\%-75\%}$) (using the same MMRM model as described for the primary efficacy variable)	Primary: hierarchical testing for the 2 doses vs placebo with reslizumab 3.0 mg/kg being the first. No control for other efficacy.
3082: 3.0 mg/kg: (245) PBO: (244) 3083: 3.0 mg/kg: (232) PBO: (232)	Primary efficacy analysis: Negative binomial model that included the treatment group and stratification factors and the logarithm of follow-up time as an offset variable. Per FDA request, the follow-up time excluded the summed duration of CAE events. An analysis with an offset variable, without the exclusion of CAE duration, was a pre-defined sensitivity analysis. Secondary efficacy endpoints: Change in FEV_1, overall change in FEV_1, change in AQLQ score, overall change in ACQ score, time to first CAE, overall change in ASUI score, overall change in SABA usage, and overall change in blood eosinophil count. Changes are from baseline to week 16 (landmark). Overall changes are from baseline over 16 weeks (weighted average across all timepoints). These endpoints were analyzed using a MMRM with treatment group, visit, treatment by visit interaction, and stratification factors as fixed effects and patient as a random effect. Time to first CAE used the Cox proportional hazard model accounting for treatment and stratification factors.	A fixed-sequence multiple-testing procedure was implemented to test the primary variable first, followed by the secondary variables according to the order presented to the left. No control for other efficacy measures.

Table 38: Summary of Statistical Analyses for Clinical Asthma Studies Utilizing the 3.0 mg/kg Dose (Continued)

Study/Phase/ Sample size	Statistical analyses	Multiplicity control
3084/ 3.0 mg/kg: (398) PBO: (98)	Primary efficacy analysis: Linear regression model, including treatment, blood EOS count at baseline, and the interaction of treatment and eosinophil count in the Full Analysis Set. Interaction was tested at the 10% significance level. (A significant interaction indicated that treatment difference varies by baseline eosinophil count.) Secondary efficacy variables: Pulmonary function as measured by % predicted FEV_1, FVC, $FEV_{25\%-75\%}$, SABA use, blood eosinophil count, and ACQ score	A fixed-sequence multiple-testing procedure was implemented to test the primary variable and key secondary variables in the order of primary variable first followed by overall change from baseline in FEV_1 over the 16 weeks and overall change from baseline in ACQ over 16 weeks. No control for other efficacy measures.
3085/ N=1051	All analyses were descriptive	

[a] Covariates for baseline values were also included in the model; for pulmonary function test analyses, covariates for height and sex were included as well. Unstructured covariance matrix was used for the within-patient correlation modeling.

ACQ=Asthma Control Questionnaire; ANCOVA=analysis of covariance; AQLQ= Asthma Quality of Life Questionnaire; ASUI= Asthma Symptom Utility Index; CAE=clinical asthma exacerbation; FDA=Food and Drug Administration; $FEF_{25\%-75\%}$=forced expiratory flow during the middle half of the forced vital capacity; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; ITT=intent-to-treat; MMRM=mixed effect model for repeated measures; PBO=placebo; SABA= short-acting beta-agonist.

Note: All studies were multicenter.

9.4.2. Sample Size Calculations

In Study 3081, the primary efficacy variable was the overall change from baseline in FEV_1 over the 16 weeks of treatment. The standardized effect size (difference/sd) used for both reslizumab doses for the sample size calculations was 0.47; this is based on results from Study Res-5-0010. A total of 300 patients (100 per group) provided at least 90% power to detect a difference between the reslizumab and placebo doses using a 2-sided t-test at a 2-sided significance level of 5%.

In Studies 3082 and 3083, a total of 460 to 480 patients (230 to 240 patients per group) provided approximately 90% power at the 2-sided significance level of 5% to detect a 33% reduction in CAE rate by reslizumab as compared with placebo. Based on literature search, the assumed placebo annualized exacerbation rate was 1.2. This power estimate was based on computer simulations and took into account 5% to 9% drop-out.

9.4.3. Analysis Sets

In Study 3081, the Full Analysis Set (FAS) included all randomized patients who were treated with at least 1 dose of study drug, and serves as the primary analysis for all efficacy endpoints; however, pulmonary function tests, ACQ, AQLQ, ASUI, and SABA assessments were excluded from the FAS 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. These medications include (1) oral or systemic corticosteroids or (2) addition of a LABA or a long-acting muscarinic antagonist if not taken at baseline. FAS without exclusion of assessment, as described above, was predefined as a sensitivity analysis.

In Studies 3082 and 3083, the Randomized Set, defined as all patients who were randomly assigned to a treatment at enrollment, regardless of whether or not a patient took any study drug, was the primary analysis set for efficacy analysis. This is the same as the Intent-to-Treat Analysis Set.

9.4.4. Handling Missing Data

The primary analysis for Studies 3081, 3082, and 3083 did not impute missing data (see Section 9.4.3). However, sensitivity for missing data included multiple imputations (MI; prespecified) and tipping point analysis (requested by the FDA at the pre-BLA meeting).

9.4.4.1. Multiple Imputations

A simulation technique in which missing values are replaced by $m > 1$ simulated plausible values representing the uncertainty about the (unobserved) right value. This step generates m complete data sets, and each is analyzed using the pre-planned analysis. The results of the m analyses are combined to produce estimates and CI which incorporate missing-data uncertainty.

MI was implemented differently for Studies 3081, 3082, and 3083 due to the difference in data nature, but a similar principle was used in all studies. Missing values occurring after early termination due to an exacerbation were classified as Not Missing At Random (NMAR), while other missing values were classified as Missing At Random (MAR). For MAR, the imputation was done from the distribution of observed values according to combinations of treatment and randomization strata. For NMAR, the imputation was done from the distribution of placebo patients at the same randomized strata (regardless of treatment arm).

9.4.4.2. Tipping Point

In the tipping point analysis, MIs were used repeatedly, and in each of its applications, the distribution of imputed values was shifted further to represent a larger distance between MAR and NMAR, making the treatment effect less and less in favor of the active drug. The methodology was implemented differently to the 3 studies due to the difference in data nature, but the common theme was that missing placebo observations were imputed based on the distribution of the observed placebo (assuming MAR). All missing values in the reslizumab arm were imputed from a shifted distribution of the nonmissing reslizumab observations to represent a smaller and smaller effect. The tipping point is the point in which the study conclusion is reversed, ie, p-value >5%. If the tipping point consists of unreasonable values, then the robustness of the study results is supported.

9.4.5. Methods for Pooling Studies in Integrated Efficacy Analyses

Pooling of studies was predefined in the statistical analysis plan for the integrated summary of efficacy for the BLA (that was finalized prior to Study 3082/3083 unblinding) and was made on a patient-level basis (as opposed to meta-analysis or integration of summary statistics). The 2 predefined efficacy cohorts were a 16-week cohort that consisted of 16-week data of patients from Studies 3081, 3082, and 3083, and a 52-week cohort that consisted of 52-week data of patients from Studies 3082 and 3083. Models used were the same models used in the individual studies with the addition of study as a covariate. No multiplicity control was applied to any of the integrated analyses.

9.5. Clinical Pharmacology

The studies that contributed patients/subjects to the characterization of the PK, PD, and/or exposure-response relationships of reslizumab were as follows:

- 4 Phase 1 studies (C38072/1102 and C38072/1107 in healthy subjects; I96-350 in adults with asthma, and P01942 in adult patients with nasal polyposis)
- 2 Phase 2 studies (P00290 and Res-5-0010 in adults with asthma)
- 4 Phase 3 studies (C38072/3081, C38072/3082, and C38072/3083 in adults with asthma and the open-label extension C38072/3085)

From these studies, the total number of subjects was as follows:

- 130 healthy subjects
- 239 adult patients with asthma or nasal polyposis in Phase 1 and 2 studies
- 1163 in Phase 3 studies

9.5.1. Pharmacokinetics Methods - Dosing and Sampling Schedules

All data for the PK analysis were obtained after iv infusion, except for the 2 lowest dose levels (0.03 and 0.1 mg/kg) in Study I96-350, which were administered via iv bolus. Generally, the duration of infusions ranged from 15 to 50 minutes. However, the rate and/or duration of infusion may have varied from subject to subject. Multiple-dose studies generally used a regimen of dosing every 4 weeks.

The sampling schedule for measurement of serum concentrations of reslizumab after administration of iv reslizumab in each study is detailed in Table 39.

Table 39: Pharmacokinetic Sampling Schedules for Measurement of Concentrations of Reslizumab after Administration of Intravenous Reslizumab

Study no./ Phase	Pharmacokinetic sampling times
I96-350 Phase 1	All groups: predose (0 hours) and 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 12, 24, and 48 hours after dose Groups 1 and 2: days 8, 15, 30, 60, 90, and 120+ Groups 3 to 5: days 8, 15, 30, 60, 90, 120, 150, and 180
P01942 Phase 1	Predose (0 hours) and 0.5, 1, 2, 4, 6, 8, 12, 16, 20. 24, and 48 hours after dose, and at weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, and 36
C38072/1102 Phase 1	Period 1: before and after infusion, 12 and 24 hours after start of infusion, and on days 3, 5, 7, 10, 14, and 21 Periods 2 and 4: before and after infusion, 12 and 24 hours after start of infusion Period 3: before and after infusion, 12 and 24 hours after the start of infusion, and on day 3 Period 5: before and after infusion, 12 and 24 hours after start of infusion, on days 3, 5, 7, 10, 14, and 21, and at follow up visits (28 [±2] days, 56 [±2] days, and 84 [±2] days after the final drug administration)
C38072/1107 Phase 1	Predose (0 hours) and 6, 12, and 24 hours after the start of study drug administration on day 1, and on days 3, 5, 7, 10, 14 (±1 day), 21 (±1 day), 28 (±1 day), 42 (±2 days), 56 (±2 days), 84 (±2 days), 112 (±3 days), and 140 (±3 days)
P00290 Phase 2	Day 1 and week 12: before dose (0 hours) and at 1, 4, and 96 hours after administration Weeks 2, 4, 9 (all ±2days), 14, 16, 20, 26, 32, and 38 (all ±1 week)
Res-5-0010 Phase 2	Baseline, week 15, and 90-day follow-up
3081 Phase 3	Baseline, before and after completion of each infusion at weeks 4, 8, and 12, and at week 16 or early withdrawal. US investigational centers: also at day 2 or 3 and week 2 or 3 Also from patients experiencing a serious adverse event, adverse event leading to withdrawal, or an exacerbation of asthma symptoms
3082 Phase 3	Before each infusion at baseline and at weeks 4, 8, 12, 16, 24, 36, and 48 After completion of the infusion at baseline and weeks 16 and 36 US investigational centers: also at days 2 and 3 and weeks 2 and 3 Also from patients experiencing a serious adverse event, adverse event leading to withdrawal, or an exacerbation of asthma symptoms
3083 Phase 3	Samples collected only in the event of a serious adverse event, adverse event leading to withdrawal, or an exacerbation of asthma symptoms
3085 Phase 3	Samples collected only in the event of a serious adverse event, adverse event leading to withdrawal, or an exacerbation of asthma symptoms

Source: Clinical Study Reports for Studies C38072/1102, C38072/1107, I96-350, P00290, P01942, Res-5-0010, C38072/3081, C38072/3082, C38072/3083, and C38072/3085.
US=United States.

9.5.2. Population Pharmacokinetic Analyses

A PPK model of reslizumab was developed to provide a comprehensive description of the PK of reslizumab in patients.

The model used data from 6 studies in patients with moderate to severe asthma, eosinophilic asthma, or nasal polyposis (Studies I96-350, P01942, P00290, Res-5-0010, 3081, and 3082) and 2 studies in healthy subjects (Studies 1102 and 1107). Covariate analysis included assessment of

the effect of select demographic factors (age, sex, race, and body size), laboratory tests, ADAs, and frequently used concomitant medications (>10% of patients) on the PK of reslizumab.

The datasets used for the PPK modeling included patients 12 years and older from all reslizumab iv treatment groups in the previously mentioned studies with available dosing data and at least 1 measurable postdose reslizumab concentration. A total of 10314 serum reslizumab concentrations from 804 subjects (130 healthy subjects from Phase 1 studies, 40 patients from Phase 1 studies, 196 patients from Phase 2 studies, and 438 patients from Phase 3 studies) were used in the development of the PPK model.

In general, the procedures for the development of the final PPK model included exploratory data analysis, base structural model development, evaluation of covariate effects, model refinement, and model evaluation. Nonlinear mixed-effect modeling was used to describe the PK characteristics of reslizumab.

The disposition of reslizumab was well described by a 2-compartment model with zero order input and first order elimination. During development of the model, 2 relationships were added into the model based upon initial findings: the influence of body weight on CL (linear relationship) and body weight on V_c (described by a power function). No other covariates were found to be significant. The final PPK model was used to generate individual estimates of reslizumab exposure after each dose.

9.5.3. Pharmacokinetic/Pharmacodynamic Methods

Data from selected patient studies (Studies I96-350, P00290, Res-5-0010, 3081, and 3082) were pooled for PPK/PD analyses using measures of efficacy and/or safety. The dataset used in the PPK/PD modeling included patients in the Phase 2 and 3 studies who received iv reslizumab or placebo and had data for the relevant endpoint(s). Patients included in the PK/PD analysis were as follows:

- 12 years and older
- had baseline sputum eosinophils ≥3% or blood eosinophils ≥400 cells/μL

Exploratory analyses were performed for the relationship between reslizumab exposure and eosinophil counts, selected pulmonary function tests (FEV_1, FVC, and $FEF_{25\%-75\%}$), ACQ scores, CAEs, adverse events of muscle disorders, and safety laboratory assessments (CPK). When model development was warranted for PD measures/measures of efficacy, stationary covariates including age, race, sex, baseline weight, baseline body mass index (BMI), and baseline value of the endpoint modeled (eg, eosinophil count, FEV_1, or ACQ score) were evaluated. Stationary covariates evaluated in the safety analysis of muscle disorder adverse events were age, race, sex, baseline weight, and baseline BMI.

The final models for eosinophil count, FEV_1, and ACQ were validated using a simulation-based visual predictive check methodology to assess concordance between the model-based simulated data and the observed data. The final model for adverse events of muscle disorders was validated using 2 methods applied to the logistic regression model.

The final PK/PD model for peripheral blood eosinophil count was an indirect response model used to describe the relationship between reslizumab concentration and inhibition of peripheral blood eosinophil response. The influence of age, body weight, sex, race (Caucasian, black or

African-American, Asian, or "other"), concomitant leukotriene antagonists, anticholinergics, or theophylline was evaluated in the model, and none of the covariates was found to be a statistically significant predictor of variability in eosinophil count.

The final PK/PD model for FEV_1 was composed of a sigmoid E_{max} time course model, including parameters estimating the baseline FEV_1, maximum response in FEV_1 (E_{max}), time to 50% of the maximum effect, and the sigmoidicity factor. Sex, race, and age were statistically related to baseline FEV_1, whereby male sex, Caucasian race, and younger age were associated with higher baseline FEV_1. Baseline BMI was statistically related to E_{max}, whereby patients with lower BMI have higher predicted maximum FEV_1 response. These significant covariate effects on baseline FEV_1 are consistent with known relationships between increasing age and reduction in FEV_1, as well as the recognized lower lung volume and capacity in females compared to males as well as racial differences in FEV_1.

The population PK/PD model for ACQ scores was an inhibitory sigmoid E_{max} time course model, including parameters estimating the baseline ACQ score, maximum reduction in ACQ score (E_{max}), time to 50% of the maximum effect, and the sigmoidicity factor. The influence of covariates (age, race, sex, baseline weight, baseline BMI, baseline ACQ, and concomitant leukotriene antagonists, anticholinergics, and theophylline) on variability in the time course of ACQ scores and reslizumab drug effect was evaluated; however, none were found to be statistically significant predictors of variability in the PK/PD response.

The final probability of muscle disorders was modeled as the sum of the drug effect described by an increasing linear function of the predicted reslizumab concentration and a linear function of age, which was found to be a statistically significant predictor of the probability of muscle disorders.

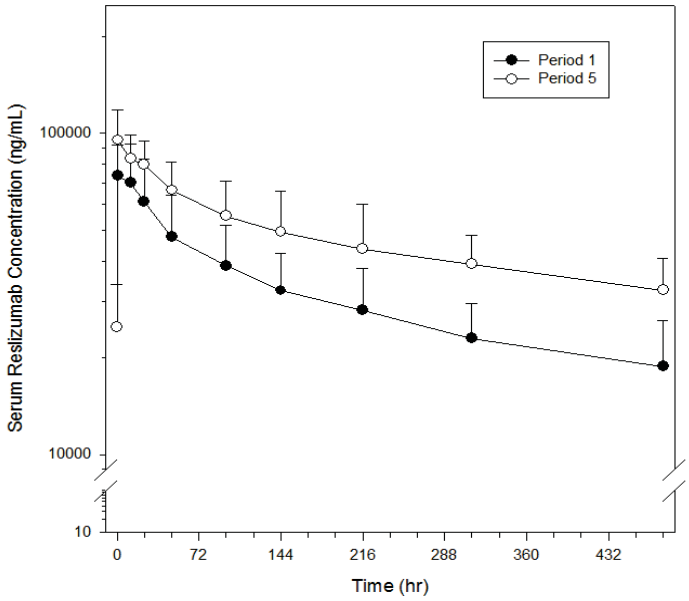
In addition, exposures from individuals experiencing a serious adverse event, adverse event leading to withdrawal, or an exacerbation of asthma symptoms in each of the previously mentioned studies as well as in Studies 3083 and 3085 were compared with the PPK model-predicted concentrations. This analysis was performed in order to evaluate whether there were differences in exposure in patients experiencing such events.

9.6. Summary of Pharmacokinetics and Pharmacokinetics/Pharmacodynamics Results

9.6.1. Pharmacokinetics

Mean (±SD) serum reslizumab concentrations after single and multiple iv infusions of 3.0 mg/kg reslizumab to healthy adults are displayed in Figure 30.

Figure 30: Mean (±SD) Serum Reslizumab Concentration-Time Profile Following Single (Period 1) and Multiple (Period 5) 3.0 mg/kg Intravenous Infusions of Reslizumab in Healthy Adults (Study 1102)



SD=standard deviation.

The PK of reslizumab are similar after iv administration in patients and in healthy subjects. After a single iv dose, maximum serum reslizumab concentrations are typically attained at the end of the infusion and generally decline from peak in a biphasic manner. The serum concentration-time curve after multiple doses is qualitatively similar to that observed after a single dose. The mean terminal half-life of reslizumab after multiple-dose administration is approximately 24 days, resulting in an accumulation ratio of approximately 1.5- to 1.9-fold. Systemic exposure, as assessed by maximum concentration (C_{max}) and area under the curve (AUC), increases in an apparently dose-proportional manner over the dose range of 0.3 through 3.0 mg/kg.

PPK analyses suggest that reslizumab has a central volume of distribution of approximately 3 L and a peripheral volume of distribution of approximately 2 L, suggesting minimal distribution to extravascular tissues. Similar to other monoclonal antibodies, reslizumab is believed to be degraded by enzymatic proteolysis into small peptides and amino acids. As reslizumab binds to a soluble target, linear non-target-mediated clearance is expected. Given the proposed clearance mechanism of reslizumab, renal or hepatic impairment is unlikely to affect systemic exposure to reslizumab. The lack of effect of mild or moderate renal impairment or normal to Grade 1/2 elevations in liver function tests on the PK of reslizumab was confirmed via the PPK analyses. Given the characteristics of reslizumab, concomitant use of other medications is unlikely to affect systemic exposure to reslizumab. Results of studies in cultured human hepatocytes indicate that IL-5 and reslizumab are unlikely to affect cytochrome P450 enzymes commonly implicated in drug-drug interactions. The results of the PPK analyses confirmed that concomitant use of leukotriene antagonists or systemic corticosteroid classes, as well as the individual drugs prednisone and montelukast, did not impact systemic exposure to reslizumab.

Other than a study performed to compare the PK, PD, and immunogenicity of reslizumab in Japanese and non-Japanese subjects, there were no dedicated studies for the assessment of the effect of demographic characteristics on the PK of reslizumab. Results of PPK analyses demonstrated that age, sex, and race (Caucasian, black, Asian, "other") have no notable impact on the PK of reslizumab. The PPK analyses also demonstrated no clear indication of reduced exposure to reslizumab in patients who developed antibodies to reslizumab (ie, were ADA positive).

PPK analyses demonstrated that heavier body weight results in more rapid clearance and larger volume of distribution with increases of approximately 50% to 60% in these parameters for a 2-fold increase in weight. These increases translate into shorter half-life and lower exposures at higher weights for a given fixed dose of reslizumab. This finding supports the appropriateness of weight-based dosing for iv reslizumab in order to produce similar exposures across the full population and minimize the potential for ineffective serum concentrations in heavier patients or higher drug exposures in lighter patients.

9.6.2. Pharmacokinetics/Pharmacodynamics

The results of the PK/PD analyses support the appropriateness of the proposed therapeutic dosing regimen of reslizumab for the treatment of patients with eosinophilic asthma (Section 3.2). The proposed 3 mg/kg dosing regimen every 4 weeks is anticipated to produce near-maximal inhibition of the eosinophil response. The model-predicted decrease in eosinophil counts with this dosing regimen exhibits limited fluctuation over a dosing interval. A statistically significant correlation between model-predicted average steady-state concentration and FEV_1 was observed, with improvement in FEV_1 being more pronounced as exposure increases. A corresponding decrease in model-predicted ACQ values is observed with the increase in model-predicted exposure. As systemic exposure to reslizumab increases, the ACQ score decreases. These findings confirm that the observed exposure-related changes in eosinophil levels and FEV_1 are associated with an exposure-related improvement in symptoms. The effect on ACQ was relatively quick: time to 50% of the maximum effect was estimated at 2.9 weeks. Time to 50% of the maximum effect on FEV_1 was 13.3 weeks.

PK/PD analyses using measures of safety indicate that there is no apparent trend toward an increase in QTcF with increasing serum concentrations of reslizumab. Likewise, no exposure-response relationship was observed for CPK. The modeled probability of experiencing a muscle disorder adverse event (based on a group of interrelated preferred terms) increases with increasing reslizumab concentration; this relationship was influenced by 5 overweight/obese female patients in the reslizumab group with concentrations of >60 µg/mL with nonspecific complaints of back pain/lower back pain (n=3) or foot pain (n=2). However, as there was no observed difference between placebo- and reslizumab-treated patients in a broad-based group of muscle disorder adverse event terms beyond the adverse drug reaction of myalgia, the clinical significance of the modeled exposure relationship is unclear.

9.7. Nonclinical Overview

Reslizumab works by binding to IL-5 and preventing its binding to the IL-5 receptor, thereby interfering with the recruitment and mobilization of eosinophils. The activity of reslizumab has been studied in vitro using IL-5 receptor binding assays and by examining IL-5-mediated

cell-based response. Additional in vitro studies have been performed to characterize the binding of reslizumab and to study reslizumab cross-reactivity. In vivo, the biological activity of reslizumab has been measured in monkeys, rabbits, guinea pigs, and mice using antigen- or human IL-5-induced bronchoprovocation as methods to induce pulmonary eosinophilia and airway hyperresponsiveness.

A series of general safety pharmacology studies have been performed with reslizumab and included examination of changes in behavior, neurologic parameters, autonomic function, and hemodynamic and electrocardiographic parameters. Toxicokinetic evaluation revealed a long residence time (half-life) of the antibody, consistent with the general feature of IgG-G4 molecules and in support of the dosing regimen. The toxicokinetic analyses also confirmed the exposure to the drug in the animal species used in the toxicology program.

A full toxicology package corresponding to the ICH-S6 guideline was performed, and it included chronic (6-month) studies in mice and monkeys, safety pharmacology studies, genotoxicity studies, reproduction toxicity studies, and juvenile toxicity and local toxicity studies.

Additionally, as required by the FDA, a nonclinical carcinogenicity evaluation with reslizumab was performed. The carcinogenicity study conducted with reslizumab was a 26-week iv study using a transgenic mouse model (001178-T [hemizygous] CByB6F1-Tg(HRAS)2Jic mice [rasH2]). The transgenic rasH2 mouse was proposed for carcinogenicity evaluation, as the model can detect both genotoxic and nongenotoxic carcinogens, and the rasH2 mouse demonstrated the expected PD response to reslizumab, a dose-related reduction in allergen-induced lung eosinophils. In that regard, the rasH2 mouse was determined to be an appropriate model for the evaluation of reslizumab carcinogenicity by the FDA Carcinogenicity Assessment Committee (CAC). Dose levels for evaluation in the 26-week carcinogenicity study were also considered to be appropriate by CAC.

The safety program was discussed with the FDA at various occasions, and at a Type B End-of-Phase-2 FDA meeting, it was noted that the nonclinical safety program appeared generally adequate to support the clinical development program and application for the proposed indication. Pivotal studies were Good Laboratory Practice compliant and were performed using validated methods to detect serum concentrations of the drug and ADAs.

In 4-week repeat-dose studies, reslizumab was well tolerated by mice and monkeys given 2 doses of 1, 5, or 25 mg/kg of reslizumab 14 days apart; the no-observed-effect level (NOEL) was 5 mg/kg in male mice and 25 mg/kg or more in female mice and monkeys. The 6-month repeat-dose studies in mice and monkeys with once-monthly treatment showed no toxicity and a NOEL of reslizumab of 25 mg/kg or more.

Reslizumab was not genotoxic and did not affect reproductive parameters. In safety pharmacology studies, reslizumab had no effect on parameters related to organ function.

Reslizumab was not considered carcinogenic nor did it increase tumor rate in a pharmacologically relevant transgenic mouse model at iv doses up to 516 mg/kg/dose administered once every 2 weeks for 26 weeks.

In studies conducted to assess local tolerability after administration of reslizumab intra-arterially, intravenously, or intramuscularly, the histopathological effects observed were similar to saline.

The nonclinical program has indicated that reslizumab is effective in relevant animal models, and no safety issues were identified. Issues such as cross-reactivity to an unrelated antigen and immunogenicity were thoroughly investigated. These investigations revealed no concern for clinical use.