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APPLICATION NUMBER:

761033Orig1s000

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

Division of Pulmonary, Allergy and Rheumatology Drug Products (HFD-570)

Application #: BLA-761033

Sponsor: Teva Respiratory, LLC

Product: Cinqair (reslizumab)

Review Date: March 14, 2016

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document	SD	eCTD	Submit Date	Receipt Date
Clinical/Safety Update	9	0008	7/27/2015	7/27/2015
Clinical/Response To Information Request; Biometrics/Response To Information Request	12	0011	8/21/2015	8/21/2015
Clinical/Response To Information Request	15	0014	9/11/2015	9/11/2015
Clinical/Response To Information Request	17	0016	9/22/2015	9/22/2015
Clinical/Response To Information Request	19	0018	10/5/2015	10/5/2015
Clinical/Response To Information Request	21	0019	10/9/2015	10/9/2015
Clinical Pharmacology/Response To Information Request; Clinical/Response To Information Request	22	0021	10/16/2015	10/16/2015
Clinical/Response To Information Request	23	0022	10/20/2015	10/20/2015
Clinical/Response To Information Request	28	0027	11/13/2015	11/13/2015
Clinical/Response To Information Request	34	0033	12/4/2015	12/4/2015
Clinical/Response To Information Request	49	0048	1/25/2016	1/27/2016

REVIEW SUMMARY: See Medical Officer Review submitted December 17, 2015

RECOMMENDED REGULATORY ACTION: None. Safe to proceed.

Medical Reviewer: Kathleen M. Donohue, MD

Medical Team Leader: Banu Karimi-Shah, MD

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/s/

KATHLEEN M DONOHUE
03/14/2016

CLINICAL REVIEW

Application Type	Biologics licensing application
Application Number(s)	761033
Priority or Standard	Standard
Submit Date(s)	April 15, 2015
Received Date(s)	April 15, 2015
PDUFA Goal Date	March 28, 2016
Division/Office	Division of Pulmonary, Allergy & Rheumatology Products
Reviewer Name(s)	Kathleen M. Donohue, MD
Review Completion Date	December 17, 2015
Established Name	Reslizumab
(Proposed) Trade Name	Cinqair
Applicant	Teva
Formulation(s)	Single-use vials of reslizumab (10 mg/mL) for intravenous administration, 100 mg per 10 mL
Dosing Regimen	3mg/kg IV every 4 weeks
Proposed Indication(s)	"reduce exacerbations, relieve symptoms and improve lung function in adults and adolescents (12 years of age and above) with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids"
Intended Population(s)	Adults and adolescents ≥ 12 years of age
Recommendation on Regulatory Action	Approval pending labeling revisions/agreement in patients ≥18 years of age and older [redacted] (b) (4)
Recommended Indication(s) (if applicable)	Asthma (exact indication language pending review)

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Glossary

ACQ	asthma control questionnaire
AE	adverse event
AQLQ	asthma quality of life questionnaire
ASUI	asthma symptom utility index
BLA	biologics licensing application
CFR	code of federal regulations
CPK	creatine phosphokinase
CRF	case report form
DB	double blind
DPI	dry powder inhaler
ECG	electrocardiogram
Eos	eosinophils
FAS	full analysis set
FEF	forced expiratory flow
FEV_1	forced expiratory volume in one second
FVC	forced vital capacity
GCP	good clinical practice
HFA	hydrofluoroalkane
ICH	International Conference on Harmonisation
ICS	inhaled corticosteroids
IgE	Immunoglobulin E
IL5	interleukin 5
IRT	interactive response technology
ISS	integrated summary of safety
LABA	long-acting beta agonist
MCID	minimal clinically important difference
MMRM	mixed-effect model repeated measurement
OCS	oral corticosteroids
OLE	open label extension
PC	placebo controlled
PEFR	peak expiratory flow rate
PG	parallel group
R	randomized
SABA	short acting beta agonist
SAE	serious adverse event
SD	standard deviation
ßHCG	beta-human chorionic gonadotropin

1 Executive Summary

1.1. Product Introduction

Teva has submitted a Biologics Licensing Application (BLA) in support of reslizumab. Reslizumab is an anti-interleukin 5 (anti-IL-5) monoclonal antibody intended as a treatment for asthma. This class also includes mepolizumab, which was discussed at an advisory committee meeting on June 11, 2015 (1). Mepolizumab subsequently was approved on November 4, 2015 as add-on maintenance treatment for patients with severe asthma aged 12 years and older with an eosinophilic phenotype. For reslizumab, the dose proposed for marketing is 3 mg/kg intravenously every four weeks. The proposed indication is to "reduce exacerbations, relieve symptoms and improve lung function in adults and adolescents (12 years of age and above) with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids."

Reslizumab has been studied in several different patient populations, including asthma, eosinophilic esophagitis, nasal polyposis, hypereosinophilic syndrome, and eosinophilic gastroenteritis. This review will focus on the asthma studies, referring to studies in other patient populations where relevant to the discussion.

Teva submitted five principal efficacy and safety studies in support of the proposed asthma indication. Three studies essentially were conducted concurrently, beginning in February, March, and April of 2011. They were a 16-week lung function study (Study 3081) and two 52-week exacerbation studies (Studies 3082 and 3083). These studies were performed in patients 12 years of age and older with moderate to severe asthma and baseline blood eosinophil counts ≥ 400/µl. A fourth study, 3084, was a 16-week lung function study in patients unselected for baseline eosinophil levels; it was designed to support Teva's inclusion criterion of an eosinophil count ≥ 400/µl in the other studies. It began in February 2012. Study 3085 was an open-label extension study that began in June 2011 and enrolled participants from Studies 3081, 3082, or 3083.

Efficacy was assessed in exacerbation studies and lung function studies. Study 3081 observed a mean 286 ml increase in forced expiratory volume in one second (FEV_1) for reslizumab 3.0 mg/kg compared to a mean 127 ml increase for placebo over 16 weeks (treatment difference of 160 ml with 95%CI (0.06, 0.26), p=0.002). Study 3082 observed an asthma exacerbation rate of 0.9 per year for reslizumab compared to 1.8 per year for placebo, a 50% reduction over 52 weeks (Rate Ratio 0.50 (95%CI 0.37, 0.67), p<0.0001). Study 3083 observed an exacerbation rate of 0.9 per year for reslizumab compared to 2.1 per year for placebo, a 59% reduction over 52 weeks (Rate Ratio 0.41 (95%CI 0.28, 0.59), p<0.0001). Study 3084 did not provide statistically significant evidence of interaction by eosinophil level. Evidence of efficacy was less

robust for subgroups with low enrollment. A paradoxical increase in asthma exacerbation rates was observed for adolescent, African American, and U.S. patients, though evidence for improvement in lung function generally was supportive.

The safety database includes the four efficacy and safety studies described above, plus an open-label extension study (3085) that evaluated the long-term safety of reslizumab. Several safety signals have emerged from a review of these data. Reslizumab treatment is associated with anaphylaxis. Reslizumab is manufactured in a murine cell line known to carry alpha-gal, and alpha-gal has been implicated in other cases of drug-induced anaphylaxis (2). However, preliminary testing conducted by the Applicant was negative for anti-alpha-gal IgE. These results are still under review by Dr. Joao Pedras Vasconcelos at the time of this review, but suggest that classic IgE-mediated anaphylaxis to another moiety in reslizumab may be a more likely mechanism. Reslizumab treatment also is associated with a muscle safety signal, characterized by muscle pain and creatine phosphokinase (CPK) elevations more so than muscle weakness (3, 4). Among patients taking oral corticosteroids at baseline, those randomized to reslizumab had a higher incidence of pneumonia compared to placebo. Lastly, the incidence of malignancy was higher in the reslizumab group compared to placebo in controlled studies (0.6% vs. 0.3%), as well as in comparison to national cancer registries.

The development program for reslizumab was marked by several limitations. First, dose-ranging data are limited. Second, there were more patients taking baseline oral corticosteroids in the placebo arm of the safety database. This imbalance could decrease the chance of detecting safety signals for which both steroids and reslizumab could play a role, such as infections or myopathy. Third, two study sites in Study 3084 were terminated for violations of good clinical practice, but adverse event data from their fifteen participants were improperly excluded from safety analyses, including a muscle safety case with CPK elevations. Lastly, there were several deficiencies in the collection of safety data, including failure to collect information regarding anaphylaxis events in a prospective manner, failure to capture post-infusion vital signs, infrequent measurement of serum chemistries, and so few details captured regarding adverse events that it was not possible to generate narratives retrospectively.

However, based on the conclusions regarding the risk-benefit assessment below and input from the Pulmonary-Allergy Drugs Advisory Committee (see Section X), this reviewer recommends reslizumab for approval in patients 18 years of age and older, with severe asthma and an eosinophilic phenotype. At this time, the risk-benefit assessment does not support approval in pediatric patients 12 to 17 years of age.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The trials for reslizumab were adequate and well controlled from an efficacy standpoint, and demonstrated statistically significant and clinically meaningful improvements in lung function and reductions in asthma exacerbations. Reslizumab 3mg/kg IV was studied in a lung function

study (n=315) and two exacerbation studies (n=953) as add-on therapy to standard of care. The lung function study observed an improvement in FEV_1 of 0.16 L with 95%CI (0.06, 0.26), p=0.002). The two exacerbation studies observed a 50% and 59% reduction in asthma exacerbations over 52 weeks (Rate Ratio 0.50 (95%CI 0.37, 0.67), p<0.0001 for Study 3082, Rate Ratio 0.41 (95%CI 0.28, 0.59), p<0.0001 for study 3083). Evidence of efficacy was less robust for subgroups with low enrollment, such as adolescents. Adolescents randomized to reslizumab had an apparent increase in asthma exacerbations, and an apparent decrease in lung function. A significant limitation of the development program is that baseline maintenance oral corticosteroid use was higher among those randomized to placebo. Sensitivity analyses suggest that the efficacy findings are robust to this imbalance. In summary, a physician who treated 1,000 patients with reslizumab for one year could expect to prevent 182 asthma exacerbations and 5 asthma hospitalizations.

1.3. Benefit-Risk Assessment

Clinical Review
Kathleen M. Donohue, MD
Biologics licensing application No. 761033
Cinqair (Reslizumab)

Benefit-Risk Summary and Assessment

Asthma with eosinophilic phenotype is a serious condition associated with chronic morbidity, including frequent exacerbations.

Reslizumab is an anti-IL5 monoclonal antibody intended for the treatment of asthma with eosinophilic phenotype. The trials for reslizumab were adequate and well-controlled, and demonstrated statistically significant and clinically meaningful improvements in lung function and reductions in asthma exacerbations. Baseline maintenance oral corticosteroid use was higher among those randomized to placebo. Sensitivity analyses suggest that the efficacy findings are robust to this imbalance. However, this limitation in the safety database would make it difficult to detect safety signals for which both oral corticosteroids and reslizumab may play a role, such as for infection or myopathy. There were additional limitations in the collection of safety data such that current risk estimates may prove to be underestimates.

A physician who treated 1,000 patients with asthma with eosinophilic phenotype with reslizumab for one year could prevent 182 asthma exacerbations and 5 asthma hospitalizations, but could expect to manage 3 additional cases of anaphylaxis, 3 additional cases of malignancy, and 46 additional cases of CPK elevations. Evidence of efficacy and safety was less robust for subgroups with low enrollment, such as adolescents. Adolescents randomized to reslizumab had an apparent increase in asthma exacerbations, and an apparent decrease in lung function. They were slightly more likely to report adverse events across a range of symptom organ classes than those randomized to placebo, though the nature of these adverse events was consistent with routine adolescent health problems.

Mepolizumab is an alternative anti-IL5 monoclonal antibody with comparable efficacy and a more favorable safety and tolerability profile. It is administered subcutaneously instead of intravenously. An increased risk of anaphylaxis, malignancy, or CPK elevations was not observed in the clinical trials for mepolizumab. This reviewer recommends approval for reslizumab, as it represents a modest addition to the armamentarium and may prove useful for patients who cannot tolerate mepolizumab. Due to the risk of anaphylaxis, reslizumab is not suitable for home administration. Labelling should be sufficient to address the safety concerns.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Asthma with eosinophilic phenotype affects 5% of asthma patients. These patients account for about 20% of those with refractory asthma. They have severe exacerbations prevented only by systemic corticosteroids. They tend to have airway remodeling with associated persistent airflow limitation. Lastly, elevated blood eosinophil levels are an independent risk factor for future asthma exacerbations	Asthma with eosinophilic phenotype is a serious condition associated with chronic morbidity.
Current Treatment Options	Mepolizumab, another anti-IL5 monoclonal antibody, administered subcutaneously Omalizumab, an anti-IgE monoclonal antibody Corticosteroids	Current treatment options for asthma with eosinophilic phenotype are reasonably effective. However, other additions to the treatment armamentarium would be useful, particularly for patients at risk of severe exacerbations who cannot tolerate mepolizumab.
Benefit	Reslizumab 3mg/kg IV was studied in a lung function study (n=315) and two exacerbation studies (n=953) as add-on therapy to standard of care. The lung function study observed an improvement in FEV1 of 0.16 L with 95%CI (0.06, 0.26), p=0.002). The two exacerbation studies observed a 50% and 59% reduction in asthma exacerbations over 52 weeks (Rate Ratio 0.50 (95%CI 0.37, 0.67), p<0.0001 for study 3082, Rate Ratio 0.41 (95%CI 0.28, 0.59), p<0.0001 for study 3083). An error in stratification led to an imbalance in baseline oral corticosteroid use; sensitivity analyses suggest that the efficacy findings are robust to this limitation.	The trials for reslizumab were adequate and well-controlled, and demonstrated statistically significant and clinically meaningful improvements in lung function and reductions in asthma exacerbations. A physician who treated 1,000 patients with reslizumab for one year could prevent 182 asthma exacerbations and 5 asthma hospitalizations.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Evidence of efficacy was less robust for subgroups with low enrollment, such as adolescents (n=35). Adolescents randomized to reslizumab had an apparent increase in asthma exacerbations, and an apparent decrease in lung function.	While the small number of adolescents makes it difficult to be certain about the efficacy in this subpopulation, and there is no reason to a priori think that the disease is different in this age group, given the safety signals and the point estimates that favor placebo, evidence for efficacy in adolescents cannot be confirmed.
Risk	Overall, 2187 patients were exposed to at least one dose of reslizumab, 1189 for more than six months and 922 for more than twelve months. More patients in the placebo arm were taking maintenance oral corticosteroids than in the reslizumab arm of the safety database; this could make it difficult to detect safety signals for which both oral corticosteroids and reslizumab may play a role, such as for infection or myopathy. There were several deficiencies in the collection of safety data, including failure to collect information regarding anaphylaxis events in a prospective manner, failure to capture post-infusion vital signs, infrequent measurement of serum chemistries, and so few details captured regarding adverse events that it was not possible to generate narratives retrospectively. Patients randomized to reslizumab were more likely to experience moderate, severe or life-threatening elevations in CPK and more likely to report muscle pain. Further, there was evidence of time-dependence, as patients randomized to reslizumab were more likely to	The overall extent of exposure in the safety database with respect to number of patients and duration of treatment is adequate for review. Despite the limitations of the safety assessments, several safety signals have emerged from a review of the safety data, including anaphylaxis, muscle toxicity, malignancy, and infection. Based on our analysis of the available safety data, a physician who treated 1,000 patients with reslizumab for one year could expect to manage 3 additional cases of anaphylaxis, 3 additional cases of malignancy, and 46 additional cases of CPK elevations. Infection remains a concern because of the imbalance in corticosteroid use and the immunosuppressive mechanism of

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	report musculoskeletal adverse events in the 24 hours following infusion. Anaphylaxis is a known safety risk for monoclonal antibodies, but it is rare to observe four cases of anaphylaxis in a clinical trials database. Patients randomized to reslizumab were more likely to develop malignancy (0.6% vs. 0.3% for placebo). Among patients taking oral corticosteroids at baseline, those randomized to reslizumab had a higher incidence of pneumonia compared to placebo (7% vs. 1%). Adolescents randomized to reslizumab were slightly more likely to report adverse events across a range of symptom organ classes than those randomized to placebo, but the nature of these adverse events was consistent with routine adolescent health problems.	action for the drug. These safety signals will need to be addressed in labeling; particularly anaphylaxis, which should appear in a boxed warning with appropriate guidance to providers.
Risk Management	Physicians should be prepared to manage potentially life-threatening cases of anaphylaxis, and patients should be closely observed for an appropriate period in a physician's office after reslizumab administration. Clinicians will want to carefully weigh the risks and benefits of reslizumab therapy in patients with a history of or increased risk for malignancy, and may wish to adjust cancer screening accordingly. Clinicians will want to carefully weigh the risks and benefits of reslizumab therapy in patients with a history of or increased risk for infections, such as tuberculosis or parasitic infection, and may wish to adjust screening accordingly. Clinicians will want to monitor for muscle events and CPK elevations.	Reslizumab is not suitable for home administration. Labeling (including a boxed warning) will need to be instituted to address these concerns.

2 Therapeutic Context

2.1. Analysis of Condition

Asthma is a syndrome marked by intermittent wheezing, cough, shortness of breath and chest tightness. Asthma is caused by inflammation of the airways, and defined by reversible airway obstruction. But not all asthma patients are alike. Some patients may have symptoms triggered by allergens, others by viral infections, air pollution, or occupational exposures (5, 6). Some have mild disease, treatable with occasional rescue medication, while others have severe disease with frequent exacerbations, hospitalizations, and need for oral corticosteroid treatment and its undesirable side effects (7).

Asthma leads to more than two million emergency room visits, nearly half a million hospitalizations, and nearly 4,000 deaths annually in the U.S. Asthma causes an estimated 14.4 million lost school days in children and 14.2 million lost work days in adults. It is a leading cause of activity limitation and costs our nation $56.0 billion in health care costs annually. Patients with severe asthma bear more of this health burden (8).

Asthma affects 26 million people in the United States, including more than 7 million children. It affects people of all races and ethnic groups worldwide, from infancy to old age, with slightly more boys than girls affected and, after puberty, more women than men. Disparities in asthma burden persist among African Americans, Puerto Ricans, those with mixed racial heritage, children, women, and the poor (9).

The natural history of asthma varies by age of onset (10). The majority of children with asthma experience clinical remission and are symptom free by early adulthood, but decrements in lung function persist into later life. For adults with asthma, there is evidence of progressive decline in lung function.

The diagnosis and treatment of asthma is outlined in several expert consensus guidelines (11, 12). These guidelines define severity by the amount of medication needed to control a patient's symptoms to prevent exacerbations and hospitalizations. The guidelines recommend stepwise therapy, beginning with short-acting beta agonist rescue treatment for those with mild intermittent symptoms. For patients with persistent symptoms, the guidelines recommend adding a daily controller medication, such as an inhaled corticosteroid. For those who still have breakthrough symptoms, the guidelines recommend higher doses of inhaled corticosteroids, plus additional medications such as long acting beta agonists, leukotriene modifiers, or theophylline. Patients with allergic asthma may be treated with omalizumab, an

anti-Immunoglobulin E (IgE) antibody. But some patients have symptoms despite these treatments, and require treatment with oral corticosteroids. Expert panels call this "severe" or "refractory" asthma (13).

Importantly, while all patients with asthma will have some airway inflammation, the causes of this inflammation may vary from patient to patient. Clinical characteristics, biomarkers, lung physiology, genetics, histopathology, epidemiology, and treatment response may identify subgroups of asthma patients with distinct pathophysiology (14, 15). Identifying these subgroups holds the potential to accelerate drug development aimed at novel inflammatory pathways (16, 17).

One subgroup of asthma patients have airway inflammation marked by eosinophils, and these patients are the focus of this application. Eosinophils are a type of white blood cell whose natural role is to defend the body against parasites. Eosinophils also accumulate during allergic reactions, including some types of asthma. Eosinophils release chemicals such as eosinophil cationic protein, eosinophil-derived neurotoxin, and eosinophil peroxidase. These chemicals are very efficient at fighting parasites, but can damage the lining of the lung in patients with asthma.

Patients with asthma marked by eosinophilic inflammation account for about 20% of those with refractory asthma (18). They have severe exacerbations prevented only by systemic corticosteroids (10). They tend to have airway remodeling with associated persistent airflow limitation (19-21). Recent, large epidemiological studies suggest that elevated blood eosinophil levels are an independent risk factor for future asthma exacerbations (22-24).

One challenge in reviewing this application is that a scientific consensus is still emerging about the best way to identify and define asthma patients with an eosinophilic phenotype. But preliminary studies with anti–IL-5 therapy suggest it may be useful for these patients, and there is unmet need for patients whose asthma is inadequately controlled by current treatments (25).

2.2. Analysis of Current Treatment Options

Asthma symptoms occur along a continuum of severity. Most patients with asthma can control their symptoms with inhaled corticosteroids and beta agonists. However, a significant minority, approximately 40%, has more severe disease that is refractory to these treatments. Patients with more severe asthma are at higher risk for emergency room visits, hospitalization, and deaths from asthma exacerbations.

Treatment options for patients with more severe asthma are limited to oral corticosteroids or anti-immunoglobulin E. Oral corticosteroids have an adverse safety profile including infection,

diabetes, adrenal suppression, cataracts and osteoporosis. Anti-immunoglobulin E is indicated only for the subset of asthma patients with documented sensitivity to perennial allergens. Anti-IL5 therapies, including mepolizumab, could address some of this unmet medical need for patients with more severe asthma (1).

Table 1. Currently available therapies for the maintenance treatment of asthma

Class	Generic Name	Brand Name
Inhaled corticosteroids	Fluticasone furoate DPI	Arnuity Ellipta
	Beclomethasone dipropionate HFA	QVAR
	Budesonide DPI/Respules	Pulmicort
	Fluticasone propionate HFA, DPI	Flovent HFA Flovent Diskus
	Mometasone DPI/HFA	Asmanex
	Ciclesonide HFA	Alvesco
Combination inhaled corticosteroids/long-acting beta agonist (ICS/LABA)	Budesonide/Formoterol HFA	Symbicort
	Fluticasone propionate/ Salmeterol HFA, Diskus	Advair
	Mometasone/Formoterol HFA	Dulera
	Fluticasone furoate/ Vilanterol	Breo Ellipta
Anti-IgE	Omalizumab	Xolair
Anti-IL5	Mepolizumab	Nucala
Leukotriene modifiers	Montelukast	Singulair
	Zafirlukast	Accolate
	Zileuton	Zyflo
Xanthines	Theophylline	Multiple
Anticholinergics	Tiotropium bromide	Spiriva Respimat

HFA = hydrofluoroalkane, DPI = dry powder inhaler, ICS = inhaled corticosteroid, LABA = long-acting beta agonist

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Reslizumab is a new molecular entity currently not marketed in the U.S. It has been studied for the treatment of nasal polyposis, hypereosinophilic syndrome, eosinophilic gastroenteritis, and asthma.

Schering Plough initially developed reslizumab under codename SCH 55700. Ception acquired reslizumab from Schering and continued development under codename CTx55700. Ception

was acquired first by Cephalon Inc. in 2010 and then by Teva in 2011, where reslizumab was further developed under the designations CEP-38072 and Cinquil. Teva assumed responsibility and accountability for the clinical development program in 2011.

3.2. Summary of Presubmission/Submission Regulatory Activity

Key regulatory interactions are listed below by date. Points of discussion or Division recommendations are provided as a bulleted list for each meeting. The development program for reslizumab occurred under IND 101399.

August 18, 2010 – End-of-Phase 2 Meeting

- Define treatment population using a clinically available test (not sputum eosinophilia)
- Evaluate reslizumab in both eosinophilic and non-eosinophilic asthma phenotypes, and if not efficacious in non-eosinophilic asthma, this information may be included in labeling
- Further dose-ranging in the phase 3 efficacy studies was advised, the applicant declined, the Agency acknowledged this was at the applicant's discretion, and also at their risk, and would be a review issue
- Replicate trials would be needed to support an asthma exacerbation claim
- Agency prefers absolute FEV_1 to percent-predicted FEV_1 as an endpoint
- Validation of the asthma control questionnaire as an endpoint to support an indication
- Adequacy of exacerbation endpoint and clinical relevance of treatment difference will be a review issue
- Address target-related safety issues such as immunoregulation, malignancy, parasitic infection, and electrocardiogram (ECG) monitoring throughout phase 3

May 2013: Type C Meeting

- Agreement was reached regarding the definition for an asthma exacerbation in Studies 3082 and 3083.
- This change was made in response to agency feedback from the End of Phase 2 meeting in 2010.
- But, it occurred three years later, <u>after</u> enrollment was complete for the two studies.
- Teva established an independent panel of experts to adjudicate all exacerbations or adverse events suggestive of exacerbations using the final agreed definition in a blinded manner prior to database lock and un-blinding.

An exacerbation originally was defined as having one of the following:

- a hospitalization for asthma

- emergency treatment because of asthma (unscheduled visits to physicians' office for urgent treatment, or a visit to emergency department)
- a decrease in FEV1 by 20% or more from baseline
- A drop in PEFR below 30% from baseline for 2 consecutive days that results in an increase in baseline ICS or oral corticosteroids, or the addition of oral corticosteroids

This was changed such that an exacerbation would be defined by whether a patient met at least 1 of the 2 following criteria:

1) Use of systemic, or an increased use of ICS, for 3 or more days; for patients already on systemic or ICS, the dose must be increased by 2 or more fold for 3 or more days
2) Asthma-related emergency treatment including at least 1 of the following:
    a. Unscheduled visit to physician's office for nebulizer treatment or other urgent treatment to prevent worsening of asthma symptoms
    b. A visit to the emergency room for asthma related treatment
    c. Asthma-related hospitalization

In addition to meeting at least 1 of the 2 criteria listed above, one of the following measurements/observations must also be present:

1) Decrease in FEV1 by 20% or more from baseline
2) Decrease in PEFR below 30% from baseline on 2 consecutive days
3) Worsening of symptoms or other clinical signs (physician assessment)

August 26, 2014: A Pediatric Study Plan was agreed. See section 8.7.3 for details.

Pre-Biologics Licensing Application Meeting, February 15, 2015

- Reslizumab does not appear to qualify for priority review because patients with asthma have many alternate therapies, including steroids.
- Adequacy of population pharmacokinetic analyses
- Anti-drug antibody assay validity
- Applicant's intention to submit anti-drug antibody data, final study report for 3085, and case report forms at the 120-day safety update.
- Agency reiterated importance of evaluating risk of helminthic parasitic infection, suggested Xolair label as guidance
- Endotoxin levels

Reviewer Comment: The development of reslizumab generally was responsive to agency feedback.

3.3. Foreign Regulatory Actions and Marketing History

Reslizumab currently is not approved for marketing in any country.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

A sponsor-level inspection was requested rather than individual sites because recruitment was widely distributed globally. Thus, each site enrolled only a small number of patients, such that inspection of any one site likely would not be especially informative. The investigation focused on Studies 3082, 3083, and 3084. The inspection was conducted from September 28-October 2, 2015. The inspection evaluated documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, and training of staff and site monitors.

For Studies 3082 and 3083, the database was unlocked after unblinding. The logs were audited and revealed minor changes. Monitoring deficiencies were identified, such as initiating interim monitoring visits within a timely manner, but there was no evidence of under-reporting of adverse events. Data for fifteen subjects from Study 3084 Sites 864 and Site 909 were excluded from safety and efficacy analyses for violations of Good Clinical Practice guidelines. An audit of adverse events for these subjects revealed cases of acute urticaria, asthma exacerbation, and acute bronchospasm. The OSI concluded that the data from the sponsor site audit was acceptable in support of the BLA, and the regulatory classification issued was No Action Indicated (NAI).

4.2. Product Quality

The final product quality review from Dr. Joao Pedras Vasconcelos was pending at the time of this review.

4.3. Clinical Microbiology

The final clinical microbiology review from Dr. Marjorie Shapiro was pending at the time of this review.

4.4. Nonclinical Pharmacology/Toxicology

The final nonclinical pharmacology/toxicology review from Dr. Carol Galvis was pending at the time of this review.

4.5. Clinical Pharmacology

4.5.1. Mechanism of Action

Reslizumab binds to IL-5 and interferes with its binding to its cell-surface receptors. IL-5 is a cytokine responsible for the differentiation, maturation, recruitment, and activation of human eosinophils. IL-5 plays a key role in the pathophysiology of eosinophilic inflammation in the lung in patients with asthma. Reslizumab has been shown in vitro to exhibit a binding affinity (Kd) for human IL-5 of 81 pM as measured by BIAcore; the IC50 for inhibition of IL-5 receptor binding and blocking the proliferation of an IL-5-sensitive cell line was 0.5 nM and 45 nM, respectively.

4.5.2. Pharmacodynamics

In clinical studies with reslizumab 3 mg/kg, decreases in blood eosinophil counts were seen following the first dose and maintained through 52 weeks of treatment. Mean blood eosinophil counts were 624/µL (n=244) and 696/µL (n=245) for the placebo and reslizumab treatment groups at baseline, respectively, and were 496/µL (n=211) and 55/µL (n=212) at the week 52 visit. Decreases in blood eosinophils were related to reslizumab serum levels. The reduction in blood eosinophil counts by reslizumab in anti-reslizumab antibody positive patients was not different from patients who were anti-reslizumab- antibody negative. Treatment-emergent anti-reslizumab antibody appeared not interfere with the reduction effect on blood eosinophil counts by reslizumab.

Data collected from a clinical study in healthy subjects at a dose of 3 mg/kg indicate that reslizumab does not prolong the QT interval and there is no apparent correlation between reslizumab concentration and QT intervals.

4.5.3. Pharmacokinetics

The pharmacokinetics of reslizumab have been characterized in healthy adults (n=130), in adolescents and adults with asthma (n=438). The pharmacokinetic characteristics of reslizumab are similar across these populations. Peak serum concentrations typically are observed at the end of infusion. Serum reslizumab concentrations generally decline from peak in a biphasic manner. The mean observed accumulation ratio of reslizumab following multiple doses of administration ranged from 1.5 to 1.9-fold. Systemic exposure to reslizumab appears to be unaffected by the presence of treatment-emergent anti-reslizumab antibodies.

Reslizumab has a volume of distribution of approximately 5 L, suggesting minimal distribution to the extravascular tissues. Reslizumab clearance is approximately 7 mL/hour. Reslizumab has a half-life of about 24 days. Similar to other monoclonal antibodies, reslizumab is degraded by enzymatic proteolysis into small peptides and amino acids. As reslizumab binds to a soluble target, it is not expected to go through a target-mediated clearance.

No significant difference in the pharmacokinetics of reslizumab was observed by age, gender, race, weight, renal impairment, or hepatic impairment.

4.6. Devices and Companion Diagnostic Issues

Blood eosinophil counts were measured via a standard complete blood count with differential blood test at PPD Global Central Labs at sites in Kentucky, Belgium, or Singapore.

4.7. Consumer Study Reviews

A proprietary name review completed June 23, 2015 by the Division of Medication Error Prevention and Analysis concluded that the proposed proprietary name, Cinqair, is acceptable.

5 Sources of Clinical Data and Review Strategy

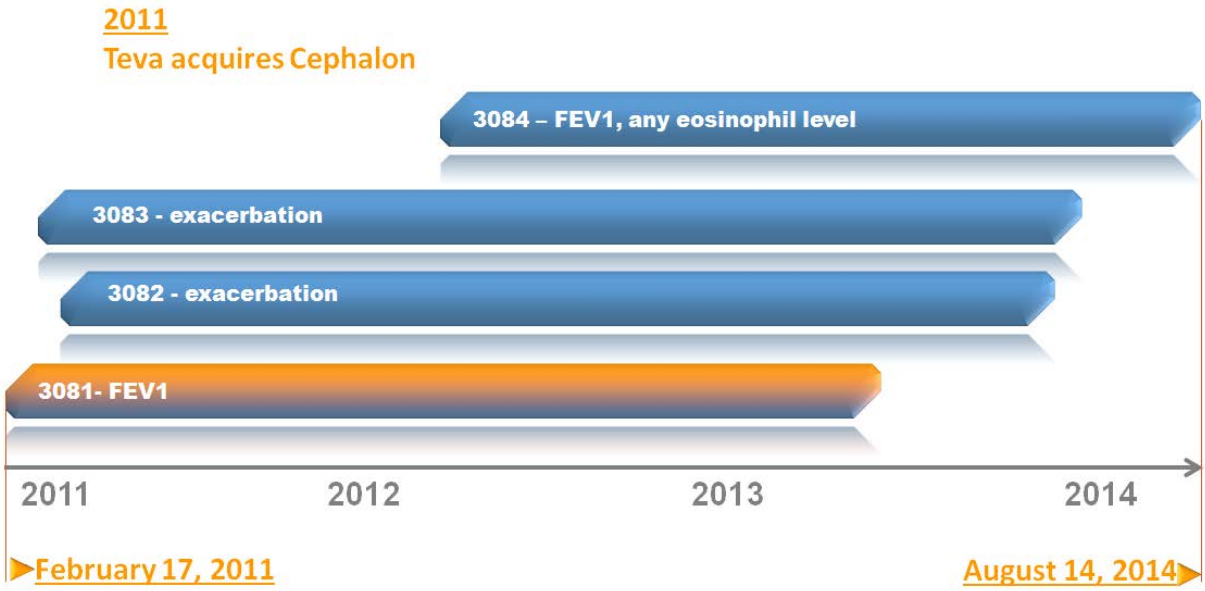
5.1. Table of Clinical Studies

Table 2. Reslizumab clinical trials

Trial (Month/Year)	Population	Design	N	Treatment	Weeks	Endpoint
		Eosinophilic Esophagitis				
Res-5-0002	Eosinophilic esophagitis	P2B/3 R DB	57	placebo	16	Esophageal
(3/08-10/09)	(age 5 to 18 years)	PC PG	56	1 mg/kg		eosinophil count
			57	2 mg/kg		
			57	3 mg/kg		
				IV q4wks		
Res-5-0004	Eosinophilic esophagitis	P3 OLE	190	1-3 mg/kg*	16	Safety
(7/08-1/12)	(age 5 to 18 years)			IV q4wks		
		Asthma				
5-0010	Asthma	P2 DB PC	53	placebo	16	ACQ
(4/08-3/10)	(sputum eosinophils ≥ 3%)		53	3mg/kg		
				IV q4wks		
3081	Asthma	P3 R DB PC PG	105	placebo	16	FEV_1
(2/11-9/13)	(blood eosinophils > 400/µl)		104	0.3 mg/kg		
			106	3 mg/kg		
				IV q4wks		
3083	Asthma	P3 R DB PC PG	232	placebo	52	Exacerbation
(3/11-4/14)	(blood eosinophils > 400/µl)		232	3mg/kg		
				IV q4wks		
3082	Asthma	P3 R DB PC PG	244	placebo	52	Exacerbation
(4/11-3/14)	(blood eosinophils > 400/µl)		245	3mg/kg		
				IV q4wks		
3085	Asthma	P3 OLE	1052	3mg/kg	104	Safety
(6/11-1/15)	(blood eosinophils > 400/µl)			IV q4wks		
3084	Moderate to Severe Asthma	P3 R DB PC PG	98	placebo	16	FEV_1
(2/12-8/13)			398	3mg/kg		
				IV q4wks		

*dose titrated at investigator discretion over course of the study
P=phase, R=randomized, DB=double blind, PC=placebo controlled, PG=parallel group, OLE=open label extension, FEV_1=forced expiratory volume in one second

Figure 1. Timeline of the clinical development program



Source: K. Donohue

Study 3081 was the only study in the intended asthma population to evaluate multiple doses. There were three limitations to the dose-ranging for this study. First, it studied only two doses. Second, it is well understood that most asthma control drugs, for example corticosteroids, show a dose separation for efficacy at a about a two-fold increase. But here, the doses tested were .3 mg and 3 mg/kg, so a tenfold increase. Third, it is important to note that reslizumab development program essentially was conducted concurrently. Therefore, the results from Study 3081 were not used to inform dose selection for the reslizumab program. The concurrent conduct of the pivotal studies has implications beyond dose-ranging. For example, the results from Study 3084, which took patients at all eosinophil levels, could not be used to inform patient selection. The simultaneous conduct also meant that it was not feasible to adjust safety monitoring as safety signals emerged.

5.2. Review Strategy

The clinical review focused on five core studies in the reslizumab development program: Studies 3081 and 3084 targeting an FEV_1 endpoint, Studies 3082 and 3083 targeting an asthma exacerbation endpoint, and Study 3085, an open-label extension study targeting long-term safety endpoints. Review of the studies was based primarily on this reviewer's independent analysis of the data sets provided by the Sponsor, and secondarily on the Sponsor's study reports. The tables and analyses presented in this report reflect the independent analysis of

the reviewer except where otherwise noted. Narratives of patients with serious adverse events or those who died were reviewed. The Sponsor's bibliography was reviewed when relevant.

The design of the four efficacy studies (3081-4) is reviewed in Section 6 and the integrated efficacy analysis is discussed in Section 7. The design of the safety study, 3085, is described in Section 7. An integrated analysis of safety, including studies in other indications where relevant, also is discussed in Section 7.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study 3081

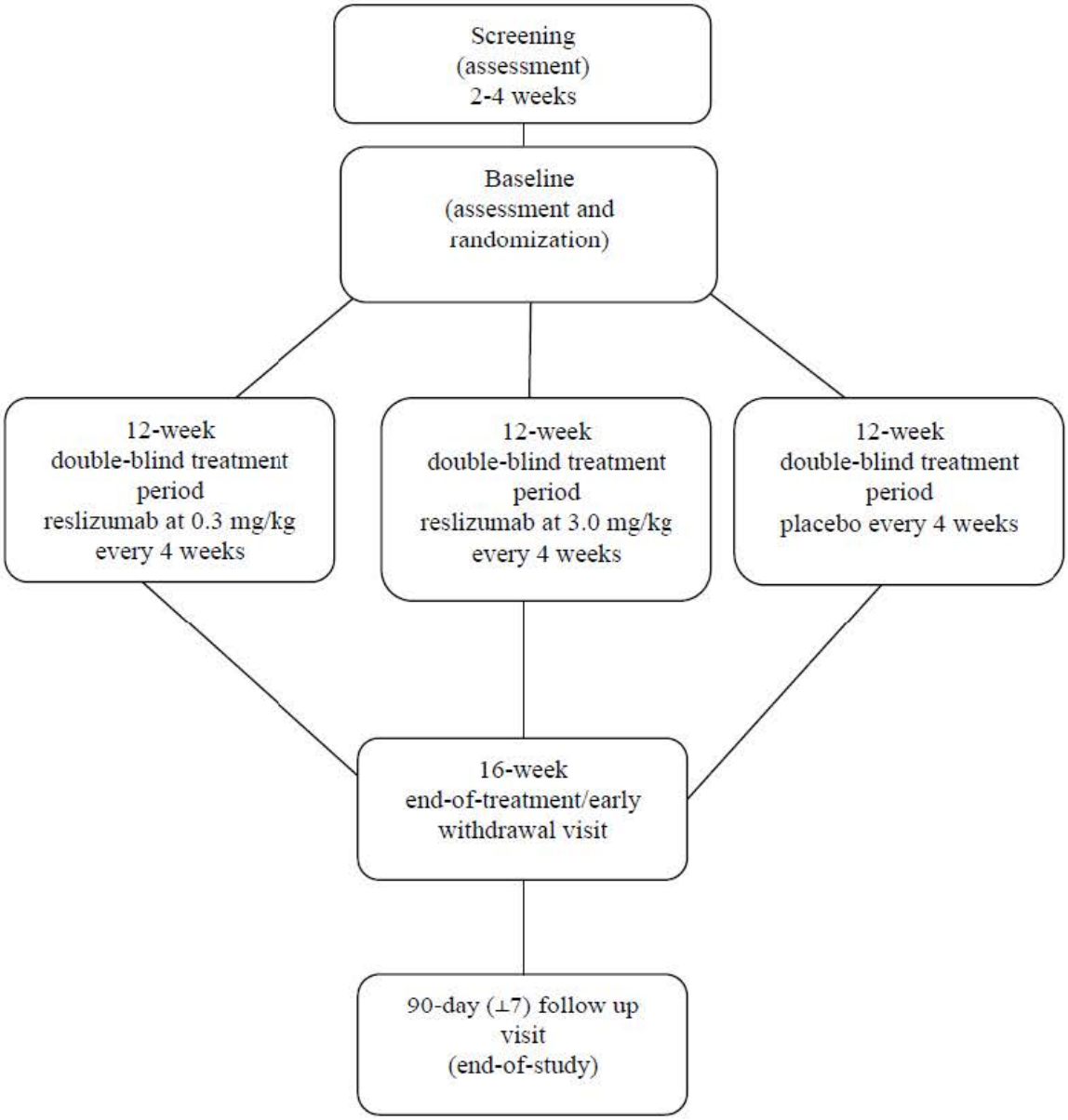
6.1.1. Study Design

Overview and Objective

The primary objective of Study 3081, "A 16-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Reslizumab (0.3 or 3.0 mg/kg) as Treatment for Patients (12-75 Years of Age) With Eosinophilic Asthma," was to determine whether reslizumab, at a dosage of 0.3 or 3.0 mg/kg administered once every 4 weeks for a total of 4 doses, is more effective than placebo in improving lung function in patients with asthma with an eosinophilic phenotype as assessed by the overall change from baseline in forced expiratory volume in 1 second (FEV_1) over 16 weeks.

Trial Design

Figure 2. Study 3081 schema



Source: Study 3081 Protocol p. 32

Study 3081 was performed in 80 centers in 12 countries, including Argentina, Belgium, Brazil,

Canada, Colombia, Hungary, Israel, Mexico, Netherlands, Poland, Sweden, and the U.S.

Pertinent inclusion criteria

- blood eosinophil count of at least 400/µL
- 12 through 75 years of age
- diagnosis of asthma
- Asthma Control Questionnaire (ACQ) score of at least 1.5
- airway reversibility of at least 12% to beta-agonist administration
- fluticasone at a dosage of at least 440 µg daily (or equivalent)
- baseline asthma therapy regimens (including but not limited to inhaled corticosteroids, leukotriene receptor antagonists, 5-lipoxygenase inhibitors, cromolyn) must be stable for 30 days before screening, and continue without dosage changes throughout study
- female patients must be surgically sterile, 2 years postmenopausal, or must have a negative pregnancy test ßHCG at screening (serum) and baseline (urine)
- female patients of childbearing potential must use a medically accepted method of contraception and must agree to continue use of this method for the duration of the study and for 30 days after the end-of-treatment visit
- The patient is in reasonable health as judged by the investigator, and as determined by a medical history, medical examination, ECG evaluation, serum chemistry, hematology, urinalysis, and serology

Pertinent exclusion criteria:

- clinically meaningful comorbidity
- known hypereosinophilic syndrome
- another lung disorder (e.g., chronic obstructive pulmonary disease, pulmonary fibrosis, or lung cancer, Churg-Strauss syndrome, allergic bronchopulmonary aspergillosis
- current smoker
- use of systemic immunosuppressive, or immunomodulating agents (anti-IgE monoclonal antibody, methotrexate, cyclosporin, interferon-α, or anti-tumor necrosis factor monoclonal antibody) within 6 months prior to study entry
- currently using systemic corticosteroids (includes use of oral corticosteroids)
- aggravating factors that are inadequately controlled e.g., gastroesophageal reflux disease
- previous treatment with anti-IL-5 monoclonal antibody (e.g., mepolizumab)
- immunodeficiency (human immunodeficiency, acquired immunodeficiency syndrome, or congenital immunodeficiency
- presence of or suspected active parasitic infestation or infection
- live attenuated vaccine within the 12-week period before study entry
- history of allergic reactions to or hypersensitivity to any component of the study drug

Prohibited medications and washout times

- any immunosuppressive or immunomodulatory agents, including but not limited to methotrexate, IgE monoclonal antibody, cyclosporin, and interferon-α - 6 months
- anti-TNF monoclonal antibody - 6 months
- anti-hIL-5 monoclonal antibody - prohibited
- all other non-biologic investigational drugs - 30 days
- systemic (including oral) corticosteroids - 30 days
- live attenuated vaccines - 12 weeks
- investigational biologic therapies - 90 days from screening
- all other biologic therapies, including omalizumab (XOLAIR®) - 6 months

Investigational Product: Reslizumab provided as a sterile solution for infusion presented as 100 mg (10 mL) per vial, formulated at 10 mg/mL in (b) (4) 7% sucrose, pH 5.5 buffer

Placebo: sterile solution for infusion presented as 10 mL per vial, formulated in (b) (4) 7% sucrose, pH 5.5 buffer

Method of Blinding & Randomization: Eligible patients were randomly assigned in a blinded fashion (1:1:1) to reslizumab 0.3 mg/kg, reslizumab 3.0 mg/kg, or placebo. They were stratified according to asthma exacerbations within the last 12 months (yes or no) and age (12 through 17 years, or 18 through 75 years) via interactive response technology. Approximately 4% of patients were misclassified due to site entry errors, but this was well-balanced between treatment arms.

Table 3. Study 3081 schedule of procedures and assessments

	Screening	Randomized Treatment Period						End of Treatment	Follow Up
Visit No.	**V1**	**V2**	**V2.1**	**V2.2**	**V3**	**V4**	**V5**	**V6**	**V7**
Day or Week No.		**BL**	**D2-3**	**W2-3**	**W4**	**W8**	**W12**	**W16**	**W29**
Complete H&P	✓								
Urine pregnancy test	✓	✓			✓	✓	✓	✓	
Adverse event queries	✓	✓	✓	✓	✓	✓	✓	✓	✓
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓	✓
ECGs	✓							✓	
Serum chemistry	✓					✓		✓	
CBC w/ diff	✓	✓	✓	✓	✓	✓	✓	✓	✓
Urinalysis	✓	✓			✓	✓	✓	✓	
Spirometry		✓			✓	✓	✓	✓	

Source: Adapted from Study 3081 Report Table 1 Schedule of Procedures and Assessments p. 29
BL = baseline, H&P = medical history and physical, ECGs = electrocardiograms, CBC w/ diff = complete blood count with differential

Study Endpoints

Primary Efficacy Measure/Variable: overall change from baseline in FEV_1 over 16 weeks

Secondary Efficacy Measures/Variables:

- Asthma Control Questionnaire (ACQ): change from baseline to weeks 4, 8, 12, 16, and endpoint
- Asthma Quality of Life Questionnaire (AQLQ): change from baseline to week 16, and endpoint
- Forced Vital Capacity (FVC): change from baseline to weeks 4, 8, 12, 16, and endpoint
- Forced Expiratory Flows (FEF25%-75%) : change from baseline to weeks 4, 8, 12, 16, and endpoint
- Asthma Symptom Utility Index (ASUI): change from baseline to weeks 4, 8, 12, 16, and endpoint
- Short Acting Beta Agonist (SABA) use: change from baseline to weeks 4, 8, 12, 16, and endpoint
- Blood eosinophils (EOS): change from baseline to weeks 4, 8, 12, 16, and endpoint
- % predicted FEV_1 : change from baseline to weeks 4, 8, 12, 16, and endpoint

Exploratory Measures/Variables:

- change in sputum eosinophil levels from baseline to endpoint (only from a subset of patients at selected study centers)
- change in biomarkers (eosinophil cationic protein, eosinophil-derived neurotoxin, and eosinophil peroxidase) from baseline to endpoint; blood samples will be drawn at screening, baseline, and at weeks 8 and 16 or early withdrawal to evaluate changes in biomarkers.

- change in the presence or absence of nasal polyps (only from patients who are at least 18 years of age at participating study centers)

Statistical Analysis Plan

The primary variable was analyzed using a mixed model for repeated measurement (MMRM) with independent variables of treatment, visit, treatment by visit interaction, asthma exacerbations within the past 12 months (yes or no), baseline age (12 -17 years or ≥18 years), sex, height, and baseline FEV_1. An unstructured covariance matrix was used for the within-patient correlation modeling. The primary analysis was based on the full analysis dataset (FAS), including all randomized patients who were treated with at least one dose of study drug. The overall treatment effect for each reslizumab dose was compared to placebo using a 2-sided t-test at the significance level of 0.05. A hierarchical testing procedure, in the order of reslizumab 3 mg/kg first and 0.3 mg/kg second, was used to control the Type I error rate for the two comparisons of reslizumab to placebo.

Protocol Amendments

- Amendment 1 was issued December 22, 2010 before any patients were enrolled. It reduced frequency of body weight measurements and documentation requirements for prior omalizumab use.
- Amendment 2 was issued April 14, 2011 after 15 of the 300 planned patients were enrolled into the study. Exclusion criterion were expanded to exclude patients who had other pulmonary conditions with symptoms of asthma and blood eosinophilia such as Churg-Strauss syndrome, a parasitic infestation/infection, or those who had received a live attenuated vaccine within 12-weeks before screening. An independent Data and Safety Monitoring Board was added to ensure patient safety. For patients who did not enroll in the open-label extension study, a 90-day follow-up evaluation was added to assess adverse events, blood eosinophils, and vital signs.
- Amendment 3 was issued April 19, 2011 after 17 of the 300 planned patients were enrolled into the study. The collection of a blood sample was added for pharmacokinetic evaluation, eosinophil determination, and anti-drug antibody assessment for patients experiencing a serious adverse event, an adverse event leading to withdrawal, or an exacerbation of asthma symptoms. Omalizumab was added as a prohibited medication within 6 months prior to screening.
- Amendment 4 was issued February 29, 2012 after 195 of the 300 planned patients were enrolled into the study. Target enrollment was increased from 180 to approximately 300 patients, to achieve 90% power for the primary efficacy variable instead of 85% power. The increase in sample size was due to an anticipated lowered effect size from 0.6 to 0.47.The lowered effect size reflected an anticipated greater variability in the FEV_1 change as the result of broader geographic enrollment than initially planned.

- Amendment 5 was issued April 19, 2013 after patient enrollment was complete. Timing of blood sample collection for biomarkers was clarified. Exploratory endpoint definitions including biomarkers, sputum eosinophil levels, and change in nasal polyps were clarified.
- Amendment 6 was issued September 30, 2013 after the last patient completed the study on September 12, 2013. It excluded endpoint data such as pulmonary function tests, ACQ, AQLQ, ASUI, and short-acting beta-agonist assessments from the full analysis set if they were obtained at scheduled visits preceded by usage within 7 days of medications such as oral or systemic corticosteroids or the addition of a new LABA or long-acting muscarinic antagonist that could significantly confound interpretation. A subgroup analysis of those with FEV_1 < 85% predicted at baseline was added as a secondary analysis for the primary endpoint and was tested at the 0.05 level with no adjustment for multiplicity. The Statistical Analysis Plan was changed to specify that endpoints were evaluated as change from baseline to endpoint. Statistical testing in the secondary efficacy analyses were based on 2-sided tests at a nominal level of 0.05, no adjustment for multiplicity was applied.

Data Quality and Integrity: Sponsor's Assurance

A statement of compliance with Good Clinical Practices is located in the study report.

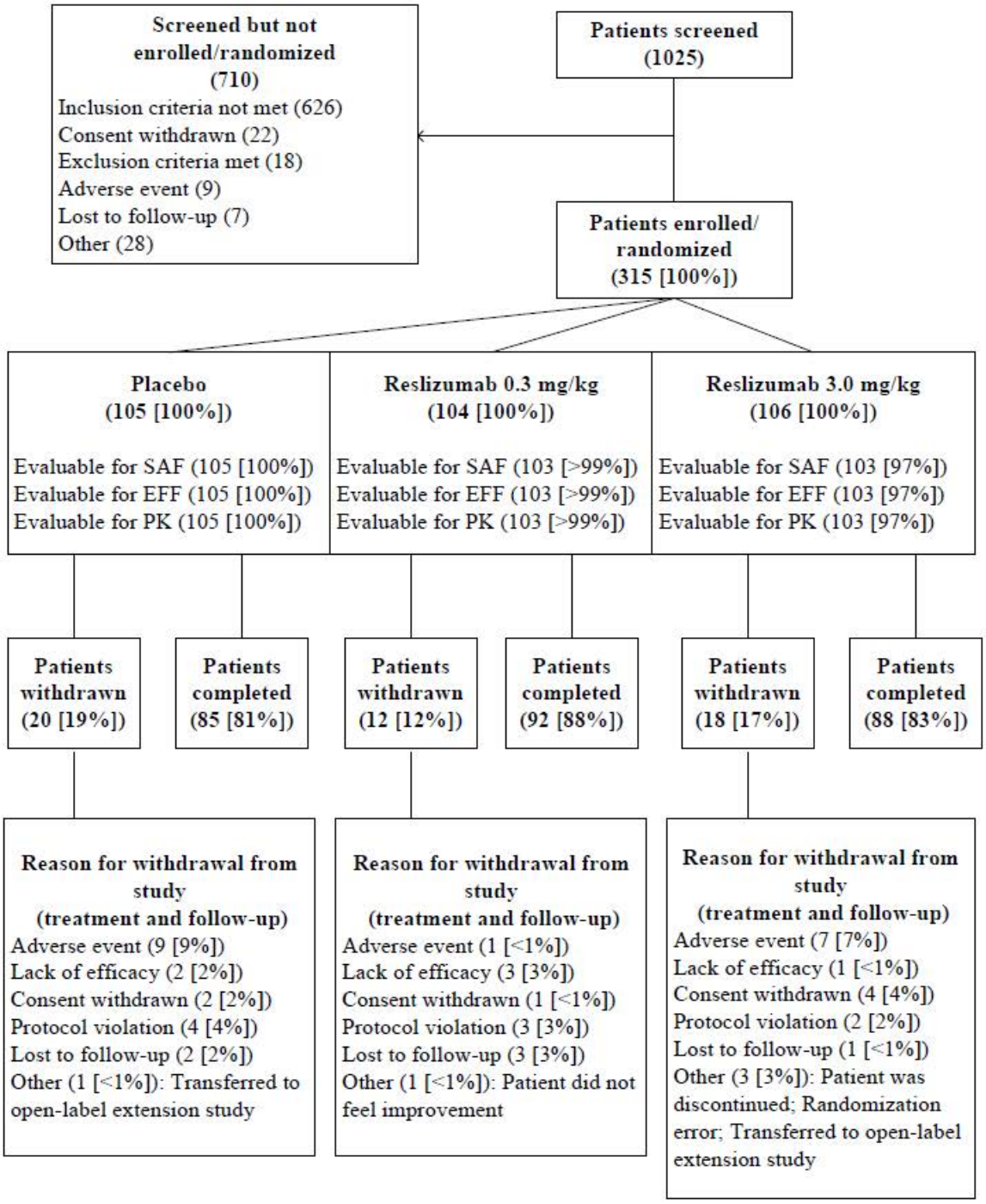
6.1.2. Study Results

Compliance with Good Clinical Practices

This Sponsor attests that the study was conducted in full accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations (e.g., Code of Federal Regulations [CFR] Title 21, Parts 50, 54, 56, 312, and 314; European Union Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical studies of medicinal products for human use).

Patient Disposition

Figure 3. Study 3081 disposition



Study 3081 Report Figure 2

A total of 315 subjects were enrolled in Study 3081, and all but four subjects received at least one dose of study drug. Forty-seven (14.9%) subjects stopped medication early and 50 (15.9%) discontinued from the study prematurely. The most common reason for discontinuation from study drug treatment was adverse events, occurring in 19 (6%) subjects. Patient disposition for each study is shown below in **Table 4.**

Table 4. Patient disposition in Study 3081

	Placebo	Reslizumab 0.3 mg/kg	Reslizumab 3.0 mg/kg	Total
Randomized	105	104	106	315
Never dosed	0	1	3	4
Treated	105	103	103	311
Completed treatment	85 (81.0%)	93 (89.4%)	90 (84.9%)	268 (85.1%)
Discontinued treatment	20 (19.0%)	11 (10.6%)	16 (15.1%)	47 (14.9%)
Completed study	85 (81.0%)	92 (88.5%)	88 (83.0%)	265 (84.1%)
Discontinued study	20 (19.0%)	12 (11.5%)	18 (17.0%)	50 (15.9%)
Discrepancies in exacerbations between IRT and CRF	4 (3.8%)	3 (2.9%)	4 (3.8%)	11 (3.5%)
Analysis Datasets				
Randomized Set	105	104	106	315
Full Analysis Set	105	103	103	311
Safety Set	105	103	103	311

Source: Lan Zeng M.S., FDA Statistical Reviewer
IRT = interactive response technology, CRF= case report form

Protocol Violations/Deviations

The most common types of violations were inclusion/exclusion screening violations (ACQ not ≥1.5), "GCP guidelines" (wrong version of consent signed), "study drug" (non-use of filter for the IV set-up), and "excluded concomitant medication" (use of systemic corticosteroid) see **Table 5**.

A total of 65/315 (21%) patients randomly assigned to a treatment group had a protocol violation and 53 of these 65 patients (82%) were approved to continue in the study. In each case, the violations were reviewed and discussed among the medical monitors. Eleven of the 315 patients (3.5%) were discontinued from the study at the decision of the medical monitors due to protocol violations, 4 patients in the placebo treatment group, 3 patients in the 0.3 mg/kg reslizumab treatment group, and 4 patients in the 3.0 mg/kg reslizumab treatment group. The most frequent protocol violation leading to withdrawal was taking an excluded concomitant medication.

Table 5. Study 3081 protocol violations

	Placebo (N=105)	Reslizumab 0.3 mg/kg (N=104)	Reslizumab 3 mg/kg (N=106)	Total (N=315)
Patients with ≥ 1 violation, n (%)	29 (28)	19 (18)	17 (16)	65 (21)
Inclusion criteria	12 (11)	5 (5)	6 (6)	23 (7)
Exclusion criteria	2 (2)	0	0	2 (<1)
GCP	8 (8)	4 (4)	4 (4)	16 (5)
Study drug	5 (5)	6 (6)	0	11 (3)
Concomitant Medication	4 (4)	2 (2)	4 (4)	10 (3)
Other	6 (6)	4 (4)	6 (6)	16 (5)

Source: Study 3081 Report Table 19
Patients could have had more than one protocol violation.
Other reasons include patient was misclassified into stratum by Interactive Response Technology (IRT); study staff did not draw blood from patient for chemistry laboratory analyses; patient refused blood draw at 90-day follow-up visit; study staff did not perform urine pregnancy test on patient at baseline visit; patient had no asthma exacerbations within the last 12 months at baseline; however, information in IRT indicates patient had an asthma exacerbation within the last 12 months at baseline; patient was noncompliant with ADVAIR® (fluticasone propionate and salmeterol, GlaxoSmithKline) for 2 weeks; and patient's baseline visit was performed <2 weeks from screening.
GCP=Good Clinical Practice.

Table of Demographic Characteristics

Selected demographic features for all randomized patients are shown in **Table 6**. In Study 3081, subject demographics and baseline characteristics were generally balanced among the three treatment groups. The majority of subjects were female, white and of non-Hispanic or non-Latino ethnicity. The median age was 45 years with 15 (5%) subjects less than 18 years old.

Table 6. Study 3081 demographics

	Placebo (N=105)	Reslizumab 0.3 mg/kg (N=104)	Reslizumab 3.0 mg/kg (N=106)	Total (N=315)
Age (years)	n=105	n=104	n=106	n=315
Mean	44.2	44.5	43.0	43.9
SD	14.89	14.03	14.41	14.42
Median	45.0	46.5	44.0	45.0
Sex, n (%)				
Male	43 (41)	45 (43)	44 (42)	132 (42)
Female	62 (59)	59 (57)	62 (58)	183 (58)
Race, n (%)				
White	85 (81)	80 (77)	90 (85)	255 (81)
Black	7 (7)	6 (6)	5 (5)	18 (6)
Asian	0	2 (2)	2 (2)	4 (1)
American Indian or Alaskan Native	1 (<1)	0	0	1 (<1)
Pacific Islander	1 (<1)	0	0	1 (<1)
Other	11 (10)	16 (15)	9 (8)	36 (11)
Ethnicity, n (%)				
Hispanic or Latino	29 (28)	29 (28)	31 (29)	89 (28)
Non-Hispanic or non-Latino	74 (70)	73 (70)	75 (71)	222 (70)
Unknown	2 (2)	2 (2)	0	4 (1)
Weight (kg)	n=105	n=104	n=106	n=315
Mean	77.0	75.9	75.7	76.2
SD	20.10	18.80	20.30	19.70
Median	73.0	74.0	74.4	74.0
Region, n (%)				
U.S.	38 (36)	35 (34)	42 (40)	115 (37)
Non-U.S.	67 (64)	69 (66)	64 (60)	200 (63)

Source: Lan Zeng M.S., FDA Statistical Reviewer
SD standard deviation

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline characteristics are shown in **Table 7**. The distributions of clinical characteristics including previous asthma history, airway reversibility, $FEV_{1,}$ and severity scores generally was similar across all treatment groups, although need for rescue short acting beta agonist treatment in the previous three days was somewhat higher in the placebo arm.

Table 7. Study 3081 disease characteristics

	Placebo (N=105)	Reslizumab 0.3 mg/kg (N=104)	Reslizumab 3.0 mg/kg (N=106)	Total (N=315)
Asthma exacerbation within 12 months per CRF, n (%)				
Yes	57 (54)	58 (56)	60 (57)	175 (56)
No	48 (46)	46 (44)	46 (43)	140 (44)
Number of exacerbation events	n=57	n=58	n=60	n=175
Mean	2.0	2.0	2.1	2.0
SD	1.27	1.68	1.63	1.53
Median	1.0	1.0	1.0	1.0
Duration of asthma (years)	n=105	n=103	n=100	n=308
Mean	20.7	20.0	20.4	20.4
SD	14.49	15.23	15.64	15.07
Median	18.3	17.8	16.3	17.3
FEV_1 (L)	n=105	n=103	n=105	n=313
Mean	2.222	2.157	2.192	2.191
SD	0.8125	0.8506	0.7923	0.8164
Median	2.120	2.060	2.140	2.140
% Predicted FEV_1	n=105	n=103	n=105	n=313
Mean	71.1	68.8	70.4	70.1
SD	19.84	18.48	18.43	18.89
Median	72.0	71.0	70.7	72.0
Airway reversibility (%)	n=105	n=104	n=106	n=315
Mean	25.4	24.2	26.2	25.3
SD	15.62	13.62	18.63	16.08
Median	20.0	20.1	19.9	20.0
Blood eosinophil count (10^9 cells/L)	n=105	n=104	n=106	n=315
Mean	0.601	0.648	0.592	0.614
SD	0.4331	0.4917	0.3878	0.4386
Median	0.504	0.500	0.500	0.500
FVC (L)	n=105	n=103	n=105	n=313
Mean	3.288	3.289	3.220	3.265
SD	1.0503	1.1232	1.0114	1.0593
Median	3.200	3.230	3.020	3.140
$FEF_{25\%-75\%}$ (L/s)	n=105	n=103	n=105	n=313
Mean	1.657	2.337	1.731	1.905
SD	0.9201	8.9642	1.5370	5.2376

Median	1.510	1.250	1.450	1.420
AQLQ total score	n=105	n=103	n=105	n=313
Mean	4.374	4.501	4.175	4.349
SD	1.2047	1.2402	1.2297	1.2283
Median	4.531	4.594	4.250	4.500
ACQ score	n=105	n=104	n=106	n=315
Mean	2.471	2.481	2.590	2.514
SD	0.8301	0.9059	0.9108	0.8819
Median	2.286	2.429	2.429	2.429
ASUI score	n=105	n=104	n=106	n=315
Mean	0.674	0.675	0.655	0.668
SD	0.1897	0.2052	0.1945	0.1961
Median	0.692	0.696	0.685	0.688
Used beta-agonist in past 3 days, n (%)				
Yes	81 (77)	72 (69)	78 (74)	231 (73)
No	23 (22)	32 (31)	28 (26)	83 (26)
Daily average number of puffs in past 3 days	n=104	n=104	n=106	n=314
Mean	2.3	1.9	2.2	2.1
SD	2.20	2.44	2.56	2.41
Median	2.0	1.3	1.5	1.7

Source: Lan Zeng M.S., FDA Statistical Reviewer, CRF = case report form

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Compliance was excellent (100%) in both arms. Concomitant medication use generally was well- balanced between treatment arms, with a few exceptions. Patients in the placebo arm were more likely than those randomized to reslizumab to use antibacterials (25 % vs. 20%), antihistamines (40% vs. 31%), anti-inflammatory/anti-rheumatic products (17% vs. 13%), systemic corticosteroids (14% vs. 4%), and psycholeptics (10% vs. 6%), and less likely to use lipid modifying agents (11% vs. 17%) and analgesics (14% vs. 18%). Rescue medication use of short acting beta agonists was evaluated as a secondary endpoint and is discussed below.

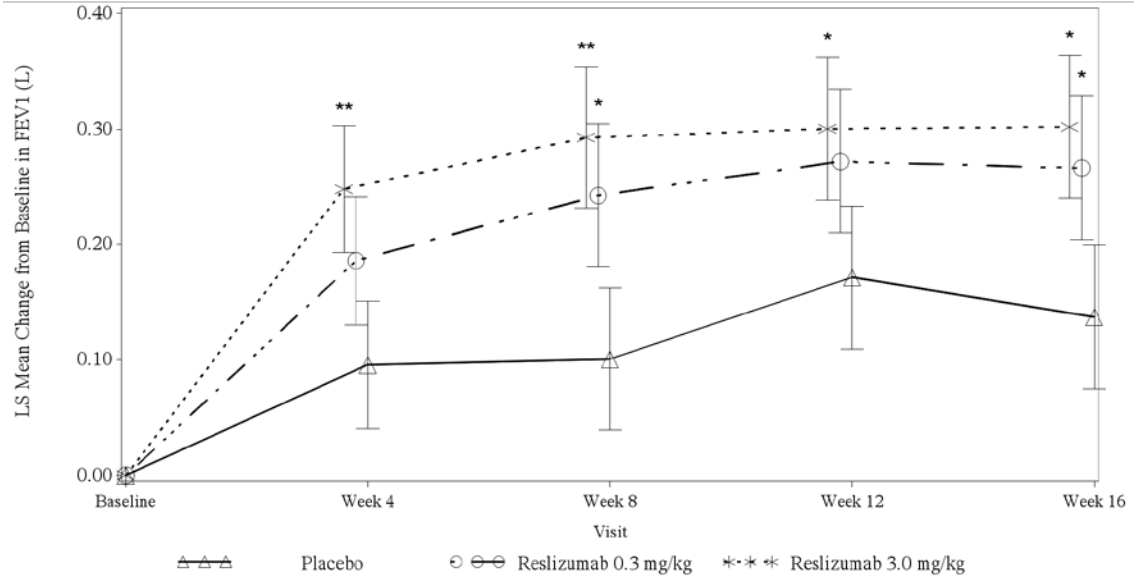
Efficacy Results – Primary Endpoint

The primary efficacy endpoint of this study was the overall change from baseline in FEV_1 over 16 weeks. Significant improvement in FEV_1 was seen for patients in both reslizumab treatment groups compared with patients in the placebo treatment group; the overall change from baseline in FEV_1 was 0.126, 0.242, and 0.286 L for patients in the placebo, reslizumab 0.3 mg/kg, and reslizumab 3.0 mg/kg treatment groups, respectively. The overall treatment effect was larger for patients in the reslizumab 3.0 mg/kg treatment group (treatment difference=0.160 L, p=0.0018) than for patients in the reslizumab 0.3 mg/kg treatment group (treatment difference=0.115 L, p=0.02).

Results from sensitivity analyses that included all FEV_1 measurements without exclusions for

concomitant medication were consistent with the primary analyses. Likewise, the statistically significant improvement in FEV_1 was supported for the reslizumab 3.0 mg/kg group with other measures of pulmonary function, including FVC, FEF25%-75%, and % predicted FEV_1. No treatment effect on FVC and FEF25%-75% was observed for patients in the reslizumab 0.3 mg/kg treatment group.

Figure 4. Mean change from baseline (±standard error) in FEV_1 to each visit and endpoint, study 3081



* p≤0.05, ** p≤0.005 versus placebo.
P-values are not adjusted to control for multiplicity.
The only time point for which multiplicity is controlled is week 16.
Source: Study 3081 Report Figure 3

Table 8. Primary endpoint: FEV_1 change from baseline over 16 weeks in study 3081

	Sponsor's Analysis excluding some measurements*			FDA Analysis including all measurements		
	Placebo	Reslizumab 0.3 mg/kg	Reslizumab 3.0 mg/kg	Placebo	Reslizumab 0.3 mg/kg	Reslizumab 3.0 mg/kg
N	103	101	102	103	101	102
Baseline mean	2.222	2.157	2.169	2.222	2.157	2.169
LS mean change	0.126	0.242	0.286	0.127	0.238	0.286
Treatment difference	NA	0.115	0.160	NA	0.111	0.159
95% CI	NA	(0.016, 0.215)	(0.060, 0.259)	NA	(0.012, 0.211)	(0.060, 0.258)
p-value	NA	0.0237	0.0018	NA	0.0283	0.0018

Source: Lan Zeng M.S., FDA Statistical Reviewer
LS = least squares
*The Applicant excluded data points if they were obtained at visits preceded by use of prohibited medications within seven days. Medications included systemic corticosteroids, long acting beta agonists, or long acting muscarinic antagonists if not taken at baseline.

Data Quality and Integrity – Reviewers' Assessment

The misclassification of the stratification variable for asthma exacerbation history was well-balanced among treatment arms and thus is unlikely to introduce significant bias in Study 3081. There were protocol violations for more than 20% of participants in Study 3081. However, in an addendum to the advisory committee briefing document, Teva clarified that the case report forms and clinical study reports allowed only for reporting of protocol violations, and did not allow for separate reporting of more minor protocol deviations, thus potentially inflating the proportion of violations reported for this program.

Efficacy Results – Secondary and other relevant endpoints

Improvements in ACQ and AQLQ scores, decreases in frequency of SABA use, and decreases in blood eosinophils were seen for patients in the reslizumab treatment groups. Except for asthma symptom score and SABA use, the changes from baseline in each of these endpoints were more consistent and larger for the reslizumab 3.0 mg/kg treatment group compared with the reslizumab 0.3 mg/kg treatment group. None of these comparisons was controlled for multiplicity; hence, p-values were nominal.

Table 9. Secondary endpoints in study 3081 (FAS with all measurements included)

Treatment difference vs placebo		Over 16 Weeks		At Week 16	
		Reslizumab 0.3 mg/kg	Reslizumab 3.0 mg/kg	Reslizumab 0.3 mg/kg	Reslizumab 3.0 mg/kg
FEV_1	Diff.			0.125	0.165
	95% CI			(–0.003, 0.253)	(0.037, 0.292)
	p-value			0.0555	0.0118
FVC	Diff.	0.044	0.129	0.027	0.113
	95% CI	(–0.062, 0.150)	(0.023, 0.235)	(–0.106, 0.159)	(–0.019, 0.246)
	p-value	0.4147	0.0173	0.6920	0.0940
$FEF_{25\%-75\%}$	Diff.	0.025	0.233	0.045	0.216
	95% CI	(-0.214, 0.263)	(-0.006, 0.471)	(–0.205, 0.296)	(–0.035, 0.467)
	p-value	0.8400	0.0559	0.7215	0.0917
AQLQ	Diff.	0.267	0.358	0.267	0.358
	95% CI	(–0.045, 0.579)	(0.047, 0.670)	(–0.045, 0.579)	(0.047, 0.670)
	p-value	0.0931	0.0241	0.0931	0.0241
ACQ	Diff.	–0.232	–0.361	–0.205	–0.352
	95% CI	(–0.451, –0.013)	(–0.580, –0.141)	(–0.481, 0.071)	(–0.629, –0.076)
	p-value	0.0379	0.0013	0.1446	0.0128
SABA	Diff.	–0.612	–0.632	–0.615	–0.711
	95% CI	(–1.114, –0.110)	(–1.133, -0.131)	(–1.244, 0.015)	(–1.341, –0.081)
	p-value	0.0170	0.0136	0.0555	0.0271
EOS	Diff.	–0.323	–0.494	–0.320	–0.460
	95% CI	(–0.370, –0.275)	(–0.542, –0.447)	(–0.383, –0.257)	(–0.523, –0.396)

p-value	<0.0001	<0.0001	<0.0001	<0.0001

Source: Lan Zeng M.S., FDA Statistical Reviewer

Additional Analyses Conducted on the Individual Trial

A responder analysis was performed for ACQ and AQLQ, as these instruments have good measurement qualities and substantial regulatory precedent for use in asthma product labels. Patients with missing data at Week 16 are treated as non-responders. A higher proportion of participants in the reslizumab arm achieved the minimum clinically important difference in ACQ and AQLQ analyses, and this finding was statistically significant for the AQLQ.

Table 10. Proportion of ACQ and AQLQ responders at week 16

Parameter	Placebo (N=105)	Reslizumab 0.3 mg/kg (N=106)	Reslizumab 3.0 mg/kg (N=106)
ACQ Responders (MCID Δ ≥0.5 Units)	n=84	n=92	n=91
Response, n (%)	49 (58)	56 (61)	58 (64)
p-value (vs. placebo)		0.806	0.479
AQLQ Responders (MCID Δ ≥0.5 Units)	n=101	n= 96	n= 99
Response, n (%)	48 (48)	57 (59)	63 (64)
p-value (vs. placebo)		0.083	0.019

Source: Lan Zeng M.S., FDA Statistical Reviewer

6.2. Studies 3082 and 3083

6.2.1. Study Design

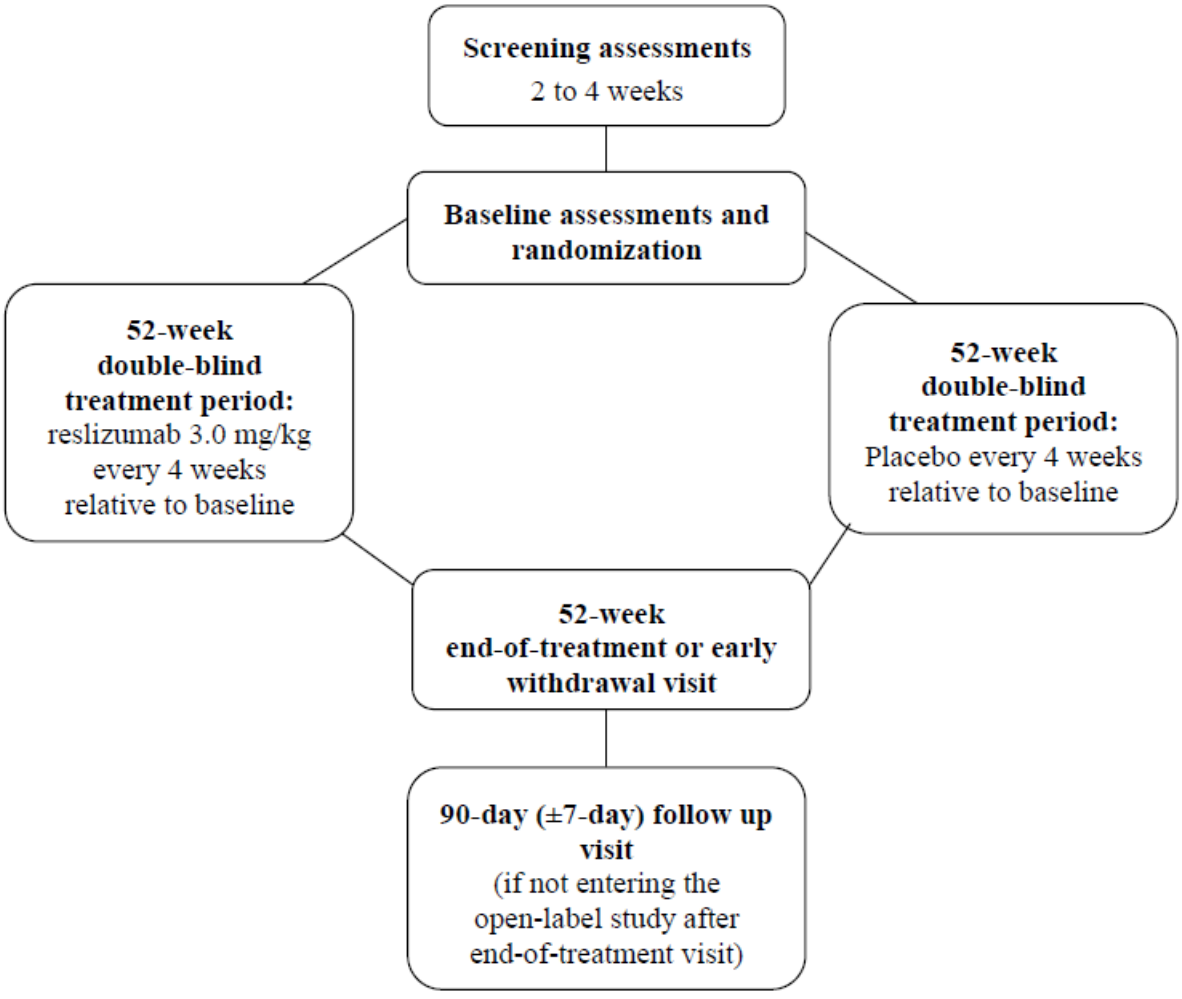
Overview and Objective

Studies 3082 and 3083 were conducted concurrently with each other and with Study 3081. As noted earlier, this timeline precluded use of dose-ranging data from 3081 to inform dose selection for Studies 3082 and 3083. Since Studies 3082 and 3083 were nearly identical, their design and results will be described together with any pertinent differences noted. Both studies were titled "A 12-Month, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Reslizumab (3.0 mg/kg) in the Reduction of Clinical Asthma Exacerbations in Patients (12-75 Years of Age) With Eosinophilic Asthma." The objective of these two studies was to demonstrate the safety and efficacy of reslizumab, at a dose of 3 mg/kg administered intravenously (IV) every 4 weeks over 12 months, as assessed by the reduction in frequency of asthma exacerbations during 12 months.

Trial Design

Studies 3082 and 3083 were phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies to evaluate the efficacy, safety, and immunogenicity of treatment with reslizumab, at a dosage of 3 mg/kg administered IV once every 4 weeks relative to baseline, in asthma patients (12 through 75 years of age) with an eosinophilic phenotype. The studies consisted of a 2- to 4-week screening period and a 52-week treatment period, including a final evaluation at week 52 (end-of-treatment visit; 4 weeks after the final infusion at week 48). After the end-of-treatment visit, patients enrolled in an available open-label, long-term study (Study 3085) or returned for an assessment 90 (±7) days after their end-of-treatment visit.

Figure 5. Schema for studies 3082 and 3083



Source: Protocols for studies 3082 and 3083

Pertinent inclusion criteria were:

- 12 to 75 years of age
- prior diagnosis of asthma
- at least 1 asthma exacerbation in the past 12 months requiring treatment with a systemic corticosteroid
- a blood eosinophil count of at least 400/μL
- an ACQ score of at least 1.5 at screening and baseline
- airway reversibility of at least 12% after short-acting beta-agonist administration
- fluticasone at a dosage of at least 440 mcg daily (or equivalent)
- female patients must be surgically sterile, 2 years postmenopausal, or must have a negative pregnancy test ßHCG at screening (serum) and baseline (urine)
- female patients of childbearing potential must use a medically accepted method of contraception and must agree to continue use of this method for the duration of the study and for 30 days after the end-of-treatment visit
- the patient is in reasonable health as judged by the investigator, and as determined by a medical history, medical examination, ECG evaluation, serum chemistry, hematology, urinalysis, and serology

Pertinent exclusion criteria

- exacerbation during or within 4 weeks before screening period (could be rescreened once only)
- known hypereosinophilic syndrome
- another lung disorder (e.g., chronic obstructive pulmonary disease, pulmonary fibrosis, or lung cancer, Churg-Strauss syndrome, allergic bronchopulmonary aspergillosis
- current smoker
- use of systemic immunosuppressive, or immunomodulating agents (anti-IgE monoclonal antibody, methotrexate, cyclosporin, interferon-α, or anti-tumor necrosis factor monoclonal antibody) within 6 months prior to study entry
- aggravating factors that are inadequately controlled e.g., gastroesophageal reflux disease
- previous treatment with anti-IL-5 monoclonal antibody (e.g., mepolizumab)
- immunodeficiency (human immunodeficiency, acquired immunodeficiency syndrome, or congenital immunodeficiency
- presence of or suspected active parasitic infestation infection
- active parasitic infection within 6 months prior to screening
- exposure to water-born parasites within 6 weeks prior to screening
- diarrheal illness of undetermined etiology within 3 months prior to screening
- live attenuated vaccine within the 12-week period before study entry
- history of allergic reactions to or hypersensitivity to any component of the study drug
- infection requiring hospitalization for at least 24 hours, or IV or oral antibiotics within 4 weeks prior to screening or during the screening period

Inclusion and exclusion criterion were revised under Amendments 1 and 2 on April 14, and April 19, 2011, respectively, after one patient was randomized in each of the two studies. Inclusion criteria were changed to state that baseline asthma therapy must be stable for 30 days prior to screening and continue without dosage changes throughout the study and regarding acceptable contraceptive methods. Exclusion criteria were revised to exclude patients with Churg-Strauss Syndrome or allergic bronchopulmonary aspergillosis, those with the presence of or suspected parasitic infestation/infection, and those who had received any live-attenuated vaccine within the 12-week period prior to screening.

Method of Blinding: Patients and investigators were blinded to treatment assignment during the study. In order to maintain the blinding in this 2-group study, each patient received a specific volume of study drug (active or placebo) based on the patient's body weight and assigned treatment group.

Investigational Product: reslizumab was provided as a sterile solution for infusion presented as 100 mg (10 mL) per vial, formulated at 10 mg/mL in (b) (4) 7% sucrose, pH 5.5 buffer. Patients randomly assigned to reslizumab were administered a dosage of 3.0 mg/kg IV once every 4 weeks relative to baseline over 52 weeks (a total of 13 doses administered).

Placebo: Placebo was provided as a sterile solution for infusion presented as 10 mL per vial, formulated in (b) (4) 7% sucrose, pH 5.5 buffer, and used in a manner identical to that of reslizumab.

Randomization & Stratification: Participants were randomized 1:1 to placebo or reslizumab. Randomization was stratified by maintenance oral corticosteroid use and region. Of note, there was no per-protocol definition of maintenance oral corticosteroid use, and there was no designated field on the case report form for recording this variable. Maintenance corticosteroid use was derived from the concomitant medication list. However, an interactive response technology was used for stratifying patients at the site level on the day of randomization based on oral corticosteroid use. There were discrepancies between these two measures, and as a result, stratification by maintenance corticosteroid use was misclassified for some participants in Studies 3082 and 3083. The misclassification rate in Study 3082 was 6.6% for placebo patients and 11.4% for reslizumab patients whereas in Study 3083 was 6.5% for placebo patients and 4.7% for reslizumab patients. For Study 3082, 40 (16%) patients in the placebo group had actual maintenance oral corticosteroid use, compared to only 24 (10%) in the reslizumab arm. For Study 3083, 18 (8%) patients in the placebo group had actual maintenance oral corticosteroid use, compared to 24 (10%) in the reslizumab arm.

Reviewer's comment: This misclassification bias based on the stratification variable was differential with respect to treatment group and would be non-conservative for Study 3082. More patients were taking maintenance oral corticosteroids in the placebo arm of Study 3082 than in the reslizumab arm. In other words, non-random error was introduced such that the placebo arm had more severe asthma than the reslizumab arm for Study 3082. This would

increase the chance that the reslizumab treatment group could demonstrate a benefit versus placebo even if there were no true effect of the drug.

Table 11. Studies 3082 and 3083 schedule of procedures and assessments

	Screening	Randomized Treatment Period													End of Treatment	Follow Up
Visit No.	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**
Week No.		**BL**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**65**
Complete H&P	✓														✓	
Urine pregnancy test	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Adverse event queries		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ECGs	✓							✓			✓				✓	
Serum chemistry	✓		✓	✓	✓		✓		✓			✓			✓	
CBC w/ diff	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Urinalysis	✓	✓			✓			✓			✓				✓	
Spirometry	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	

Source: Modified from Studies 3082 and 3083 Reports, Schedule of Procedures and Assessments
H&P = medical history and physical, CBC w/ diff = complete blood count with differential, BL = baseline

Study Endpoints

Primary

Frequency of asthma exacerbations per patient during the 52-week treatment period

An event was described as an exacerbation if the patient met at least one of the two criteria listed below, corroborated with at least one other measurement to indicate the worsening of clinical signs and symptoms of asthma:

1. use of systemic, or an increase in the use of inhaled corticosteroid treatment, for 3 or more days (For patients already being treated with systemic or inhaled corticosteroids, the dose of corticosteroids will need to be increased 2 or more fold for at least 3 or more days.)

AND/OR

2. asthma-related emergency treatment including at least one of the following:
   - an unscheduled visit to the physician's office for nebulizer treatment or other urgent treatment to prevent worsening of asthma symptoms
   - a visit to the emergency room for asthma related treatment
   - asthma-related hospitalization

The above criteria need to be corroborated with at least one other measurement to indicate worsening in clinical signs and symptoms of asthma as follows:
   - decrease in FEV_1 by 20% or more from baseline
   - decrease in Peak Expiratory Flow Rate (PEFR) below 30% from baseline on 2 consecutive days

- worsening of symptoms or other clinical signs per physician evaluation of the event

Reviewer's Comment: Agreement with the agency regarding this definition was reached in a Type C meeting in May 2013.

Secondary

1) FEV_1: change from baseline to week 16
2) FEV_1: change from baseline over 16 weeks
3) AQLQ: change from baseline to week 16
4) ACQ: change from baseline over 16 weeks
5) Time to first clinical asthma exacerbation
6) ASUI: change from baseline over 16 weeks
7) SABA use: change from baseline over 16 weeks
8) Blood eosinophils: change from baseline over 16 weeks and 52 weeks

Statistical Analysis Plan

For the primary endpoint, analysis of exacerbations was conducted using adjudicated data. The frequency of exacerbations was analyzed using the generalized linear model with negative binomial distributions and had the treatment group and randomization stratification factors (baseline usage of oral corticosteroid and geographical region) as factors. The offset variable was logarithm of follow-up time excluding the summed duration of exacerbations in the treatment period. Exacerbations that occur between the completion of the first dose of study drug and 2 weeks after the end of treatment/early withdrawal visit were counted for the analysis. The primary analysis was based on randomized data set including all patients who were randomly assigned to a treatment at enrollment, regardless of whether or not a patient took any study drug.

As secondary analyses for the primary endpoint, the same generalized linear model was used to analyze the following:

- frequency of asthma exacerbations requiring courses of systemic corticosteroids prescribed for 3 or more days
- frequency of asthma exacerbations requiring courses of oral corticosteroids prescribed for 3 or more days
- frequency of asthma exacerbations resulting in hospitalization or a visit to the emergency room

Furthermore, in response to the Division's request, the Applicant submitted additional analysis of exacerbations by severity level. Any asthma exacerbation resulting in an emergency room visit that required hospital admission was classified as severe, any asthma exacerbation resulting in an emergency room visit that required systemic corticosteroid was classified as moderate, and any emergency room visit that was not associated with the use of systemic corticosteroids or hospitalization was classified as mild. The analyses were based on the same

negative binomial model applied for each severity level or worse (rather than for each severity level on its own) as treatment would affect both the number and severity of exacerbations.

The analyses for the secondary efficacy endpoints were as follows. Change from baseline in FEV_1 were analyzed using a mixed effect model for repeated measures (MMRM) with independent variables of treatment, visit, and treatment by visit interaction, OCS use at baseline, region, sex, height, and baseline FEV_1. Analysis of AQLQ, ACQ, ASUI, SABA use, and blood eosinophils were conducted using MMRM with independent variables of treatment, visit, and treatment by visit interaction, OCS use at baseline, region, and respective baseline value. The proportion of patients achieving the minimal clinically important difference (MCID, at least a 0.5 improvement in AQLQ score, or at least a 0.5 reduction in ACQ score, or at least 0.09 improvement in ASUI score) were analyzed by the Cochran-Mantel-Haenszel test with stratification for baseline usage of oral corticosteroid and region. Time to first exacerbation was analyzed using the Kaplan-Meier method with a log-rank test adjusting for baseline usage of oral corticosteroid and region. Patients without exacerbation were censored at two weeks after the treatment completion date or study discontinuation, whichever occurred first.

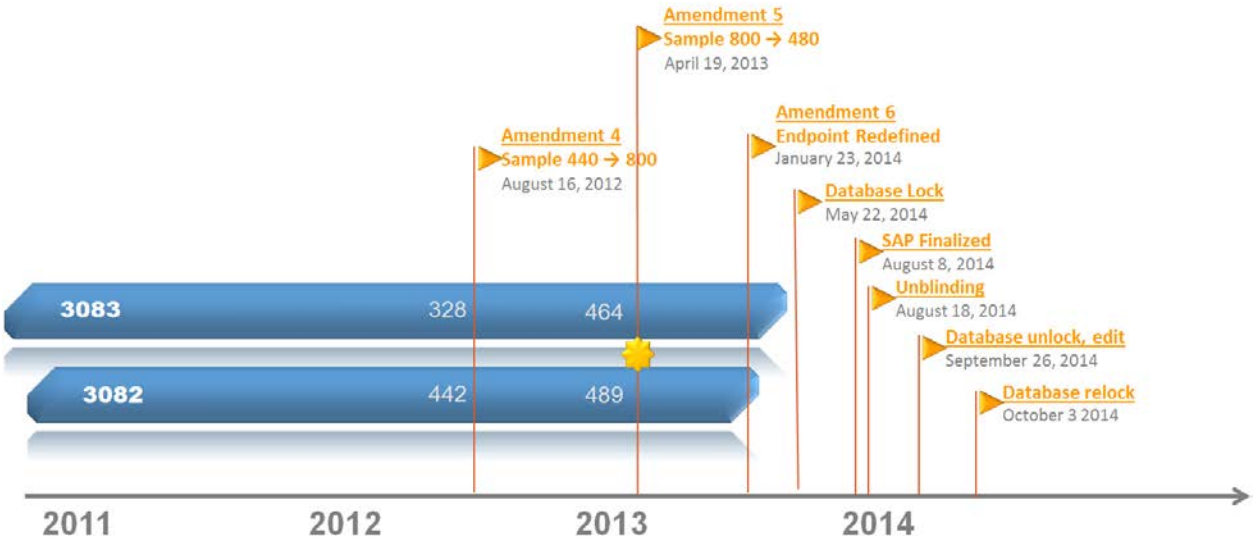
To control the overall Type I error rate at 0.05, a fixed sequence multiple testing procedure was implemented to test the primary and secondary variables in the order specified in the "Study Endpoint" section. At the point where p-value >0.05, no further comparisons were interpreted inferentially. If the analyses of each of the secondary endpoints resulted in $p<0.05$, then the secondary analysis of the primary efficacy variable (frequency of exacerbations requiring systemic corticosteroids for ≥3 days) was considered controlled for Type I error rate.

Missing data were not imputed in the negative binomial regression model for the primary analysis. A sensitivity analysis using a multiple imputation method and a tipping-point sensitivity analysis were performed. The primary analysis was also repeated using an offset that did not exclude the summed duration of exacerbations from the follow-up time.

Protocol Amendments & Study Conduct

Studies 3082 and 3083 underwent six protocol amendments. The first three amendments occurred early in study conduct, when ten or fewer patients had been randomized in each study, on April 14, 2011, April 19, 2011, and August 11, 2011, respectively. Inclusion criteria were changed to allow enrollment of patients using oral corticosteroids at a stable dose of up to 10 mg prednisone daily or equivalent. The definition of a clinical asthma exacerbation was changed such that a fall in peak expiratory flow rate must be accompanied by both symptomatology and the addition or increase in dosage of asthma corticosteroid therapy.

Figure 6. Amendments & conduct for studies 3082 and 3083



Source: K. Donohue

The last three amendments occurred late in study conduct. Amendment 4 was filed on August 16, 2012 after 442 patients had been randomized in Study 3082 and n=328 patients to Study 3083. Amendments 5 and 6 were filed after enrollment was complete in both studies, on April 19, 2013 and January 23, 2014. Amendment 4 increased the sample size from n=440 to n=800, citing papers showing a lower-than-expected exacerbation rate (26, 27). Amendment 5 was associated with a change in leadership at Teva and a reduction in sample size from n=800 to n=480, at a time when enrollment equaled n=489 patients in Study 3082 and n=464 in Study 3083. The rationale given was the publication by Pavord et al. in August 2012 showing a slightly higher exacerbation rate (28). Amendment 6 altered the definition of the primary endpoint. The definition of an exacerbation was changed to require that a decrease in lung function be significant enough to require an increase in asthma treatment. Amendment 6 of Study 3082 also removed the co-primary endpoint of FEV_1 change from baseline to Week 16 or the onset of first exacerbation so that exacerbation became the single primary endpoint as in Study 3083.

The Division agreed to the changed exacerbation definition in written responses for a Type C meeting May 17, 2013, but Amendment 6 was not filed until January 23, 2014.

The database was locked May 22, 2014, the statistical analysis plan finalized August 8, 2014, and unblinded on August 18, 2014. Of note, the database was unlocked September 26, 2014 for editing, and then re-locked October 3, 2014. An audit of the logs was performed and revealed that the changes were minor (See section 4.1 Office of Scientific Investigations). The audit found that:

- The clinical database field AEACNOTH (a SAS annotated variable ("Other Action Taken" on the AE CRF page) was added to the database bit was never incorporated to the final locked SDTM (Study Data Tabulation Module).

- For Study 3082 only: Subject 3082_185201 Week #32 FVC value was incorrectly entered as 63.2 units, and corrected by the study site.
- For Study 3083 only: Subject 3083_371301 Week #44 FVC value was incorrectly entered as 111.1 units, and corrected by the study site. Further, the German study site database demographic fields "AGE" (age) and "YEAR" (birthdate) were added. Since these issues were identified after database lock and unblinding, the above missing database fields were added to the SDTM AE dataset.

Reviewer Comment: It is noted that the sample size was reduced from n=800 to n=480, at a time when enrollment equaled n=489 patients for Study 3082, and n=464 for Study 3083, ostensibly based on a single academic paper. Though the change to the exacerbation definition is minor on its face, it is noteworthy that the definition of the primary endpoint was changed after enrollment was completed for the trials. Both the timing of these amendments and editing of the database after unblinding is less than ideal, but does not a priori discredit the data.

Data Quality and Integrity: Sponsor's Assurance

The Applicant asserts that data handling was conducted according to International Conference on Harmonisation and Good Clinical Practice guidelines.

6.2.2. Study Results

Compliance with Good Clinical Practices

Written informed consent or assent was obtained from all participants. The sponsor attests that the study was conducted in full accordance with the International Conference on Harmonisation, Good Clinical Practice Consolidated Guideline E6 and any applicable national and local laws and regulations.

Patient Disposition

A total of 953 subjects were enrolled into Studies 3082 and 3083, of which 952 subjects received at least 1 dose of study drug and 835 subjects completed the trial. In Study 3082, 56 (11%) subjects stopped medication early and 56 (11%) discontinued from the study prematurely. In Study 3083, 62 (13%) subjects terminated study drug early and 63 (14%) prematurely discontinued from the study. The most common reason for discontinuation from study drug treatment was consent withdrawn (5% of patients overall in each study). Patient disposition for each study is shown in **Table 12**.

Reviewer's comment: The rate of treatment withdrawal was balanced across treatment arms in each of the exacerbation studies and is consistent with what typically is observed in 52-week asthma exacerbation studies.

Table 12. Studies 3082 and 3083 disposition

	Study 3082		Study 3083	
	Placebo	Reslizumab	Placebo	Reslizumab
Randomized	244	245	232	232
Never dosed	1	0	0	0
Treated	243	245	232	232
Completed treatment	215 (88%)	218 (89%)	200 (86%)	202 (87%)
Discontinued treatment	29 (12%)	27 (11%)	32 (14%)	30 (13%)
Completed study	215 (88%)	218 (89%)	199 (86%)	202 (87%)
Discontinued study	29 (12%)	27 (11%)	33 (14%)	30 (13%)
Discrepancies in OCS use between IRT and CRF	16 (6.6%)	28 (11.4%)	15 (6.5%)	11 (4.7%)
Analysis Datasets				
Randomized Set	244	245	232	232
Full analysis set	243	245	232	232
Safety Set	243	245	232	232

Source: Lan Zeng M.S., FDA Statistical Reviewer
OCS = oral corticosteroid, IRT = interactive response technology, CRF = case report form

Protocol Violations/Deviations

Table 13. Studies 3082 and 3083 protocol violations

	Study 3082			Study 3083		
	Placebo (N=244)	Reslizumab 3 mg/kg (N=245)	Total (N=489)	Placebo (N=232)	Reslizumab 3 mg/kg (N=232)	Total (N=464)
Patients with ≥ 1 violation, n (%)	59 (24)	57 (23)	116 (24)	55 (24)	53 (23)	108 (23)
Inclusion criteria	22 (9)	19 (8)	41 (8)	13 (6)	16 (7)	29 (6)
Exclusion criteria	1 (<1)	1 (<1)	2 (<1)	3 (1)	0	3 (<1)
Good Clinical Practice	17 (7)	15 (6)	32 (7)	7 (3)	15 (6)	22 (5)
Study drug	6 (2)	9 (4)	15 (3)	7 (3)	10 (4)	17 (4)
Concomitant Medication	5 (2)	5 (2)	10 (2)	2 (<1)	1 (<1)	3 (<1)
Exacerbation criteria	1 (<1)	2 (<1)	3 (<1)	1 (<1)	2 (<1)	3 (<1)
Other	13 (5)	15 (6)	28 (6)	23 (10)	16 (7)	39 (8)

Source: Studies 3082 and 3083 Reports
Patients could have had more than one protocol violation.

Table of Demographic Characteristics

Selected demographic features for all randomized patients are shown in **Table 14** below. Within each study, subject demographics and baseline characteristics generally were balanced among the two treatment groups. The majority of subjects were female, white and of non-Hispanic or non-Latino ethnicity. The median age was 48 years in both studies. There were 13 (3%) subjects in Study 3082 and 12 (3%) subjects in Study 3083 who were less than 18 years old.

Table 14. Studies 3082 and 3083 demographics

	Study 3082		Study 3083	
	Placebo (N=244)	Reslizumab (N=245)	Placebo (N=232)	Reslizumab (N=232)
Age (years)	n=244	n=245	n=232	n=232
Mean	46.7	46.6	47.5	46.4
SD	14.83	13.82	13.75	13.79
Median	49.0	48.0	48.0	48.0
Sex, n (%)				
Male	83 (34)	103 (42)	82 (35)	88 (38)
Female	161 (66)	142 (58)	150 (65)	144 (62)
Race, n (%)				
White	182 (75)	173 (71)	169 (73)	168 (72)
Black	20 (8)	14 (6)	4 (2)	6 (3)
Asian	33 (14)	50 (20)	21 (9)	16 (7)
American Indian or Alaskan Native	0	0	4 (2)	7 (3)
Pacific Islander	0	1 (<1)	1 (<1)	0
Other	9 (4)	7(3)	33 (14)	35 (15)
Ethnicity, n (%)				
Hispanic or Latino	21 (9)	28 (11)	53 (23)	54 (23)
Non-Hispanic or non-Latino	223 (91)	216 (88)	178 (77)	177 (76)
Unknown	0	1 (<1)	1 (<1)	1 (<1)
Weight (kg)	n=244	n=245	n=232	n=232
Mean	76.5	75.6	73.9	74.7
SD	18.71	19.05	15.93	15.72
Median	74.9	73.8	72.0	73.2
Region, n (%)				
U.S.	37 (15)	37 (15)	15 (6)	16 (7)
Non-U.S.	207 (85)	208 (85)	217 (94)	216 (93)

Source: Lan Zeng M.S., FDA Statistical Reviewer

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline characteristics are shown in **Table 15**. Within each study, the distributions of clinical characteristics such as FEV_1, airway reversibility, previous asthma history, and severity scores, generally were similar across both groups. However, the placebo arm in Study 3082 had greater need for rescue beta-agonist treatment in the prior three days.

Table 15. Studies 3082 and 3083 baseline characteristics

	Study 3082		Study 3083	
	Placebo (N=244)	Reslizumab (N=245)	Placebo (N=232)	Reslizumab (N=232)
Asthma exacerbations in the previous 12 months, n (%)				
Yes	242 (>99)	242 (99)	232 (100)	231 (>99)
No	2 (<1)	3 (1)	0	1 (<1)
Number of events	n=242	n=242	n=232	n=232
Mean	2.1	1.9	2.0	1.9
SD	2.31	1.63	1.78	1.58
Median	1.0	1.0	1.0	1.0
Duration of asthma (years)	n=234	n=233	n=231	n=232
Mean	18.8	19.7	18.7	18.2
SD	14.2	15.19	13.28	14.43
Median	15.8	15.3	15.5	14.2
FEV_1 (L)	n=244	n=245	n=232	n=232
Mean	1.928	1.894	2.004	2.129
SD	0.7908	0.7258	0.6682	0.7848
Median	1.800	1.780	1.910	2.005
% predicted FEV_1	n=244	n=245	n=232	n=232
Mean	65.0	63.6	68.0	70.4
SD	19.80	18.55	18.93	20.98
Median	65.0	64.0	65.3	68.9
Airway reversibility (%)	n=244	n=245	n=232	n=232
Mean	26.3	26.1	28.7	28.1
SD	18.10	15.47	23.75	16.06
Median	20.4	21.1	21.9	23.8
Blood eosinophil count (10^9 cells/L)	n=244	n=245	n=232	n=232
Mean	0.624	0.696	0.688	0.610
SD	0.5903	0.7677	0.6824	0.4115
Median	0.500	0.500	0.500	0.500
AQLQ total score	n=242	n=243	n=231	n=229
Mean	4.159	4.303	4.223	4.352
SD	1.0883	1.1208	1.0794	1.0220
Median	4.125	4.344	4.219	4.313
ACQ score	n=244	n=245	n=232	n=232
Mean	2.763	2.657	2.605	2.570
SD	0.8782	0.8541	0.7943	0.8876
Median	2.714	2.571	2.429	2.429
ASUI score	n=241	n=241	n=229	n=228
Mean	0.613	0.633	0.649	0.664
SD	0.2029	0.1938	0.1919	0.2005
Median	0.618	0.660	0.663	0.694
Used beta-agonist in past 3 days, n (%)				
Yes	188 (77)	170 (69)	181 (78)	182 (78)
No	53 (22)	72 (29)	46 (20)	44 (19)
Daily average number of puffs in past 3 days	n=241	n=242	n=201	n=204
Mean	2.7	2.4	2.7	2.9
SD	3.18	2.82	2.41	2.82
Median	2.0	2.0	2.0	2.0

Source: Lan Zeng M.S., FDA Statistical Reviewer

Treatment Compliance, Prior Medications, and Rescue Medication Use

Compliance was excellent (approximately 100%) in both arms in both studies. Prior medication use generally was well-balanced between treatment arms in both studies, with a few exceptions. For Study 3082, patients in the placebo arm were more likely than those randomized to reslizumab to use systemic corticosteroids (18 % vs. 12%) and nasal preparations (34% vs. 30%), and less likely to use lipid modifying agents (8% vs. 11%). For Study 3083, patients in the placebo arm were more likely than those randomized to reslizumab to use nasal preparations (30% vs. 26%) and antihistamines (26% vs. 18%), and less likely to use systemic corticosteroids (10% vs. 13%). Rescue medication use of short-acting beta-agonists was evaluated as a secondary endpoint and is discussed below.

Efficacy Results - Primary Endpoint

The primary efficacy assessment for both studies was based on the frequency of asthma exacerbations for each patient during the 52-week treatment period. Results are shown in **Table 16**. Compared to placebo, the mean rate of asthma exacerbation was significantly reduced among patients administered reslizumab in both studies. The point estimate for exacerbation rate ranged from 0.86 to 0.90 per year in reslizumab-treated patients versus 1.80 to 2.11 per year in placebo patients. These results were consistent when the actual values for oral corticosteroid use from the clinical database were used in the model, indicating a significantly lower frequency of exacerbations due to reslizumab treatment (analysis by Lan Zeng M.S., FDA Statistical Reviewer).

Table 16. Studies 3082 and 3083 asthma exacerbation rates

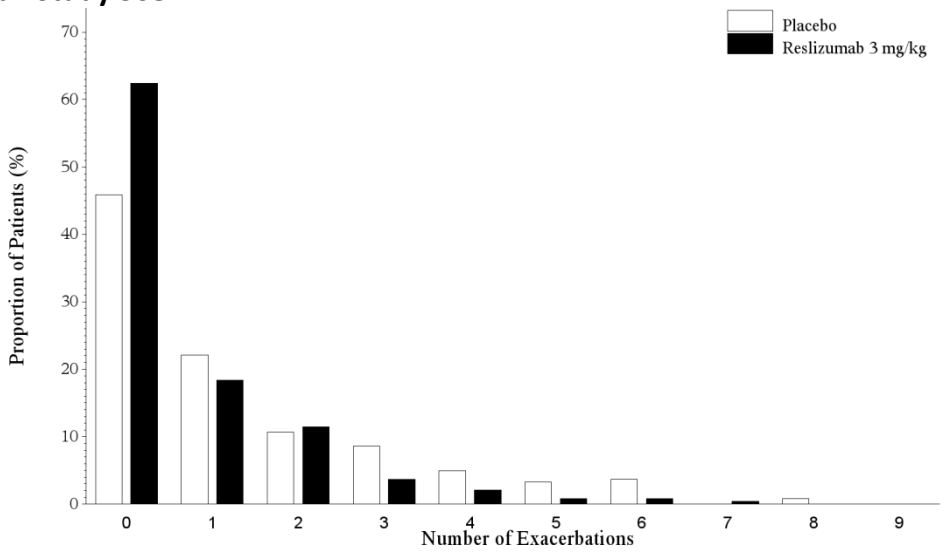
Parameter	Study 3082		Study 3083	
	Placebo (N=244)	Reslizumab (N=245)	Placebo (N=232)	Reslizumab (N=232)
Patients with ≥1 exacerbation, n (%)	132 (54.1)	92 (37.6)	105 (45.3)	59 (25.4)
Sponsor's Analysis*				
Adjusted exacerbation rate	1.80	0.90	2.11	0.86
(95% CI)	(1.37, 2.37)	(0.68, 1.20)	(1.33, 3.36)	(0.55, 1.35)
exacerbation rate ratio		0.5010		0.4063
(95% CI)	-	(0.3726, 0.6737)	-	(0.2819, 0.5855)
p-value		<0.0001		<0.0001
Reviewer's Analysis**				
Adjusted exacerbation rate	1.92	1.0	2.17	0.87
(95% CI)	(1.45, 2.55)	(0.73, 1.35)	(1.33, 3.54)	(0.55, 1.40)
exacerbation rate ratio		0.5173		0.4021
(95% CI)	-	(0.3845, 0.6959)	-	(0.2786, 0.5803)
p-value		<0.0001		<0.0001

*Based on a negative binomial regression model with adjustment for IRT stratification factors (baseline usage of OCS [yes or no] and geographical region [U.S. or other]).
**Based on a negative binomial regression model with adjustment for CRF record (baseline usage of OCS [yes or no] and geographical region [U.S. or other]).
Source: Lan Zeng M.S., FDA Statistical Reviewer

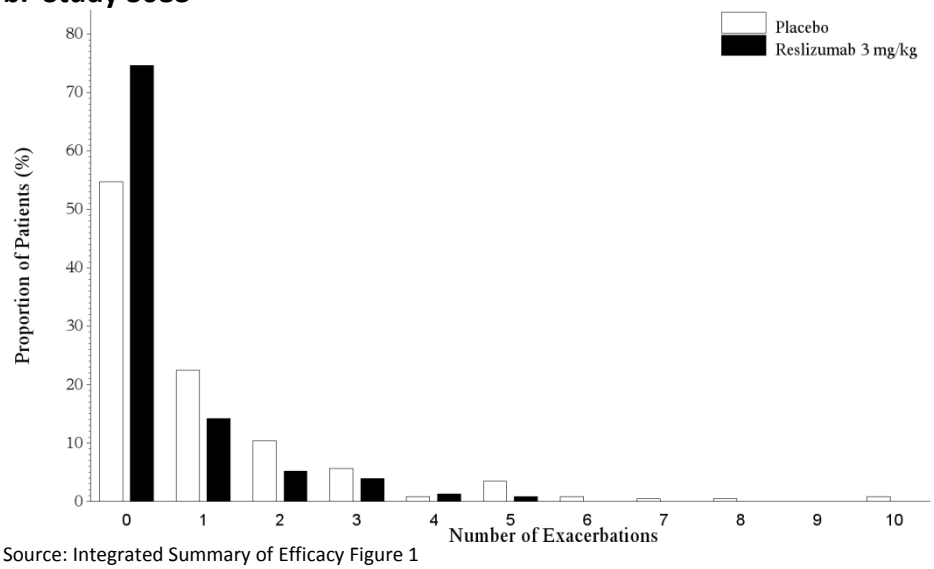
The frequency distribution of exacerbations during the 52-week treatment period is shown in Figure 7. The proportion of patients who did not experience an asthma exacerbation during the entire treatment period was higher in the reslizumab group (62% and 75%) compared with the placebo group (46% and 55%), in Studies 3082 and 3083, respectively.

Figure 7. Number of asthma exacerbations per patient

a. Study 3082



b. Study 3083



Source: Integrated Summary of Efficacy Figure 1

A secondary analysis was performed stratified by level of treatment needed for the exacerbations. The efficacy of reslizumab in reducing the frequency of exacerbations compared to placebo in patients with exacerbations requiring oral or systemic corticosteroids for three or more days was consistent with results of the primary efficacy analysis. For patients with exacerbations requiring an emergency room visit and/or hospitalization during the study, the

adjusted exacerbation rate was lower in the reslizumab group compared to placebo but the difference was not statistically significant. These analyses were not controlled for multiplicity. Hence, p-values were nominal.

Table 17. Studies 3082 and 3083 frequency of asthma exacerbations by treatment*

	Study 3082		Study 3083	
	Placebo (N=244)	**Reslizumab (N=245)**	**Placebo (N=232)**	**Reslizumab (N=232)**
Systemic corticosteroid use				
exacerbation rate (95% CI)	1.60 (1.195, 2.15)	0.72 (0.53, 0.99)	1.66 (1.00, 2.74)	0.6463 (0.3967, 1.0531)
exacerbation rate ratio (95% CI) p-value	-	0.4499 (0.3255, 0.6220) <0.0001	-	0.3893 (0.2621, 0.5782) <0.0001
Oral corticosteroid use				
exacerbation rate (95% CI)	1.59 (1.18, 2.14)	0.6974 (0.509, 0.956)	1.60 (0.95, 2.72)	0.65 (0.39, 1.07)
exacerbation rate ratio (95% CI) p-value	-	0.4383 (0.3158, 0.6085) <0.0001	-	0.4027 (0.2660, 0.6096) <0.0001
Hospital and/or emergency room visit				
exacerbation rate (95% CI)	0.207 (0.107, 0.400)	0.137 (0.068, 0.274)	0.0473 (0.0133, 0.1676)	0.0325 (0.0088, 0.1203)
exacerbation rate ratio (95% CI) p-value	-	0.6595 (0.3210, 1.3550) 0.2572	-	0.6886 (0.2878, 1.6479) 0.4020

*Based on a negative binomial regression model with adjustment for IRT stratification factors (baseline usage of OCS [yes or no] and geographical region [U.S. or other]).
Source: Lan Zeng M.S., FDA Statistical Reviewer
OCS = oral corticosteroid

The frequency of asthma exacerbations was further analyzed by severity level (**Table 18**). Reslizumab reduces the number of severe exacerbations compared with placebo with a reduction of 45% to 56% although the difference was not statistically significant. Reslizumab reduces the frequency of moderate and/or severe exacerbations by 55% to 61% (p-value <0.0001). The analyses show a consistent percent of reduction for severe, moderate or worse, and all exacerbations. Results also are consistent between the two studies.

Table 18. Studies 3082 and 3083 frequency of asthma exacerbations by severity

Variable	Study 3082		Study 3083	
	Placebo (N=244)	Reslizumab (N=245)	Placebo (N=232)	Reslizumab (N=232)
Number of patients with at least 1 Severe Asthma Exacerbation (%)	11 (4.5)	9 (3.7)	8 (3.4)	5 (2.2)
Frequency of severe exacerbation during treatment period				
Mean (SD)	0.09 (0.5)	0.04 (0.2)	0.04 (0.2)	0.02 (0.1)
Adjusted exacerbation rate* (95% CI)	0.00000061 (0.0000003, 0.00000124)	0.00000027 (0.00000011, 0.00000066)	0.0363 (0.0088, 0.1503)	0.0201 (0.0044, 0.0923)
exacerbation rate ratio (95% CI)	-	0.4 (0.1, 1.3)	-	0.6 (0.2, 1.7)
p-value		0.1		0.3
Number of patients with at least 1 Moderate or Worse Asthma Exacerbation (%)	120 (49.2)	81 (33.1)	92 (39.7)	51 (22.0)
Frequency of moderate or worse exacerbation during treatment period				
Mean (SD)	1.14 (1.6)	0.56 (1.1)	0.81 (1.4)	0.36 (0.8)
Adjusted exacerbation rate* (95% CI)	1.6 (1.2, 2.2)	0.7 (0.5, 1.0)	1.7 (1.0, 2.8)	0.7 (0.4, 1.1)
exacerbation rate ratio (95% CI)		0.5 (0.3, 0.6)		0.4 (0.3, 0.6)
p-value		<0.0001		<0.0001
Number of patients with at least 1 Mild or Worse Asthma Exacerbation (%)	132 (54.1)	92 (37.6)	105 (45.3)	59 (25.4)
Frequency of mild or worse exacerbation during treatment period				
Mean (SD)	1.34 (1.8)	0.72 (1.2)	1.01 (1.7)	0.46 (1)
Adjusted exacerbation rate* (95% CI)	1.8 (1.4, 2.4)	0.9 (0.7, 1.2)	2.1 (1.3, 3.4)	0.9 (0.6, 1.4)
exacerbation rate ratio (95% CI)	-	0.5 (0.4, 0.7)	-	0.4 (0.3, 0.6)
p-value		<0.0001		<0.0001

*Based on a negative binomial regression model with adjustment for IRT stratification factors (baseline usage of OCS [yes or no] and geographical region [U.S. or other]).
Source: Lan Zeng M.S., FDA Statistical Reviewer
Severe – hospitalization
Moderate – initiation of or increase in systemic corticosteroids
Mild – anyone else meeting the exacerbation definition and not captured in the above categories

Data Quality and Integrity - Reviewers' Assessment

This misclassification of oral corticosteroid use in the stratification process introduced bias into both studies. Moreover, this bias was differential with respect to treatment group and was non-conservative for Study 3082. Sensitivity analyses were robust to the imbalance, making this misclassification less relevant to the efficacy discussion. However, given that the patients in the placebo arm of Study 3082 were considerably sicker than those in the treatment arm, this remains pertinent to the safety evaluation and is discussed in Section 8.

Efficacy Results - Secondary and other relevant endpoints

The eight secondary endpoints were tested sequentially at α=0.05 if the primary analysis was significant. Sequential testing continued until non-significance was noted. Since the primary endpoint was significant in each study, the secondary endpoints were tested. The results are shown in **Table 19**.

Table 19. Studies 3082 and 3083 summary of secondary endpoints

		Study 3082			Study 3083		
	Statistic	Placebo	Res	Res - Pbo (95% CI) p-value	Placebo	Res	Res - Pbo (95% CI) p-value
FEV_1 Δ to Week 16	LS mean (SE)	0.136 (0.033)	0.208 (0.032)	0.072 (0.001, 0.144) 0.0483	0.122 (0.045)	0.223 (0.045)	0.101 (0.023, 0.179) 0.0109
FEV_1 Δ over 16 weeks	LS mean (SE)	0.110 (0.031)	0.248 (0.030)	0.137 (0.076, 0.198) <0.0001	0.094 (0.041)	0.187 (0.041)	0.093 (0.030, 0.155) 0.0037
AQLQ Δ to Week 16	LS mean (SE)	0.695 (0.088)	0.933 (0.088)	0.238 (0.048, 0.428) 0.0143	0.777 (0.115)	0.987 (0.116)	0.209 (0.025, 0.393) 0.0259
ACQ Δ over 16 weeks	LS mean (SE)	-0.676 (0.066)	-0.941 (0.065)	-0.266 (-0.399, -0.132) 0.0001	-0.660 (0.088)	-0.857 (0.087)	-0.196 (-0.327, -0.066) 0.0032
SABA Δ Over 16 weeks	LS mean (SE)	-0.36 (0.158)	-0.64 (0.156)	-0.276 (-0.597, 0.045) 0.0919	-0.44 (0.233)	-0.50 (0.230)	-0.062 (-0.411, 0.287) 0.7263
EOS Δ Over 16 weeks	LS mean (SE)	-0.118 (0.023)	-0.584 (0.0230)	-0.466 (-0.514,-0.418) <0.0001	-0.076 (0.027)	-0.555 (0.027)	-0.479 (-0.519, -0.439) <0.0001
Blood EOS Δ Over 52 weeks	LS mean (SE)	-0.127 (0.017)	-0.582 (0.017)	-0.455 (-0.491, -0.419) <0.0001	-0.076 (0.023)	-0.565 (0.023)	-0.489 (-0.525, -0.453) <0.0001

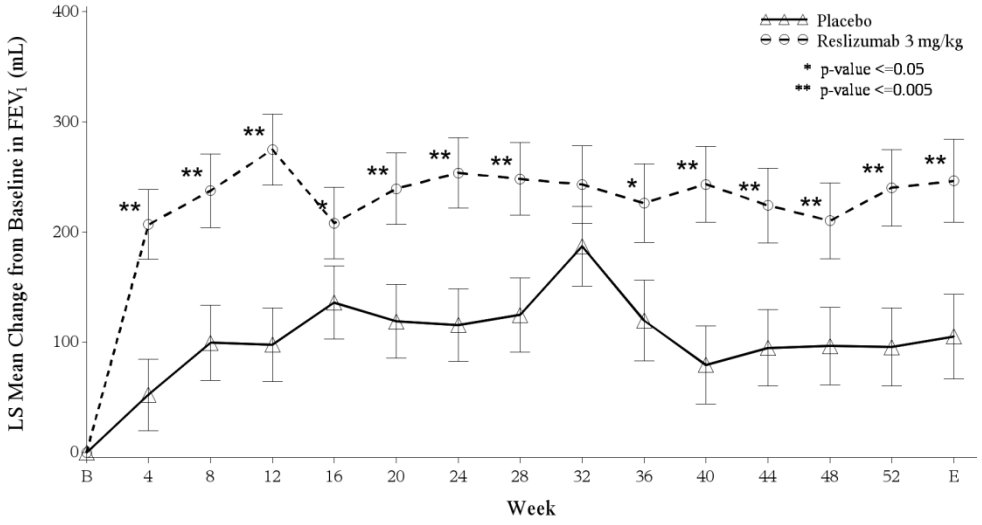
Source: Lan Zeng M.S., FDA Statistical Reviewer

Figure 8 illustrates the mean change from baseline in FEV_1 to each visit. In both studies, statistically significant improvement (increase) was observed for both the change from baseline to week 16 and overall change over 16 weeks in the reslizumab group compared with placebo.

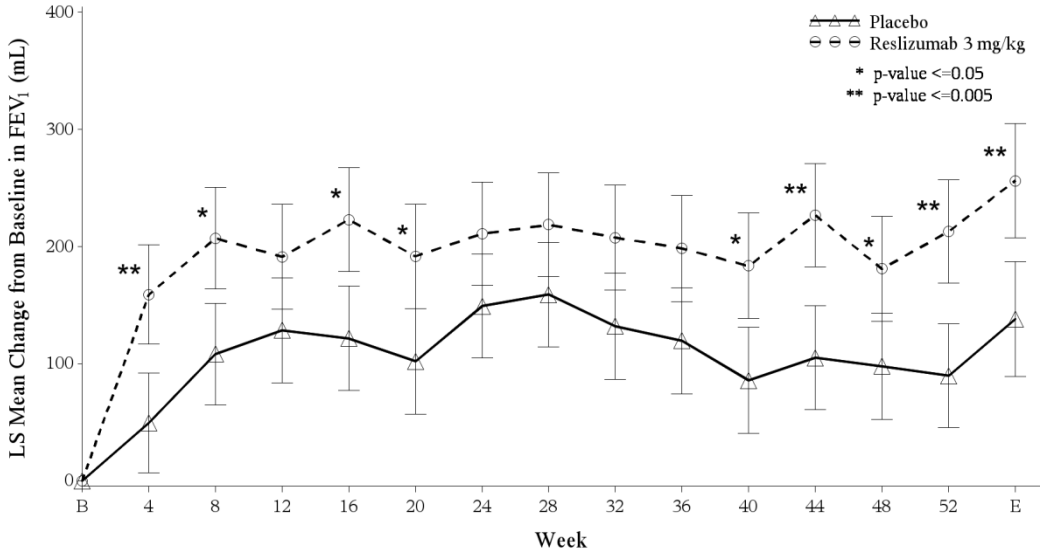
Based on the hierarchical testing procedure, the other secondary endpoints were tested sequentially.

Figure 8. Mean change from baseline in FEV_1 to each visit and endpoint

a. Study 3082*



b. Study 3083*



*Week 16 was the only time point for which multiplicity was controlled
Source: Integrated Summary of Efficacy Figure 3

Additional Analyses Conducted on the Individual Trial

In both studies, treatment with reslizumab resulted in significant improvement over placebo for the following endpoints: change from baseline in AQLQ score to Week 16, overall change from baseline in ACQ score over 16 weeks, time to first exacerbation, and overall change from

baseline in ASUI score over 16 weeks. The Kaplan-Meier estimates of probability of not experiencing an exacerbation by week 52 were higher in patients receiving reslizumab than in patients receiving placebo in Studies 3082 (61.3% vs. 44.2%) and 3083 (73.2% vs. 51.9%). The hazard ratio (95%CI), reslizumab versus placebo, was 0.575 (0.440, 0.750) (p<0.0001) in Study 3082 and 0.486 (0.353, 0.670) (p<0.0001) in Study 3083, respectively. The median time to first exacerbation could not be estimated for the reslizumab treatment group in either study because less than 50% of patients in that group experienced an exacerbation.

With regard to the overall change from baseline in SABA use over 16 weeks, there was an improvement in favor of reslizumab in both studies, but the results were not statistically significant. Based on the hierarchical testing procedure, the testing hierarchy stopped at this endpoint for both studies. The results for the blood eosinophils endpoints, overall change from baseline in blood eosinophil (EOS) count over 16 weeks and 52 weeks were not considered significant and were not discussed further.

Table 20 shows the responder analysis results based on proportion of patients achieving the minimal clinically important difference at Week 16. Patients with missing data at Week 16 are treated as non-responders. While not controlled for multiplicity of testing, the proportion of ACQ or AQLQ responders at Week 16 was numerically greater in the reslizumab group compared with placebo and the results are statistically significant in Study 3083.

Table 20. Studies 3082 and 3083 proportion of ACQ and AQLQ responders at week 16

Parameter	Study 3082		Study 3083	
	Placebo (N=244)	Reslizumab (N=245)	Placebo (N=232)	Reslizumab (N=232)
ACQ Responders (MCID Δ ≥0.5 Units)	n=228	n=232	n=214	n=214
Response, n (%)	149 (65)	159 (69)	124 (58)	149 (70)
p-value (vs. placebo)		0.4706		0.0103
AQLQ Responders (MCID Δ ≥0.5 Units)	n=229	n= 228	n= 216	n= 213
Response, n (%)	133 (58)	151 (66)	119 (55)	142 (67)
p-value (vs. placebo)		0.0620		0.0140

Source: Lan Zeng M.S., FDA Statistical Reviewer

6.3. Study 3084

6.3.1. Study Design

Overview and Objective

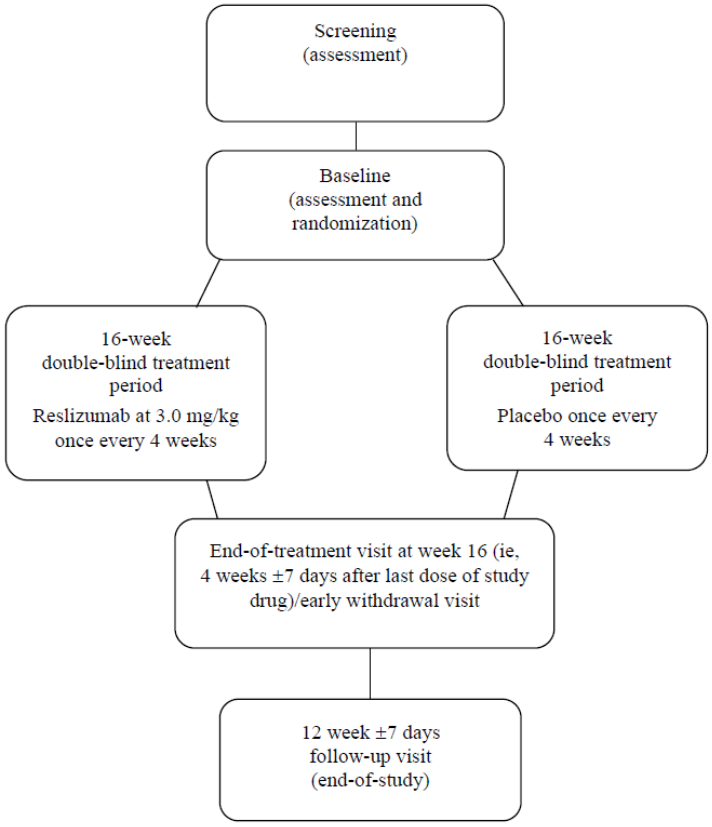
Study 3084 was titled "A 16-Week, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Reslizumab (3.0 mg/kg) Treatment in Patients With Moderate to Severe Asthma." The primary objective was to characterize the efficacy of

reslizumab treatment compared with placebo in improving lung function, as assessed by the change from baseline to week 16 in FEV_1, in patients with moderate to severe asthma who were unselected for baseline blood eosinophil levels. The study was initiated February 17, 2012, completed August 14, 2013, and the report approved March 24, 2015.

Trial Design

Study 3084 was a phase 3, multicenter, randomized, 16-week, double-blind, placebo-controlled study in patients (aged 18 through 65 years) with moderate to severe asthma. Randomization was stratified by occurrence of asthma exacerbation(s) during the previous year (yes or no). Within each stratum, eligible patients were randomly assigned in a 4:1 ratio to receive reslizumab 3.0 mg/kg or placebo every 4 weeks over 16 weeks.

Figure 9. Study 3084 schema



Source: Study 3084 Report Figure 1

Pertinent inclusion criteria:

- 18 through 65 years of age
- diagnosis of asthma
- ACQ score of at least 1.5
- airway reversibility of at least 12% to beta-agonist

- fluticasone at a dosage of at least 440 µg daily (or equivalent)
- baseline asthma therapy regimens (including, but not limited to, ICS, leukotriene antagonists, 5-lipoxygenase inhibitors, cromolyn) must have been stable for 30 days before screening and were expected to continue without dosage changes throughout study
- female patients must have been surgically sterile, 2 years postmenopausal, or must have had a negative beta-human chorionic gonadotropin (ßHCG) result for a pregnancy test at screening (serum) and baseline (urine)
- female patients of childbearing potential must have used a medically accepted method of contraception
- the patient is in reasonable health as judged by the investigator, and as determined by a medical history, medical examination, ECG evaluation, serum chemistry, hematology, urinalysis, and serology

Pertinent exclusion criteria:

- clinically meaningful comorbidity
- known hypereosinophilic syndrome
- another lung disorder (e.g., chronic obstructive pulmonary disease, pulmonary fibrosis, or lung cancer, Churg-Strauss syndrome, allergic bronchopulmonary aspergillosis
- current smoker
- use of systemic immunosuppressive, or immunomodulating agents (anti-IgE monoclonal antibody, methotrexate, cyclosporin, interferon-α, or anti-tumor necrosis factor monoclonal antibody) within 6 months prior to study entry
- currently using systemic corticosteroids (includes use of oral corticosteroids)
- aggravating factors that are inadequately controlled e.g., gastroesophageal reflux disease
- previous treatment with anti-IL-5 monoclonal antibody (e.g., mepolizumab)
- immunodeficiency (human immunodeficiency, acquired immunodeficiency syndrome, or congenital immunodeficiency)
- presence of or suspected active parasitic infestation infection
- live attenuated vaccine within the 12-week period before study entry
- history of allergic reactions or hypersensitivity to any component of the study drug

Prohibited concomitant medications and washout times

- All other non-biologic investigational drugs - 30 days
- Systemic (including oral) corticosteroids - 30 days
- Live attenuated vaccines - 12 weeks
- Any immunosuppressive or immunomodulatory agents including but not limited to IgE monoclonal antibody, methotrexate, cyclosporin, and interferon-α - 6 months
- Anti-TNF monoclonal antibody - 6 months
- All other biologic therapies including omalizumab (XOLAIR®) - 6 months
- Anti-IL-5 monoclonal antibody - no previous exposure allowed

Investigational Product: Reslizumab was provided as a sterile solution for infusion presented as 100 mg (10 mL) per vial, formulated at 10 mg/mL in [redacted] (b) (4) 7% sucrose, pH 5.5 buffer.

Placebo: Placebo was provided as a sterile solution for infusion presented as 10 mL per vial, formulated in [redacted] (b) (4) 7% sucrose, pH 5.5 buffer

Method of Blinding & Randomization: Randomization was stratified by occurrence of asthma exacerbation(s) during the previous year (yes or no). Of note, the stratification variable was misclassified for 15 patients in the placebo arm (6.5%) and 11 patients in the reslizumab arm (4.7%). Within each stratum, eligible patients were randomly assigned in a 4:1 ratio to receive reslizumab 3.0 mg/kg or placebo every 4 weeks over 16 weeks via interactive response technology. Approximately 2% of patients were misclassified and imbalance between arms was not observed.

Table 21. Study 3084 schedule of procedures and assessments

	Pretreatment		Randomized Treatment Period				End of Treatment	Follow Up
Visit No.	**V1.1**	**V1.2**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**
Week No.			**BL**	**W4**	**W8**	**W12**	**W16**	**W29**
Complete H&P	✓							
Urine pregnancy test	✓		✓	✓	✓	✓	✓	
Adverse event queries	✓	✓	✓	✓	✓	✓	✓	✓
Vital signs	✓		✓	✓	✓	✓	✓	✓
ECGs	✓						✓	
Serum chemistry	✓			✓	✓		✓	
CBC w/ diff	✓			✓	✓	✓	✓	✓
Urinalysis	✓			✓	✓	✓	✓	
Spirometry		✓		✓	✓	✓	✓	

Source: Modified from Study 3084 Report Schedule of Procedures and Assessments
BL = baseline, H&P = medical history and physical, ECG = electrocardiogram, CBC w/diff = complete blood count with differential

Study Endpoints

Primary

- FEV_1: change from baseline to Week 16

Key Secondary

- FEV_1: change from baseline over 16 weeks
- ACQ: change from baseline over 16 weeks

Other Secondary

- ACQ: change from baseline to the planned time points or endpoint
- FEV_1, % predicted FEV_1, FVC, and $FEF_{25\%-75\%:}$ change from baseline to the planned time points or endpoint

- SABA: change from baseline to the planned time points or endpoint
- Blood EOS: change from baseline (measured at screening) to the planned time points or endpoint

Statistical Analysis Plan

The analysis for the primary endpoint was a linear regression model to test the treatment by baseline blood eosinophil count interaction. The dependent variable was defined as change from baseline in FEV_1 at Week 16. Factors in the model were treatment, blood eosinophil count at baseline, and treatment by eosinophil count interaction. Interaction was tested at the 0.10 level using the full analysis set including all randomized patients who received at least one dose of study drug. The Applicant's analysis excluded some measurements due to prohibited medication use. The FDA analysis included all measurements.

For key secondary endpoints, a mixed model for repeated measurements was planned. The dependent variable was defined as FEV_1 or ACQ change from baseline over 16 weeks. Factors included in the model were treatment, visit, and treatment by visit interaction, asthma exacerbation in the previous 12 months (yes or no), sex, height, and respective baseline value. For both primary and key secondary endpoints, summary statistics were also provided by treatment group and baseline eosinophils category ($\geq 0.4\ 10^9$/L, $<0.4\ 10^9$/L, $\geq 0.3\ 10^9$/L, $<0.3\ 10^9$/L, $\geq 0.2\ 10^9$/L, $<0.2\ 10^9$/L, $\geq 0.1\ 10^9$/L, and $<0.1\ 10^9$/L). Analysis of other secondary endpoints was performed using the same mixed model for repeated measures as that for key secondary endpoint.

A fixed sequence step-down multiple testing procedure was implemented to test the primary and key secondary variables. If the resulting 2-sided p-value for the primary comparison was significant at level 0.10, then the procedure continued to test sequentially key secondary variables in the order specified (FEV1 followed by ACQ) at the alpha level 0.05. If the key secondary variables were significant, then the secondary analysis of the primary variable (by baseline eosinophils category $\geq 0.4\ 10^9$/L) was performed at significance level of 0.10 and interpreted inferentially.

Protocol Amendments

The protocol was amended twice, April 19 and then September 24, 2013. Both occurred after enrollment was complete at 510 patients. The primary purpose of Amendment 1 was to clarify the pharmacokinetic/pharmacodynamic and immunogenicity assessments. It addressed withholding of short-acting beta-agonists before lung function testing. Adverse event inquiries were added at visits 1.1 and 1.2. Clarification was added to note that patients were prohibited from using any biologic therapy, including omalizumab, within the six months prior to screening. Amendment 2 clarified definitions for secondary endpoints and methods of analysis for those endpoints. It defined the primary efficacy analysis, clarified that patients taking oral or systemic corticosteroids during the run-in or treatment periods would be withdrawn from the study, specified a secondary subgroup analysis in patients with $FEV_1 < 85\%$ predicted, and

specified a sequential testing procedure. Amendment 2 clarified that patients would be considered compliant with study drug administration if they received at least 75% of each infusion while in the study.

Data Quality and Integrity: Sponsor's Assurance

The Applicant states that the study was performed in compliance with Good Clinical Practices (GCP), including the archiving of essential documents.

6.3.2. Study Results

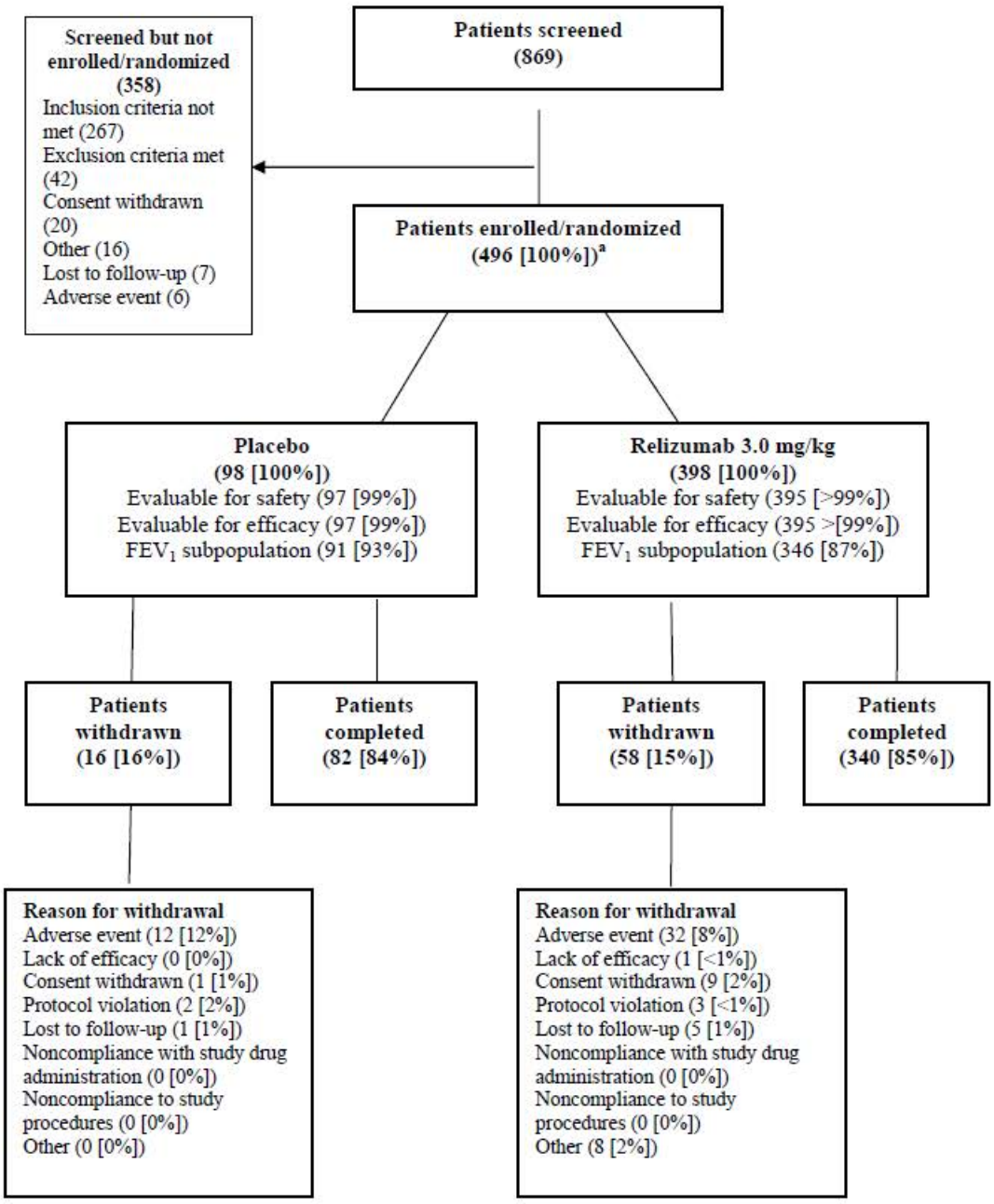
Compliance with Good Clinical Practices

Fifteen patients were randomized at two study sites subsequently terminated for violations of good clinical practice. Data from these fifteen patients were excluded from analyses, including safety analyses. Site 864 was terminated due to numerous, unresolved Good Clinical Practice issues, suspicious data, and potential safety risks to patients being enrolled (letter to the U.S. Food and Drug Administration [FDA] dated August 14, 2013). Site 909 was terminated due to an Acquisition/Petition to Revoke filed with the Medical Board of California (letter to FDA dated June 5, 2013).

Apart from these deviations, the applicant attests that the study was conducted in full accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations (e.g., Code of Federal Regulations [CFR] Title 21, Parts 50, 54, 56, 312, and 314; European Union Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use).

Patient Disposition

Figure 10. Study 3084 disposition



Study 3084 Report Figure 2

A total of 496 subjects were enrolled in Study 3084, and all but four subjects received at least one dose of study drug. Seventy-four (15%) subjects stopped study medication early and 87 (18%) discontinued from the study prematurely. The most common reason for discontinuation

from study drug treatment was adverse events, occurring in 44 (9%) subjects. Patient disposition for Study 3084 is shown in **Table 22.**

Table 22. Study 3084 disposition

	Placebo	Reslizumab 3.0 mg/kg	Total
Randomized	98	398	496
Never dosed	1	3	4
Treated	97	395	492
Completed treatment	82 (84%)	340 (85%)	422 (85%)
Discontinued treatment	16 (16%)	58 (15%)	74 (15%)
Completed study	79 (81%)	330 (83%)	409 (82%)
Discontinued study	19 (19%)	68 (17%)	87 (18%)
Discrepancies in exacerbation history between IRT and CRF	3 (3.1%)	11 (2.8%)	12 (2.4%)
Analysis Datasets			
Randomized Set	98	398	496
Full Analysis Set	97	395	492
Safety Set	97	395	492

Source: Lan Zeng M.S., FDA Statistical Reviewer
IRT= interactive response technology, CRF = case report form

Protocol Violations/Deviations

Table 23. Study 3084 protocol violations

	Placebo (N=98)	Reslizumab 3 mg/kg (N=398)	Total (N=496)
Patients with ≥1 violation, n (%)	26 (27)	81 (20)	107 (22)
Inclusion	7 (7)	22 (6)	29 (6)
Exclusion	0	3 (<1)	3 (<1)
Primary endpoint criteria	2 (2)	2 (<1)	4 (<1)
Good Clinical Practice	5 (5)	19 (5)	24 (5)
Study Medication	4 (4)	18 (5)	22 (4)
Concomitant medication	7 (7)	13 (3)	20 (4)
Other	5 (5)	12 (3)	17 (3)

Source Study 3084 Report Table 16
Patients could have had more than one protocol violation.
Other reasons include incorrect reporting of asthma exacerbation history, incorrect stratification, and three pregnancies that occurred in the follow up period.

A total of 21 patients discontinued from the study due to protocol violations, 6 (6%) patients in the placebo treatment group and 15 (4%) patients in the reslizumab group. The most frequent protocol violation leading to discontinuation was taking an excluded medication.

The incidence of protocol violations that did not lead to discontinuation was comparable for the placebo (20/26, 77%) and the reslizumab treatment group (67/81, 83%).

Table of Demographic Characteristics

Selected demographic features for all randomized patients are shown in **Table 24**. In Study 3084, subject demographics and baseline characteristics were generally balanced between the two treatment groups. The majority of subjects were female, white, and of non-Hispanic or non-Latino ethnicity. The median age was 44.9 years old.

Table 24. Study 3084 demographics

	Placebo (N=98)	Reslizumab 3.0 mg/kg (N=398)	Total (N=496)
Age, years			
n	98	398	496
Mean	45.1	44.9	44.9
SD	13.38	12.00	12.27
Sex, n (%)			
Male	44 (45)	137 (34)	181 (36)
Female	54 (55)	261 (66)	315 (64)
Race, n (%)			
White	73 (74)	260 (65)	333 (67)
Black	21 (21)	113 (28)	134 (27)
Asian	2 (2)	10 (3)	12 (2)
American Indian or Alaskan Native	0	3 (<1)	3 (<1)
Pacific Islander	2 (2)	0	2 (<1)
Other	0	12 (3)	12 (2)
Ethnicity, n (%)			
Non-Hispanic and Non-Latino	90 (92)	354 (89)	444 (90)
Hispanic or Latino	8 (8)	44 (11)	52 (10)
Weight, kg			
n	98	398	496
Mean	90.9	90.6	90.7
SD	20.68	23.92	23.30
Region, n (%)			
U.S.	98 (100)	398 (100)	496 (100)

Source: Lan Zeng M.S., FDA Statistical Reviewer

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline characteristics are shown in **Table 25**. For Study 3084, the distributions of clinical characteristics including airway reversibility, FEV_1, and medication use, were similar across both treatment groups.

Table 25. Study 3084 baseline disease characteristics

	Placebo (N=98)	Reslizumab 3.0 mg/kg	Total (N=496)
Duration of asthma (years)	n=93	n=390	n=483
Mean	25.8	26.2	26.1
SD	16.75	15.69	15.88
Median	23.0	23.9	23.9
FEV_1(L)	n=98	n=396	n=494
Mean	2.180	2.101	2.117
SD	0.6355	0.6950	0.6837
Median	2.100	2.070	2.075
%FEV_1 predicted	n=98	n=396	n=494
Mean	66.5	66.8	66.7
SD	15.53	16.26	16.10
Median	67.0	67.0	67.0
Airway reversibility (%)	n=98	n=397	n=495
Mean	24.2	26.0	25.6
SD	13.97	17.71	17.04
Median	19.7	20.1	20.1
Blood eosinophil count, x 10^9/L	n=96	n=397	n=493
Mean	0.277	0.281	0.280
SD	0.2209	0.2448	0.2401
Median	0.218	0.215	0.217
FVC, liters	n=98	n=396	n=494
Mean	3.215	3.047	3.081
SD	0.9076	0.9577	0.9494
Median	3.150	2.905	2.959
FEF, L/sec	n=96	n=393	n=489
Mean	1.553	1.650	1.631
SD	0.6791	0.9037	0.8645
Median	1.468	1.480	1.480
ACQ score	n=98	n=396	n=494
Mean	2.564	2.558	2.559
SD	0.6909	0.6992	0.6969
Median	2.571	2.429	2.429
Used beta agonist in past 3 days			
Yes	76 (78)	301 (76)	377 (76)
No	22 (22)	94 (24)	116 (23)
Daily average number of puffs in past 3 days	n=98	n=395	n=493
Mean	2.0	1.9	1.9
SD	1.82	1.84	1.83
Median	1.7	1.3	1.3

Source: Lan Zeng M.S., FDA Statistical Reviewer

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was excellent in both arms. Concomitant medication use generally was well-balanced between treatment arms in both studies, with a few exceptions. Patients in the placebo arm were more likely than those randomized to reslizumab to use renin-angiotensin agents (24 % vs. 18%), anti-inflammatory and anti-rheumatic preparations (28% vs. 25%), antithrombotic agents (10% vs. 6%), lipid modifiers (20% vs. 14%), ophthalmologicals (11% vs. 4%) and less likely to use lipid modifying agents (8% vs. 11%), and drugs for acid related disorders (28% vs. 23%). Rescue medication use of short-acting beta-agonists was evaluated as a secondary endpoint and is discussed below.

Efficacy Results - Primary Endpoint

The primary efficacy analysis, a linear regression model, did not show a significant interaction between baseline blood eosinophil count and change in FEV_1 at week 16**.** The slope difference (active –placebo) was 0.3007 (p-value=0.2407) if measurements taken with 7 days of use of confounding medication were excluded or 0.3082 (p-value=0.2291) otherwise.

Table 26. Study 3084 primary endpoint

	Sponsor's Analysis excluding some measurements		FDA Analysis including all measurements	
Variable (unit) Statistic	**Placebo (N=97)**	**Reslizumab 3.0 mg/kg (N=395)**	**Placebo (N=97)**	**Reslizumab 3.0 mg/kg (N=395)**
Slope estimate	-0.2778	0.0229	-0.2780	0.0302
Slope difference		0.3007		0.3082
SE		0.2559		0.2559
P-value		0.2407		0.2291

Source: Lan Zeng M.S., FDA Statistical Reviewer

Table 27 shows results from a pre-specified analysis of FEV_1 by baseline eosinophil category. Change from baseline in FEV_1 at week 16 was analyzed for the overall population and stratified by blood eosinophils 'less than' and 'greater than or equal to' 400/µL. A modest treatment effect was seen in the overall population unselected for baseline eosinophils (treatment difference=0.066L) and in patients with a baseline eosinophil count < 400/µL (treatment difference=0.031L). In contrast, a larger treatment effect was noted for patients with a baseline eosinophil level ≥400/µL (treatment difference=0.270L, p-value=0.0436). Interpretation is limited because of the small number of subjects in this category.

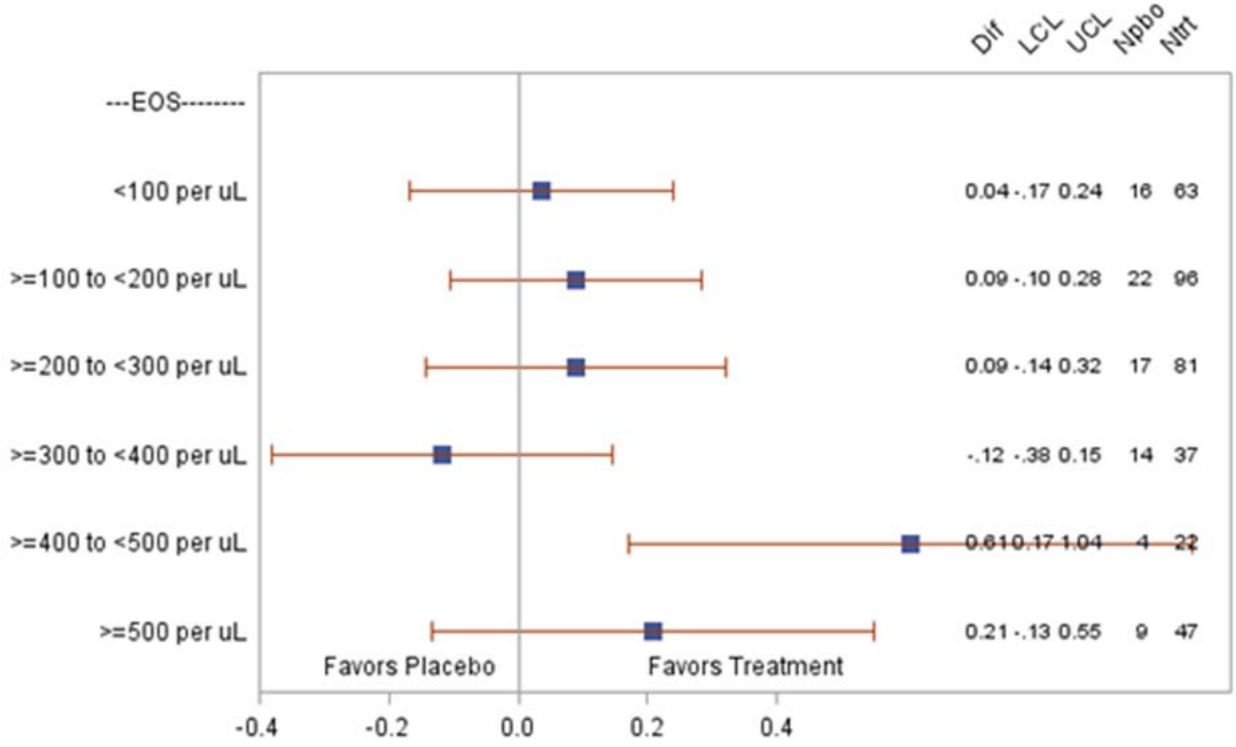
Table 27. Study 3084 change from baseline in efficacy variables at week 16 by baseline blood eosinophil count and treatment group, full analysis set with all measurements included

Variable (unit) Statistic	Overall population		Baseline Blood EOS (<400 cells/µL)		Baseline Blood EOS (≥400 cells/µL)	
	Placebo (N=97)	Reslizumab 3.0 mg/kg (N=395)	Placebo (N=76)	Reslizumab 3.0 mg/kg (N=317)	Placebo (N=19)	Reslizumab 3.0 g/kg (N=77)
FEV_1 (L)	n=84	n=345	n=69	n=276	n=13	n=69
Baseline mean (SE)	2.172 (0.0643)	2.098 (0.0350)	2.182 (0.0746)	2.068 (0.0372)	2.153 (0.1392)	2.224 (0.0928)
LS mean change (SE)	0.186 (0.0447)	0.252 (0.0232)	0.213 (0.0486)	0.244 (0.0256)	0.002 (0.1216)	0.272 (0.0557)
Treatment diff. (95% CI)	0.066 (–0.032, 0.163)		0.031 (–0.076, 0.137)		0.270 (0.008, 0.532)	
p-value	0.1859		0.5678		0.0436	

Source: Lan Zeng M.S., FDA Statistical Reviewer

A post hoc analysis was performed to explore the change from baseline to week 16 in FEV_1 by baseline eosinophil count (See Figure 11).

Figure 11. FEV_1 change from baseline to week 16 by baseline eosinophil count, study 3084



Source: Lan Zeng M.S., FDA Statistical Reviewer

Data Quality and Integrity - Reviewers' Assessment

The misclassification of the stratification variable for asthma exacerbation history was well balanced between treatment arms and thus was unlikely to introduce significant bias in study 3084.

Efficacy Results - Secondary and other relevant endpoints

Table 28 presents the summary of secondary endpoints for the FAS with all measurements included. There is no meaningful treatment effect for the overall population and for patients with a baseline eosinophil count <400/µL. Reslizumab treatment effect is more evident in patients with a baseline eosinophil level ≥400/µL where larger treatment differences at Week 16 were observed for FVC (0.175 L), ACQ score (-0.490 U), and SABA use (-0.708 inhalation/day; -0.657 all measurements analysis). However, none of these differences was statistically significant.

Interpretation of results in the ≥400 cells/µL group is limited due to the small sample size. In addition, the study was not designed to test this group of patients: only 20% of the Study 3084 population had a blood eosinophil count of ≥400 cells/µL at randomization.

Table 28. Study 3084 summary of secondary endpoints (FAS with all measurements included)

Variable (unit) Statistic	Overall population		Baseline blood eosinophils (<400 cells/µL)		Baseline blood eosinophils (≥400 cells/µL)	
	Placebo (N=97)	Reslizumab 3.0 mg/kg (N=395)	Placebo (N=76)	Reslizumab 3.0 mg/kg (N=317)	Placebo (N=19)	Reslizumab 3.0 g/kg (N=77)
FVC (liters)						
Baseline mean	3.209	3.041	3.217	2.973	3.206	3.321
(SE)	(0.0924)	(0.0481)	(0.1095)	(0.0513)	(0.1757)	(0.1234)
LS mean change	0.234	0.246	0.254	0.246	0.055	0.230
(SE)	0.0506	0.0264	(0.0537)	(0.0284)	(0.1449)	(0.0681)
Treatment diff.	0.012		-0.008		0.175	
(95% CI)	(-0.098, 0.122)		(-0.126, 0.109)		(-0.137, 0.487)	
p-value	0.8366		0.8896		0.2675	
ACQ score						
Baseline mean	2.574	2.559	2.564	2.574	2.677	2.501
(SE)	(0.0698)	(0.0353)	(0.0778)	(0.0390)	(0.1692)	(0.0839)
LS mean change	–0.654	–0.835	–0.719	–0.826	–0.368	–0.858
(SE)	(0.0881)	(0.0455)	(0.0958)	(0.0502)	(0.2407)	(0.1105)
Treatment diff.	–0.181		–0.107		–0.490	
(95% CI)	(–0.374, 0.011)		(–0.318, 0.103)		(–1.010, 0.030)	
p-value	0.0644		0.3161		0.0643	
SABA (puffs/day)						
Baseline mean	2.0	1.9	1.978	1.914	2.105	1.908
(SE)	(0.19)	(0.09)	(0.2103)	(0.1026)	(0.4328)	(0.2147)
LS mean change	-0.43	-0.34	-.455	-.223	-.127	-.785
(SE)	0.183	0.095	(0.2045)	(0.1077)	(0.4117)	(0.1864)
Treatment diff.	0.084		0.232		-.657	
(95% CI)	(-0.314, 0.482)		(-.218, 0.681)		(-1.54, 0.224)	
p-value	0.6795		0.3112		0.1419	

Source: Lan Zeng M.S., FDA Statistical Reviewer
FAS = Full Analysis Set

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

Table 29. Summary table primary endpoints, FDA analyses

Study	Endpoint	Placebo	Reslizumab 0.3 mg/kg	Reslizumab 3 mg/kg
3081	**FEV_1 Δ baseline over 16 weeks**			
	N	103	101	102
	Baseline mean	2.22	2.16	2.17
	Least squares mean change	0.13	0.24	0.29
	Treatment difference vs. placebo		0.11	0.16
	95%CI		(0.01, 0.211)	(0.06, 0.26)
	p-value		0.03	0.0002
3082	**Exacerbations**			
	N	244		245
	Adjusted exacerbation rate*	1.92		1.0
	(95%CI)	(1.45, 2.55)		(0.73, 1.25)
	Exacerbation rate ratio			0.52
	(95%CI)			(0.28, 0.70)
	p-value			< 0.0001
3083	**Exacerbations**			
	N	232		232
	Adjusted exacerbation rate*	2.17		0.87
	(95%CI)	(1.33, 3.54)		(0.55, 1.40)
	Exacerbation rate ratio			0.40
	(95%CI)			(0.28, 0.58)
	p-value			< 0.0001
3084	**Interaction EOS*ΔFEV_1 at 16 weeks**			
	N	97		395
	Slope estimate	-0.28		0.03
	Slope difference			0.31
	Standard error			0.26
	p-value			0.2

FEV_1 - forced expiratory volume in one second
EOS - eosinophils
CI - confidence interval
* Adjusted for actual baseline oral corticosteroid use (Yes or No) and geographical region (U.S. or other)

7.1.2. **Secondary and Other Endpoints**

Table 30. Summary table of secondary endpoints

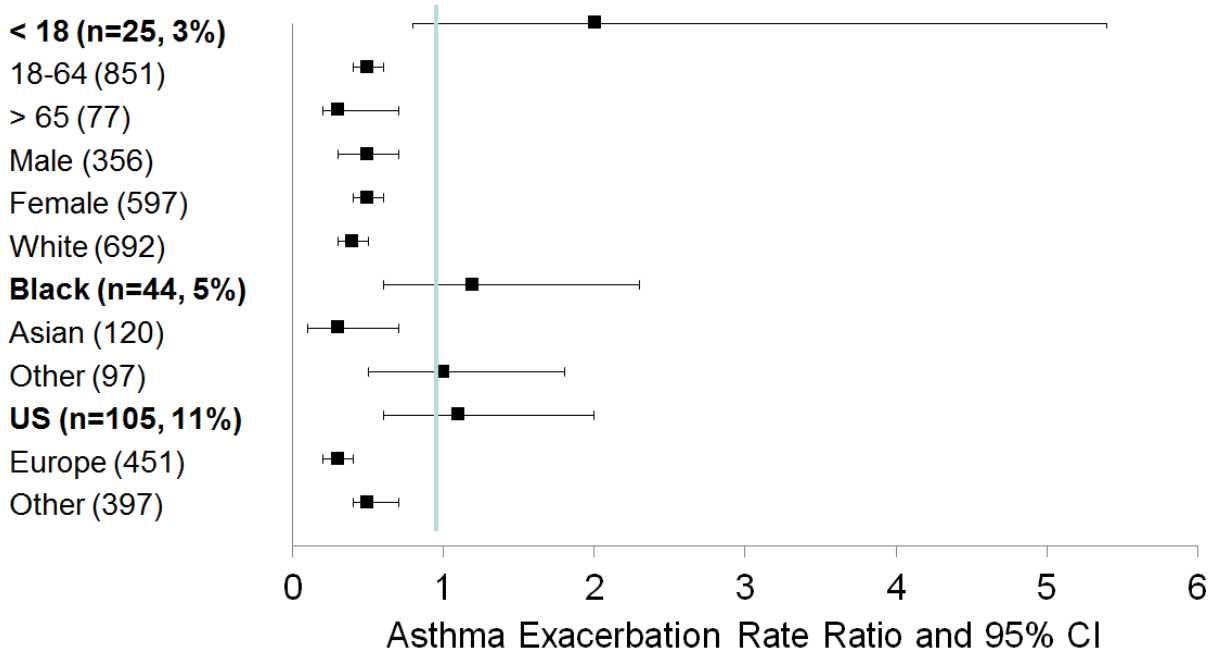
	3081	3082	3083
FEV_1 Δ to Week 16	0.165 (0.037, 0.292) 0.0118	0.072 (0.001, 0.144) 0.0483	0.101 (0.023, 0.179) 0.0109
FEV_1 Δ over 16 weeks	Primary endpoint	0.137 (0.076, 0.198) <0.0001	0.093 (0.030, 0.155) 0.0037
AQLQ Δ to Week 16	0.358 (0.047, 0.670) 0.0241	0.238 (0.048, 0.428) 0.0143	0.209 (0.025, 0.393) 0.0259
ACQ Δ over 16 weeks	–0.361 (–0.580, –0.141) 0.0013	-0.266 (-0.399, -0.132) 0.0001	-0.196 (-0.327, -0.066) 0.0032
SABA Δ Over 16 weeks	–0.632 (–1.133, –0.131) 0.0136	-0.276 (-0.597, 0.045) 0.0919	-0.062 (-0.411, 0.287) 0.7263
EOS Δ Over 16 weeks	–0.494 (–0.542, –0.447) 0.0000	-0.466 (-0.514,-0.418) <0.0001	-0.479 (-0.519, -0.439) <0.0001
Blood EOS Δ Over 52 weeks	NA	-0.455 (-0.491, -0.419) <0.0001	-0.489 (-0.525, -0.453) <0.0001

7.1.3. **Subpopulations**

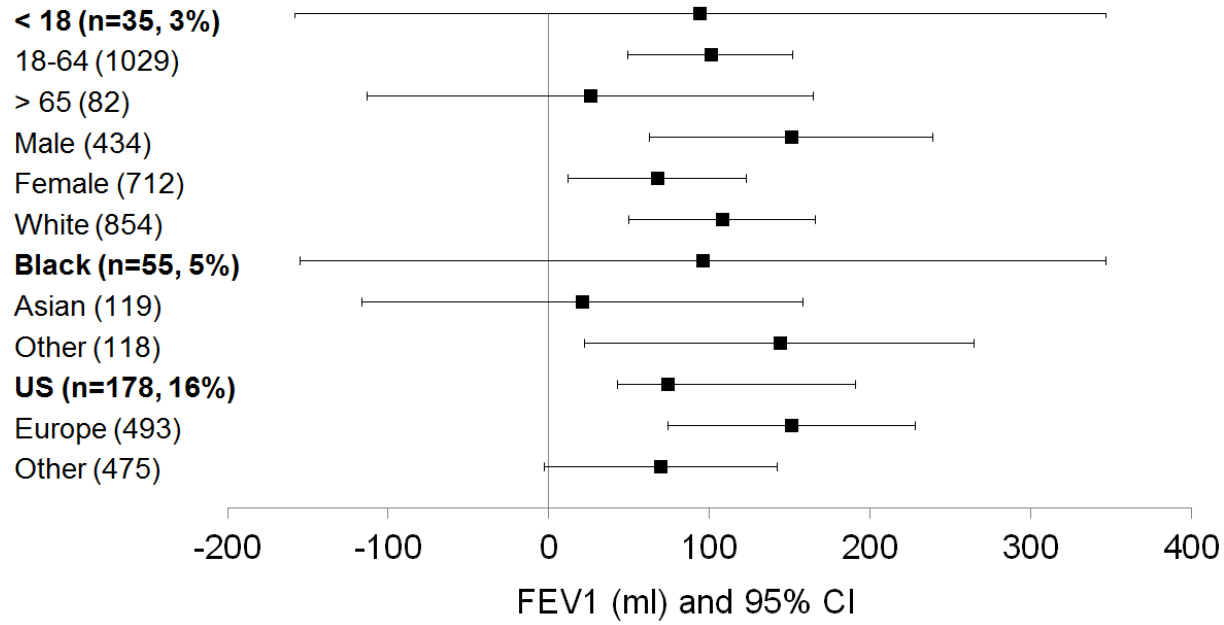
Evidence of efficacy was less robust for some subgroups with low enrollment. A paradoxical increased risk of exacerbation was observed in three subgroups: patients 12 to 17 years of age, black patients, and U.S. patients. For adolescents, evidence for lung function was conflicting. Adolescents in Study 3081 had an apparent decrease in FEV_1 *(*treatment difference -0.08 L, 95%CI -0.23 to 0.06), but evidence from pooled analyses was more reassuring (See Figure 12). *A priori*, there is little evidence to suggest that the pathophysiology of asthma with eosinophilic phenotype differs markedly among these subgroups, and although it is most likely that the paradoxical findings are due to chance, due to small sample sizes and multiplicity. Evidence of efficacy is derived largely from participants at foreign study sites.

Figure 12. Primary efficacy analyses by subgroup

a. Clinical asthma exacerbation rate for reslizumab vs. placebo by subgroup



b. Mean difference in FEV_1 for reslizumab vs. placebo by subgroup



Source: Figure generated by K. Donohue from subgroup analyses of pooled data reported in the Integrated Summary of Efficacy

7.1.4. Dose and Dose-Response

Study 3081 was the only study to perform dose ranging. However, it included only two doses, at a ten-fold difference. Data from Study 3081 could not meaningfully inform phase 3 dose selection, because all phase 3 trials were initiated before Study 3081 was completed.

Study 3081 evaluated the efficacy of two doses of reslizumab: the proposed IV dose (3.0 mg/kg) and an IV dose one log lower (0.3 mg/kg), both administered every four weeks over 16 weeks. Results for the primary endpoint, change from baseline in FEV_1 over 16 weeks, demonstrated statistically significant improvement at both dose levels, with a larger treatment effect observed for the higher dose (0.159 L vs 0.111 L). Both dose levels of reslizumab produced overall improvements in patient-reported measures of asthma control such as ACQ, and again the magnitude of the improvement was larger for the higher dose (-0.36 vs. -0.23).

The Applicant's rationale for choosing the higher dose is that improvement in AQLQ, FVC and $FEF_{25\%-75\%}$ were observed only for the reslizumab 3.0 mg/kg dose, arguing that dosing of reslizumab at 0.3 mg/kg was less effective in treating the small airways where asthma pathology predominantly resides.

Reviewer's Comment: The paucity of dose-ranging data is a significant limitation of the reslizumab program, particularly in light of the need to weigh potential benefit with the risks observed. The 0.3 mg/kg dose of reslizumab showed statistically significant evidence of efficacy for FEV_1, which is commonly used as a clinically meaningful endpoint. It is unknown whether a lower dose may have demonstrated a more favorable risk-benefit profile.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

The onset, duration, and durability of clinical efficacy were not specifically evaluated in the phase 3 studies. However, following single doses of reslizumab, at each dose level, blood eosinophils started to decline rapidly from baseline values at approximately 12 hours post dose, reaching a nadir (generally <0.1 × 109/L) by approximately day 3 (48 hours post dose) which was maintained throughout the treatment period. The recrudescence of blood eosinophil counts at the 90-day (±7 days) follow-up visit (i.e., 90 days after the end of treatment visit or approximately 4 months after the last scheduled dose of reslizumab) indicates that the clinical effects of reslizumab would be expected to wane gradually after the last dose. These findings are consistent with the prolonged half-life of reslizumab (3 to 4 weeks) and the known exposure-response relationship. Blood eosinophil counts were obtained from the small number of patients in Studies 3081, 3082, and 3083 who did not enroll into the open-label extension study, Study 3085, and who returned for a 90-day follow-up visit. The follow-up mean eosinophil counts in these patients had substantially returned towards baseline.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

No differences are anticipated in how the drug was administered and used in the clinical trials versus its expected use in the postmarket setting that would be likely to affect efficacy.

7.2.2. Other Relevant Benefits

None.

7.3. Integrated Assessment of Effectiveness

In summary, efficacy for the product is supported by data from the exacerbation studies and lung function studies, but interpretation is limited by the lack of sufficient dose-ranging data underpinning them. Study 3081 observed a mean 286 ml increase in FEV_1 for reslizumab 3.0 mg/kg compared to a mean 127 ml increase for placebo over 16 weeks (treatment difference of 160 ml with 95%CI (0.06, 0.26), p=0.002). Study 3082 observed an exacerbation rate of 0.9 per year for reslizumab compared to 1.8 per year for placebo, a 50% reduction over 52 weeks (Rate Ratio 0.50 (95%CI 0.37, 0.67), p<0.0001). Study 3083 observed an exacerbation rate of 0.9 per year for reslizumab compared to 2.1 for placebo, a 59% reduction over 52 weeks (Rate Ratio 0.41 (95%CI 0.28, 0.59), p<0.0001). Study 3084 did not observe statistically significant evidence of interaction by eosinophil level. However, a subgroup analysis showed a mean increase in FEV_1 of 270 ml for patients with eosinophil levels ≥ 400/µl compared to a 33 ml increase in FEV_1 for those with an eosinophil level of < 400/µl at 16 weeks. Evidence of efficacy was less robust for subgroups with low enrollment. A paradoxical increase in asthma exacerbation rates was observed for adolescent, African American, and U.S. patients. Evidence from secondary endpoints generally was supportive.

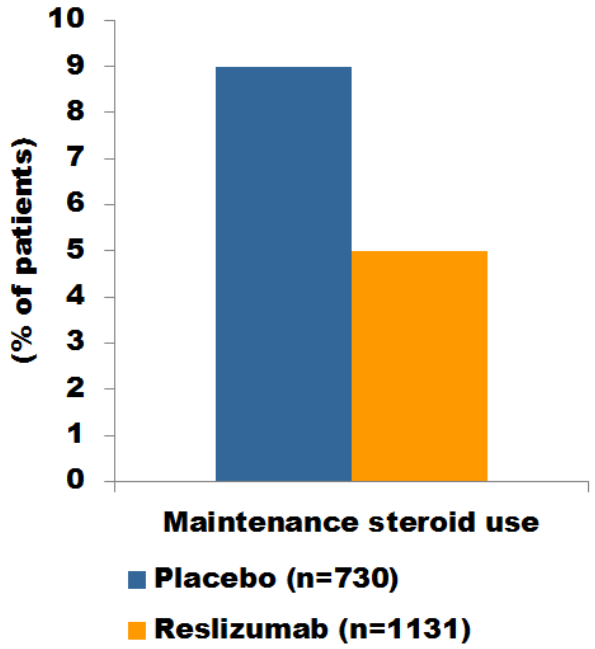
8 Review of Safety

8.1. Safety Review Approach

The safety review focuses on the population of asthma patients who received at least one dose of study drug in controlled studies through 52 weeks. This includes Studies 3081, 3082, 3083, 3084 and Res-5-0010. Data from Study 3085, an open label extension study, are reviewed separately in section 8.6 Specific Safety Studies/Clinical Trials. Review was based primarily on this reviewer's independent analysis of the data sets provided by the Sponsor, and secondarily on the Sponsor's study report. The tables and analyses presented in this report reflect the independent analysis of the reviewer except where otherwise noted. Narratives of patients with serious adverse events were reviewed.

A priori, malignancy and infections are a concern in the evaluation of all immunomodulators. Infections are discussed in detail in section 8.5.1 Analysis of Submission-Specific Safety Issues, and malignancy in section 8.7.1 Human Carcinogenicity or Tumor Development. Anaphylaxis and muscle adverse events are two safety signals that have emerged in the reslizumab program, and they are discussed in section 8.4.4 Significant Adverse Events.

Figure 13. Maintenance oral corticosteroid use



Source: K. Donohue

Due to errors in study conduct, more patients in the placebo arm of the safety population were taking oral corticosteroids at baseline (Figure 13). This imbalance could lead to underestimation of adverse events for which both steroids and reslizumab could play a role, such as infections and myopathy. Thus, analyses stratified by oral corticosteroid use are presented and discussed where relevant.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Overall, 2187 patients were exposed to at least one dose of reslizumab, 1189 for more than six months and 922 for more than twelve months. Overall, 1596 patients were treated at the 3mg/kg to-be-marketed dose, 994 for more than six months and 743 for more than twelve months. However, it is worth noting that the safety population is derived from the placebo-controlled trials (Res-5-0010, 3081, 3082, 3083, 3084), in which there were subtle differences in exposure between the placebo and reslizumab arms. Overall, total patient years of exposure were longer in the reslizumab arm because more patients were randomized to reslizumab, but average duration of treatment was longer in the placebo arm.

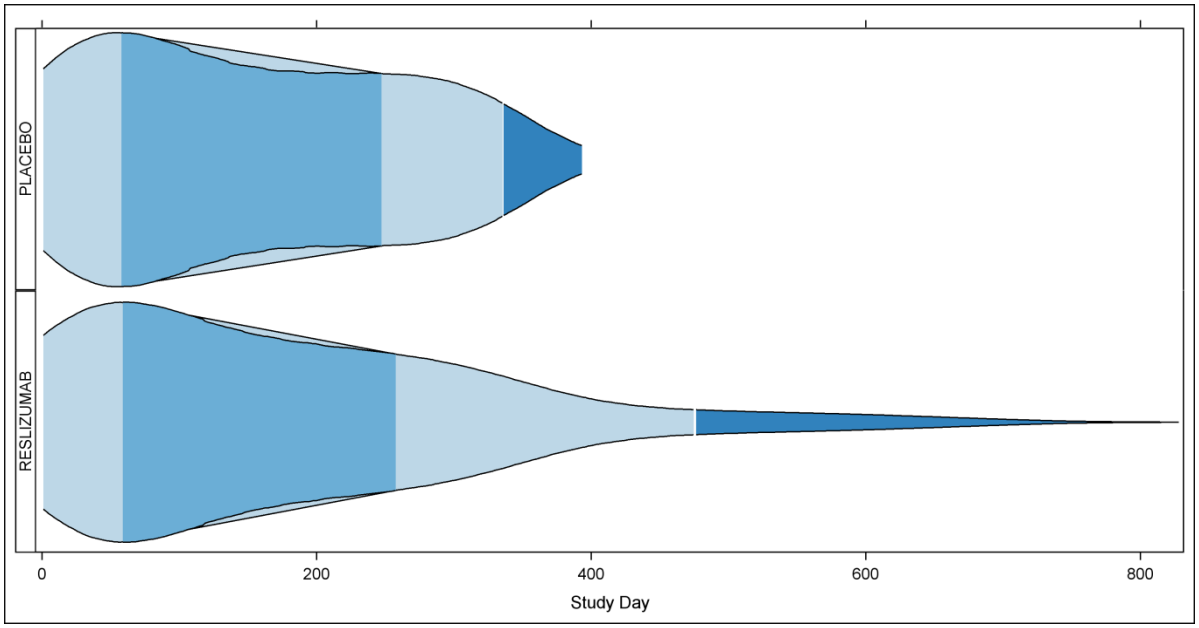
Reviewer Comment: The longer average duration of treatment in the placebo arm in controlled trials could obscure detection of a safety signal for which duration is important, such as malignancy.

Table 31. Study drug exposure in controlled trials, safety population

	Placebo (N=730)	Reslizumab (N=1131)
Patient-years exposure	517	644
Duration of treatment (days), mean ± SD	259 ± 131	208 ± 127
Duration of treatment n (%)		
≥ 6 months	436 (60)	440 (39)
≥ 12 months	388 (53)	389 (34)

Source: Integrated Summary of Safety table 11

Figure 14. Relative distribution of duration of exposure, including open-label extension



Violin plot with shaded quartile bounds created by this reviewer from the following data source: ISS DDEX.XPT

8.2.2. Relevant characteristics of the safety population

The safety database generally was well-balanced between reslizumab and placebo and generalizable to the target U.S. population with respect to baseline characteristics, with the following exceptions. First, the program included very few adolescents (n=39). Patients ≥ 65 years were somewhat better represented, though proportionally more were randomized to placebo than reslizumab (8% vs. 5%) and overall representation was still somewhat sparse for detection of rare events (n=108). With regard to baseline disease characteristics, lung function, bronchodilator reversibility, and eosinophil count were evenly balanced, but a larger percentage of patients randomized to placebo had a history of an asthma exacerbation in the

past twelve months compared to those randomized to reslizumab (78% vs. 67%). Importantly, the proportion of patients on baseline oral corticosteroids was nearly double for the placebo vs. reslizumab groups (9 vs. 5%).

Reviewer's comment: This imbalance in baseline corticosteroid use could obscure safety signals such as infection and myopathy that might reasonably be associated both with oral corticosteroid use and with reslizumab.

Table 32. Baseline characteristics, safety population

	Placebo (N=730)	Reslizumab (N=1131)
Age		
12 to 17	16 (2)	23 (2)
18 to 64	658 (90)	1056 (93)
≥65	56 (8)	52 (5)
Sex		
Male	276 (38)	432 (38)
Female	454 (62)	699 (62)
Race Group		
White	549 (75)	808 (71)
Black	61 (8)	151 (13)
Asian	57 (8)	81 (7)
Other	63 (9)	91 (8)
Geographic Region		
U.S.	224 (31)	552 (49)
Europe	260 (36)	265 (23)
Other	246 (34)	315 (28)
Concomitant asthma medications		
Oral corticosteroids	64 (9)	53 (5)
Short acting ß agonist	656 (90)	1013 (90)
Combination long acting ß agonist & inhaled corticosteroid	498 (68)	810 (72)
Long acting ß agonist	125 (17)	131 (12)
Inhaled corticosteroid, N (%)	262 (36)	365 (32)
Inhaled corticosteroid, mean total daily dose (µg) ± SD	785 ± 361	750 ± 363
Long acting muscarinic antagonist	33 (5)	41 (4)
Xanthines	51 (7)	65 (6)
Leukotriene inhibitors	146 (20)	211 (19)
Concomitant illness		
Hepatobiliary disorder	54 (7)	70 (6)
Renal disorder	45 (6)	65 (6)
Baseline disease characteristics		
FEV_1 (L), mean ± SD	2 ± 0.7	2 ± 0.7
FEV_1 % Predicted, mean ± SD	67 ± 19	67 ± 18
Airway reversibility, %, mean ± SD	27 ± 19	26 ±17
Asthma exacerbation in past twelve months, n (%)	567 (78)	754 (67)
Eosinophil count (10^9/L), mean ± SD	0.6 ± 0.6	0.5 ± 0.5

Sources: Integrated Summary of Safety Tables 16 to 20

8.2.3. **Adequacy of the safety database**

The overall extent of exposure in the safety database with respect to number of patients and duration of treatment is adequate for review. However, as discussed below, information regarding important safety signals, such as anaphylaxis and a muscle safety signal, may not have been optimally collected.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Assessment Quality

Insufficient detail was collected regarding adverse events to generate narratives about safety signals such as anaphylaxis and muscle adverse events. For example, time of onset for adverse events and post-infusion vital signs were s not captured. Commonly, case report forms for newer biologic therapies will prospectively collect information about anaphylaxis reactions based on National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network 2006 criteria, but this was not done for the reslizumab program. In addition to lacking relevant details, completed case report forms were provided for only a small minority of participants.

8.3.2. Categorization of Adverse Events

The Applicant's process for recording, coding, and categorizing AEs met minimum standards, with a few exceptions as noted below. The Applicant provided accurate definitions of adverse events and serious adverse events in the protocols.[1] Adverse events were defined as illnesses, injuries, worsening of asthma or pre-existing conditions, drug interactions, events related to diagnostic procedures and laboratory or diagnostic abnormalities requiring withdrawal, medical treatment or follow up. Serious adverse events were defined as death, life threatening, requiring hospitalization, persistent or significant disability or incapacity, a congenital anomaly, or a need for medical treatment to prevent one of these outcomes.

Adverse events were recorded from signature of the informed consent form through the end of the follow-up period, which was 90 days after the end-of-treatment visit. At each contact with the patient, the investigator asked the patient an open-ended question such as, "Have you had any unusual symptoms or medical problems since the last visit? If yes, please describe." Severity was assessed by the investigator, rather than via a standardized grading scale. Mild was defined as "no limitation of usual activities," moderate as "some limitation of usual activities, and severe as "inability to carry out usual activities." No definition for treatment emergent adverse events was reported.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 15.0. Verbatim terms were included in the file. The Applicant's translation of verbatim terms to preferred terms and subsequent categorization of preferred terms was adequate. No

[1] 21 CFR 312.32(a) and 314.80

definition of treatment emergent adverse events was provided. Whether an event was considered treatment related was determined by the investigator based on timing, biological plausibility, and presence of comorbid illnesses or concomitant medications.

Of note, this reviewer's independent analysis of the adverse event dataset revealed 25 adverse events that were excluded from safety analyses. The dataset contains a reported verbatim term for these events, but no MedDRA coding that would have supported their inclusion in subsequent analyses. All occurred in patients on treatment with reslizumab 3 mg/kg in the open label extension study, 3085. The events were notable for one case of respiratory failure, ten asthma attacks or exacerbations, and a case of tendonitis.

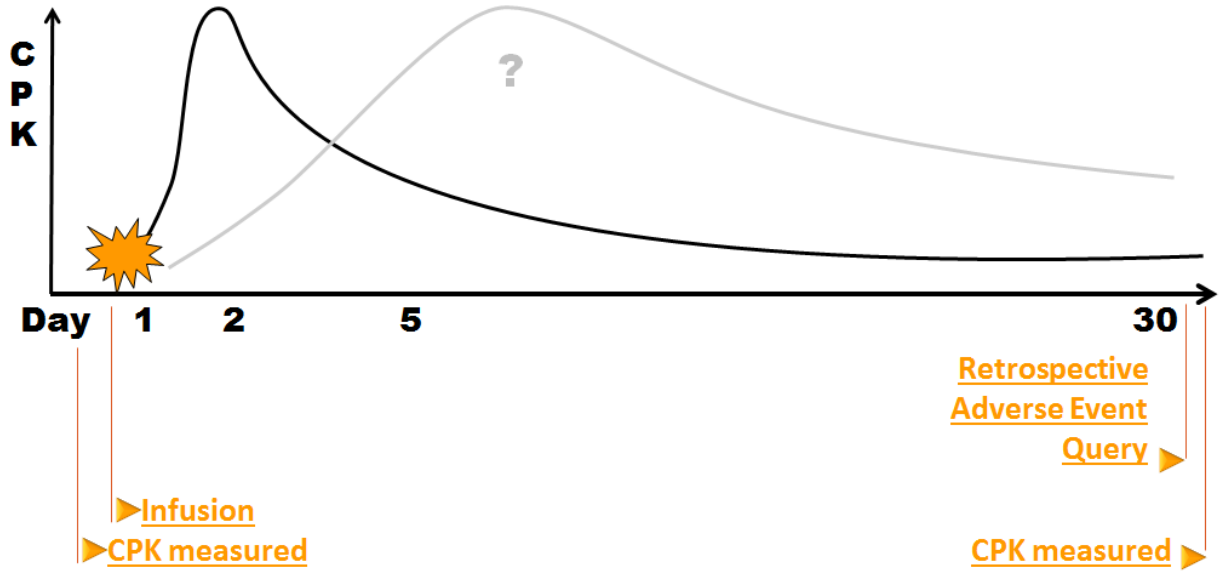
8.3.3. Routine Clinical Tests

Routine clinical testing generally was acceptable, with two deficiencies discussed in more detail below. Complete blood counts with differentials were measured at all study visits for studies 3081, 3082 and 3083, and at all but two study visits for study 3084. Urinalysis and urine pregnancy testing likewise were performed with adequate frequency. Serum chemistry testing included an adequate panel but was performed infrequently: at three visits for study 3081, eight visits for studies 3081 and 3082, and four visits for study 3084. See **Table 3, Table 11,** and **Table 21** for schedules of procedures and assessments. Laboratory specimens were analyzed at a central lab, PPD Global Central Labs, at sites in Kentucky, Belgium, or Singapore.

The first deficiency in routine clinical testing is that creatine phosphokinase (CPK) measurements were performed before infusion, monthly at most (weeks 4, 8, 12, 20, 28, 40 and 52), and were not routinely collected at unscheduled visits. Patients in the reslizumab arm reported more musculoskeletal adverse events in the first 24 hours after infusion and more cases of CPK elevations than patients in the placebo arm. It is important to note that CPK rises within 12 hours of the onset of muscle injury, peaks in 1 to 3 days, and declines 3 to 5 days after the cessation of muscle injury (29). Thus, measuring CPK levels one or more months after infusion may have failed to detect elevations associated with musculoskeletal adverse events observed in the 24 hours after reslizumab infusion (See Figure 15).

Reviewer's comment: A priori, monoclonal antibodies are not known to cause CPK elevations, and so monthly or less frequent measurements were not unreasonable in the original reslizumab study protocols. However, the concurrent timing of the studies meant that protocols could not be adjusted to increase monitoring as this safety signal emerged. Additionally, our understanding of drug-induced muscle injury comes mostly from small molecules. The time course, magnitude, and nature of CPK elevations for large molecules are not well understood. The CPK elevations observed in the reslizumab program may best be understood as trough measures.

Figure 15. Timing of CPK measurements relative to infusion and adverse event queries



Source: K. Donohue

The second deficiency in routine clinical testing was that post-infusion vital signs were not systematically collected and reported in the safety database. This omission precludes an analysis of vital signs for a pattern consistent with anaphylaxis such as decreased blood pressure with increased heart and respiratory rate. The post-infusion safety data reported for the asthma development program of reslizumab is notable for reduced quantity and quality compared to what was collected earlier for reslizumab in the eosinophilic esophagitis program, where vital signs were captured prior to infusion, and again at 20, 40 and 60 minutes after infusion.

Reviewer's Comment: The failure to capture and report frequent post-infusion vital sign data is notable in the setting of intravenous administration of an investigational monoclonal antibody in a severe asthma population known to be at increased risk of anaphylaxis. This deficiency in vital sign data is especially unfortunate combined with the failure prospectively to collect adverse event information about anaphylaxis reactions based on National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network criteria. Collectively these omissions limit a detailed analysis of the anaphylaxis safety signal.

8.4. Safety Results

8.4.1. Deaths

There were four deaths in the reslizumab development program, three during the open-label extension Study 3085, and one in the placebo arm of Study 3082. A 56-year-old female from

the placebo group of Study 3082 enrolled in the open label extension study and presented with anal cancer after the 15th dose of reslizumab and died four months later. A 67-year-old male from the reslizumab group in Study 3083 had a history of pulmonary tuberculosis and bronchiectasis. He enrolled in the open-label extension study, and after 821 days on reslizumab, he had massive hemoptysis and died. A 59-year-old female with hypertension, obstructive sleep apnea, and craniotomy due to tumor was in the reslizumab 0.3 mg/kg group in Study 3081. After 163 total days of exposure to reslizumab, 4 weeks after her last infusion, the patient was found dead at home. No autopsy was performed and the cause of death attributed to cardiac arrest. A 26-year-old male in the placebo arm of study 3082 died of fentanyl overdose one month after his second placebo infusion. No deaths occurred in Studies 1102, 1107, I96-350, P01942, P00290, NIH 01-10155, Res-5-0002, Res-5-0004, Res-5-0010, 3081, 3083, or 3084.

8.4.2. Serious Adverse Events

Serious adverse events that were more common in the reslizumab than the placebo arm included chest pain, anaphylaxis, and falls (see **Table 33**). Overall, more serious adverse events occurred in the placebo arm than in the reslizumab arm.

Table 33. Serious adverse events (>1 patient in any treatment group), safety population

	Placebo (N=730)	Reslizumab 3 mg/kg (N=1028)
Patients with at least 1 serious adverse event	66 (9)	65 (6)
Respiratory, thoracic, and mediastinal disorders	27 (4)	26 (3)
Asthma	23 (3)	23 (2)
Infections and infestations	22 (3)	18 (2)
Pneumonia	7 (< 1)	7 (<1)
Sinusitis	2 (<1)	2 (<1)
Bronchitis	2 (<1)	0
Urinary tract infection	2 (<1)	0
Injury, poisoning, and procedural complications	11 (2)	8 (<1)
Fall	0	2 (<1)
Road traffic accident	3 (<1)	2 (<1)
Contusion	2 (<1)	0
Immune system disorders	0	4 (<1)
Anaphylactic reaction	0	4 (<1)
General disorders and administration site conditions	0	3 (<1)
Chest pain	0	2 (<1)

Source: Integrated Summary of Safety Table 39

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Adverse events leading to discontinuation generally were well-balanced between the treatment and placebo arm. Notable imbalances in adverse events leading to discontinuation included anaphylaxis (3 patients in the reslizumab group vs. 0 in the placebo group), and increased

blood CPK (one reslizumab patient vs. no placebo patients). There was no imbalance in discontinuations due to musculoskeletal disorders.

Table 34. Adverse events leading to discontinuation, by system organ class

	Placebo (N=730)	Reslizumab 3 mg/kg (N=1028)
Patients with at least 1 AE leading to discontinuation	40 (5)	48 (5)
Respiratory, thoracic, and mediastinal disorders	23 (3)	28 (3)
Infections and infestations	8 (1)	5 (<1)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	3 (<1)	4 (<1)
Investigations, including CPK elevations	3 (<1)	3 (<1)
Immune system disorders, including anaphylaxis	0	3 (<1)
Musculoskeletal and connective tissue disorders	2 (<1)	2 (<1)
Gastrointestinal disorders	1 (<1)	1 (<1)
General disorders and administration site conditions	1 (<1)	1 (<1)
Nervous system disorders	1 (<1)	1 (<1)
Skin and subcutaneous tissue disorders	4 (<1)	0
Cardiac disorders	3 (<1)	0
Injury, poisoning, and procedural complications	2 (<1)	0
Renal and urinary disorders	1 (<1)	0

Source: Integrated Summary of Safety Table 41.

Reviewer's comment: With respect to SAEs and AEs, the sum of events by preferred terms in the source table often totaled more than what was reported for the system organ class, which in turn summed to more than the overall totals listed at the top of the table for each treatment group. One could assume that patients may have had more than one event leading to discontinuation, but no explanation was provided.

8.4.4. Significant Adverse Events

Reslizumab was associated with two significant adverse events, anaphylaxis and a muscle safety signal.

Anaphylaxis

A higher rate of anaphylaxis was observed in patients treated with reslizumab, compared to those treated with placebo. The Sponsor was asked to perform a retrospective investigation and adjudication for anaphylaxis. Since time of adverse event was not available in the safety database, the Sponsor was asked to perform a broad standard MedDRA query for anaphylactic reaction either the day of or day after infusion. The Sponsor was asked to query all of the asthma studies, including both reslizumab and placebo patients. The resulting cases were to be assessed by two blinded independent adjudicators according to NIAID/FAAN criteria. If discordant, they were to be discussed by the full committee of three, including the chair. It is the agency's usual practice to include all cases identified as anaphylaxis by the investigator at the bedside, as well as all cases adjudicated as anaphylaxis by NIAID/FAAN criteria. Three cases

were identified by investigators at the bedside, and two additional cases, one reslizumab and one in a placebo patient, were identified during the adjudication process.

- The first case was a 45-year-old white female with a history of drug hypersensitivity (novalminsulfon allergy and aspirin sensitivity) who participated in Study 3083. On day 22, the patient experienced a reaction 14 minutes after initiation of the second reslizumab 3.0 mg/kg infusion characterized by dyspnea, shivering, vomiting, flushing and oxygen saturation of 89%. The patient was treated with systemic corticosteroids, antihistamines, and IV fluids and discontinued from the study. The episode resolved with no residual effect. The infusion was administered without a filter.
- The second case was a 47-year-old white female with a history of allergies (mold and dog hair) and drug hypersensitivities (penicillin and aspirin) who participated in Study 3083. On day 302, shortly after completing the 11th reslizumab 3.0 mg/kg infusion, the patient 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 patient was treated with systemic corticosteroids, antihistamines, and IV fluids and discontinued from the study. The anaphylaxis reaction resolved with no residual effect.
- The third case was a 52-year-old black female with a history of allergic rhinitis who participated in Study 3084. On day 36, shortly after the completion of the 2nd reslizumab 3.0 mg/kg infusion, the patient experienced an anaphylactic reaction to the study drug (shortness of breath, wheezing, could not speak, swollen eyes, and flushing). The reaction was considered a serious adverse event of moderate intensity, related to study therapy. The patient was treated with epinephrine, prednisone, albuterol, and montelukast and was discontinued from the study. The anaphylactic reaction resolved with no residual effect.
- A fourth case occurred in a 52 year old woman in the setting of an ongoing asthma exacerbation. After her 12th infusion, her respiratory status deteriorated precipitously, requiring intubation. The next day she developed a rash on her arms and face. Teva does not consider this a case of anaphylaxis as the patient continued on reslizumab, but this is the case that was identified retrospectively and adjudicated as (+) for anaphylaxis by the committee.
- The adjudication process also identified one case meeting NIAID criteria in the placebo arm. A 45 year old man developed hypotension (BP 137/81->77/68) and a rash on his left arm that were self-limited and resolved within fifteen minutes.

Two additional anaphylaxis cases were noted in placebo controlled asthma trials, one likely due to walnut exposure in a nut-allergic patient, and another after allergy immunotherapy injection.

- The first case was a 21-year-old white female with a history of latex and food allergies (including nut allergy) who participated in Study 3082. On day 186, the patient experienced anaphylaxis to walnut exposure. The anaphylaxis was considered a nonserious adverse event of moderate intensity. The event resolved with no residual effect and the patient continued in the study on reslizumab 3.0 mg/kg.

- The second case was a 38-year-old white female with a history of nickel allergy and allergic rhinitis who participated in Study 3084. On day 137, the patient experienced an anaphylactic reaction after receiving an allergy immunotherapy injection. The patient was treated with an Epi-Pen injection and prednisone and the event resolved with no residual effect, and the patient remained in the study.

In addition, there were several cases of anaphylaxis reported in the eosinophilic esophagitis program. Seven were in the reslizumab arm and one in the placebo arm. The apparent imbalance may be due in part to the underlying randomization scheme: study Res-5-0002 randomized patients 3:1 to reslizumab vs. placebo, and study Res-5-0004 was an open label extension study. Teva reports that there were seven cases of anaphylaxis in the eosinophilic esophagitis program, and that "were related to previously known food allergies." However, a review of study reports, narratives, case report forms and line listings from the two eosinophilic esophagitis trials calls into question both the number of cases and attributions of causality. One case attributed by Teva to food allergy may be drug related given timing and discontinuation of treatment, and an eighth case of potential drug-related anaphylaxis was identified by this reviewer, both from study Res-5-0004:

- One patient was a 6-year-old boy who had an anaphylactic reaction on day 404 of the study, 2 days after administration of reslizumab at 1.0 mg/kg. The event was considered serious and severe. Reslizumab administration was not continued. The patient had a known allergy to wheat, described as a food allergy.
- Another patient was a 14-year-old boy who had a hypersensitivity reaction on the day of the fifth administration of reslizumab at 2.0 mg/kg. The event was described as an allergic reaction post drug infusion and treated with corticosteroids, antihistamines, and IV fluids. He recovered after three days. The patient continued with reslizumab therapy with no dose reduction and without recurrence of symptoms with subsequent doses.

One case, from study Res-5-0002, has too little information to speculate regarding causality:

- The patient was a 7-year-old black or African American female in the reslizumab 3 mg/kg arm who had anaphylaxis after eating a cookie on study day 64, May 22, 2009. The time since last dose of reslizumab, whether study drug was continued, and whether the patient had known food allergies were not reported.

The remaining five cases of anaphylaxis appear less likely to be drug-related, as they occurred several days or weeks after infusion, reslizumab treatment was continued, or they were related to known food allergies or immunotherapy injections. The first three are from study Res-5-004, and the last two from study Res-5-0002.

- A 6-year-old boy who had three events of anaphylactic reaction on day 580, day 858, and day 1106 of the study (ranging from 11 to 15 days after administration of reslizumab at 2.0 mg/kg). The first event was described as having an unknown etiology (treated with epinephrine, corticosteroids and antihistamines), the second was due to

almonds (treated with antihistamines), and the third was due to pizza (treated with antihistamines). After each occurrence, reslizumab administration was continued with no dose change.

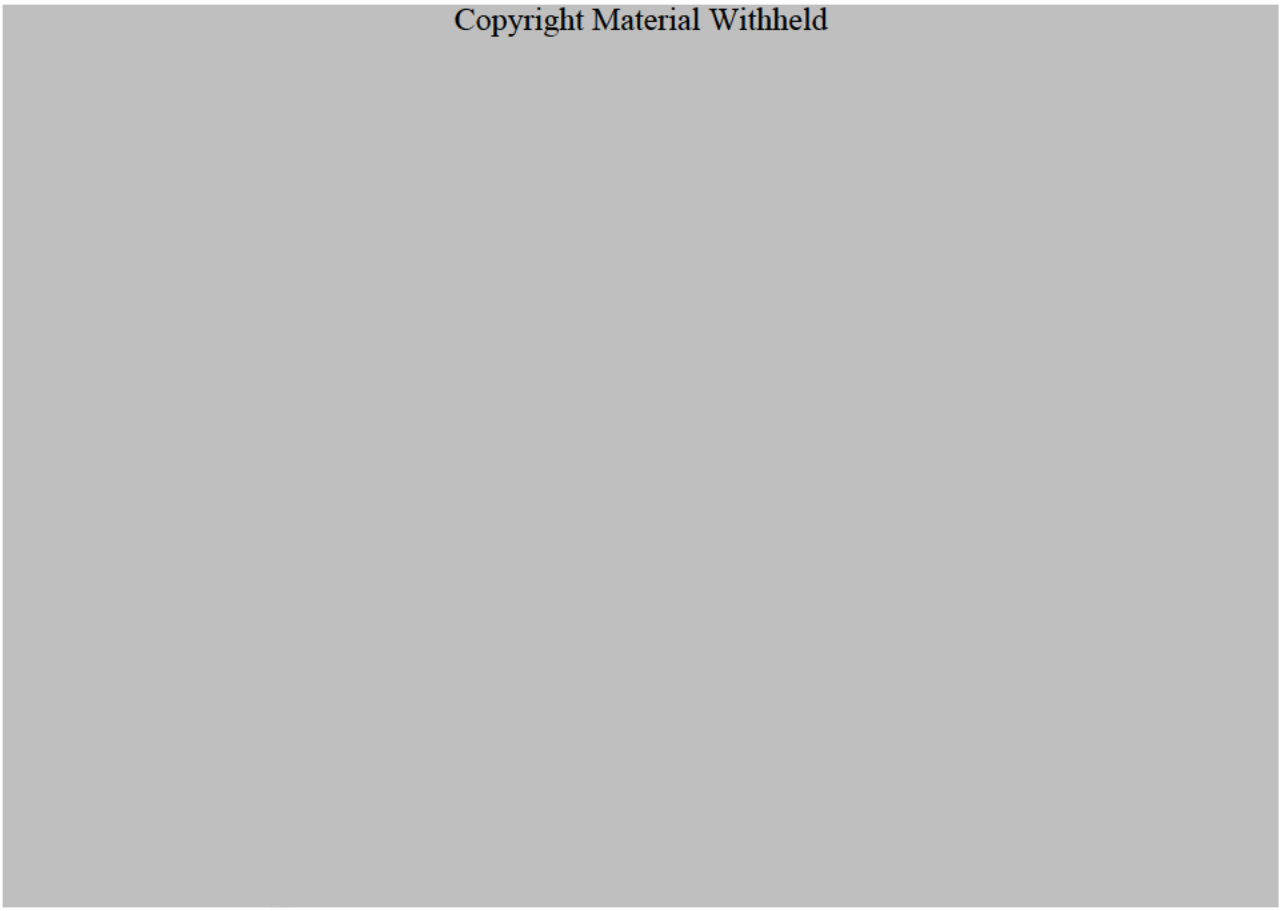
- A 10-year-old boy who had six events of anaphylactic reaction or allergic reaction on day 118, day 240, day 419, day 537, day 580, and day 771 of the study (ranging from 6 to 22 days after administration of reslizumab at 2.0 mg/kg). Events 1, 3, 4, and 5 were described as due to allergy shots. The second event was described as due to exposure to a cat and the sixth event was due to an allergic reaction to eggs. Treatments of the events included epinephrine, corticosteroids, antihistamines, and bronchodilators, and recovered by the next day. Additionally, the patient had an event of infusion-related reaction on day 342 described as fever following start of study infusion, treated with paracetamol, and recovered the same day. After each occurrence, reslizumab administration was continued with no dose change. The patient had known environmental and food allergies.
- An 11-year-old boy who had three events of anaphylactic reaction on day 682, day 756, and day 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. After each occurrence, reslizumab administration was continued with no dose change. The patient had known allergies to eggs, many other foods, and nuts.
- A 17-year-old white male who was given epinephrine IV for anaphylaxis secondary to peanut allergy on study day 16, March 31, 2009, fifteen days after his first infusion of reslizumab 3mg/kg.
- A 16-year-old Caucasian male with known peanut allergy had anaphylaxis after an accidental peanut ingestion more than two weeks after his last placebo infusion.

All of the above cases were anti-drug antibody negative, however the assay was not sensitive enough to detect clinically relevant IgE (see section 8.4.10 Immunogenicity).

The Division was concerned that the higher rate of anaphylaxis observed in the reslizumab arm of the asthma program may be due to an impurity known as alpha-gal, though the mechanism by which this may occur remains an open question. Reslizumab is a monoclonal antibody manufactured in an NS0 murine cell line. Murine cell lines synthesize a blood group oligosaccharide, galactose-alpha-1,3-galactose, known as alpha-gal (30). An increased risk of anaphylaxis also has been observed with cetuximab, a monoclonal antibody manufactured in a different murine cell line, Sp2/0. Two unusual characteristics were observed with the cetuximab anaphylaxis cases. First, anaphylaxis occurred with first-time infusions of cetuximab, suggesting pre-existing sensitization. Consistent with the pre-sensitization hypothesis, IgE antibodies specific for alpha-gal were identified in pretreatment serum samples from patients who later had anaphylaxis to cetuximab,(31) and mass spectrometry identified the presence of alpha-gal on the heavy chain of the Fab portion of cetuximab (32). The second unusual feature of the cetuximab anaphylaxis signal was significant regional variability, with the highest number of U.S. cases observed in the Southeast. This led to the hypothesis that tick bites may cause patients to develop IgE antibodies specific for alpha-gal (See Figure 16). Evidence for the tick bite hypothesis comes from ecological data showing an increase in prevalence of cetuximab

anaphylaxis in a geographic region matching the distribution of the lone star tick, the observation that IgE to alpha-gal is correlated with IgE levels for the lone star tick, and prospective data showing an increase in IgE to alpha-gal after lone star tick bites (33).

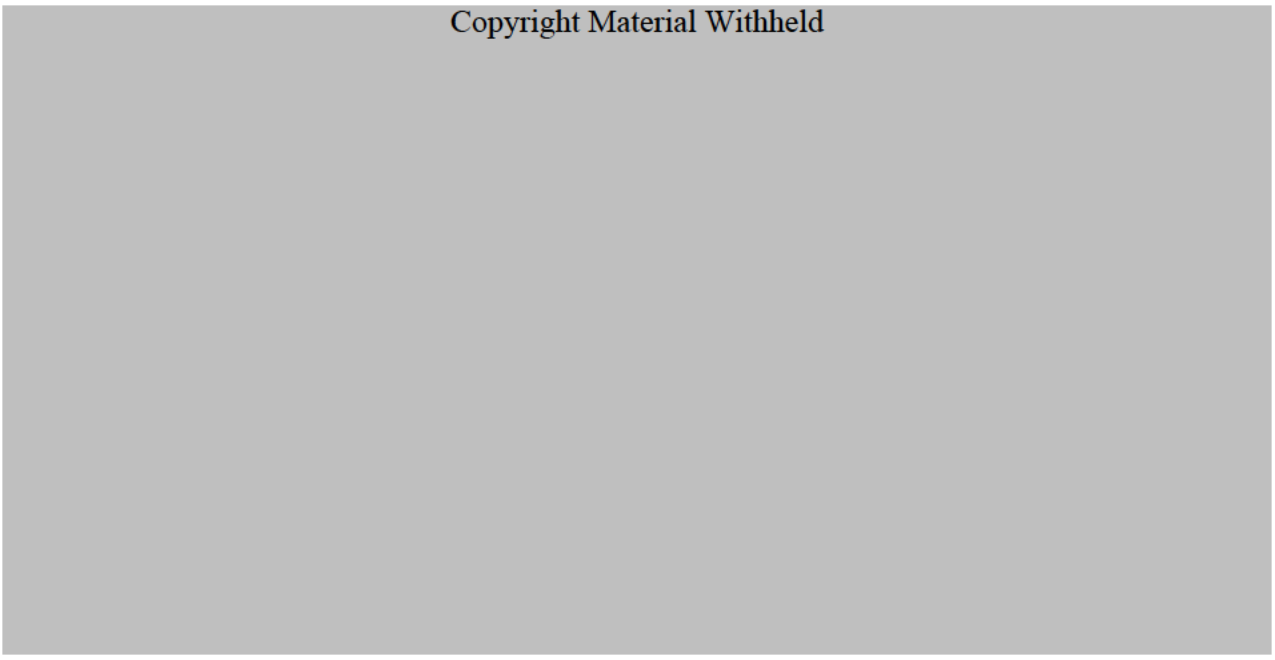
Figure 16. The alpha-gal hypothesis



Steinke, Platts-Mills & Commins JACI 2015

Three of the reslizumab related cases of anaphylaxis in the asthma program occurred in locations consistent with the tick bite hypothesis of alpha-gal sensitization. There were two cases from Germany, in the distribution of the *Ixodes ricinus* tick, and one in New York, in the distribution of the *Amblyomma americanum* tick. A fourth case occurred in Thailand. Though alpha-gal anaphylaxis cases have not yet been reported in the literature in Thailand, reports of alpha-gal anaphylaxis from new locations emerge regularly, including some recently from Australia. In addition, several related Amblyomma and Ixodes tick species have been identified in Thailand.

Figure 17. Distribution of reslizumab anaphylaxis cases relative to tick species



(Map adapted from Stanek et al. (34))

Teva tested stored serum samples from the four cases of reslizumab anaphylaxis for anti-alpha-gal IgE antibodies. Preliminary results were submitted December 4, 2015 showing that both baseline and follow-up samples tested negative (b) (4) for anti-alpha-gal IgE for all four patients. These results were still under review by Dr. Joao Pedras Vasconcelos at the time this review was finalized, but overall would diminish the likelihood of an alpha-gal mechanism for the anaphylaxis observed thus far in the program.

Classic IgE mediated anaphylaxis to another moiety in reslizumab is another possible mechanism. This has been reported for several monoclonal antibodies not known to contain alpha-gal, including rituximab, adalimumab, etanercept and trastuzumab. Successful induction of drug tolerance to these entities supports an IgE mediated mechanism for anaphylaxis. That the reslizumab anaphylaxis cases observed so far have occurred after the second or later infusion also supports this hypothesis

Muscle Adverse Events

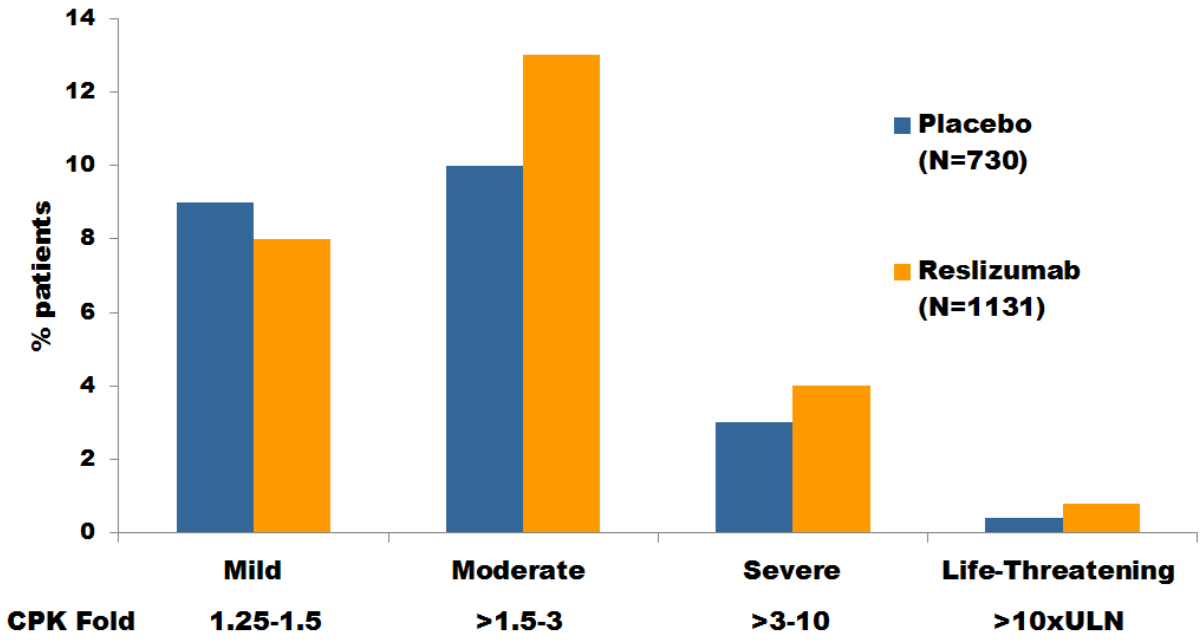
Reslizumab treatment is associated with a muscle safety signal, and the risk is higher among patients taking concomitant oral corticosteroids. Three lines of evidence, including time dependence, support this observation. First, patients randomized to reslizumab had a higher incidence of elevations in CPK. Second, patients randomized to reslizumab were more likely to report muscle pain. Third, the incidence of musculoskeletal adverse events occurring within 24 hours of infusion was higher in the reslizumab group compared to placebo.

Table 35. Maximum CPK per participant, safety population

	Placebo N (%) N=730	All Reslizumab N (%) N=1131
Missing post-baseline CPK	13 (2)	8 (< 1)
Normal (<1.25 ULN)	552 (76)	829 (73)
Any elevated CPK	165 (23)	294 (26)
Mild (Grade 1, 1.25 - 1.5 x ULN)	65 (9)	88 (8)
Moderate (Grade 2, 1.6-3 x ULN)	73 (10)	152 (13)
Severe (Grade 3, 3.1-10 x ULN)	24 (3)	45 (4)
Potentially Life-Threatening (Grade 4, > 10 x ULN)	3 (0.4)	9 (0.8)

Categories based on the FDA "Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials"
ULN = upper limit of normal
Source: Response to FDA Request for Information dated October 5, 2015.

Figure 18. Percentage of participants with CPK elevations



Source: K. Donohue

CPK elevations occurred more often in the reslizumab arm for moderate, severe, and potentially life-threatening categories of severity. Overall, 18% of patients randomized to reslizumab experienced one of these classes of elevation, compared to 14% of those randomized to placebo. Indeed, the incidence of potentially life-threatening CPK elevations (> 10 x ULN) was double in the reslizumab arm (0.8%) compared to the placebo arm (0.4%).

Reviewer's comment: If reslizumab does cause CPK elevations, given the timing of the measurements one month after the prior infusion, the prevalence of CPK elevations observed so

far in the clinical development program is likely to be an underestimate.

Cases were reviewed in detail if they were coded by an investigator as rhabdomyolysis, led to discontinuation, had CPK elevations > 10x ULN, or reported musculoskeletal adverse events within 24 hours of infusion of reslizumab.

- One 22 year old male patient had an adverse event of coded as rhabdomyolysis by the investigator, with CPK elevation to 6,940 U/L thought secondary to recent intense weightlifting after his second infusion, but his renal function was normal and he continued on reslizumab therapy.
- A 35-year old white male developed an increase in CPK (1263 U/L, day 31) from a normal baseline associated with adverse events of severe back spasm and mild backache. His case is reviewed here as his data were improperly excluded from safety analyses, as he was one of the 15 patients recruited at study sites terminated for GCP violations. He too continued on reslizumab.
- The eight patients in the reslizumab 3mg/kg group who had elevations > 10X ULN did not have concomitant musculoskeletal complaints. Some had elevated CPKs at baseline. Most experienced a return of their CPK to baseline with continued reslizumab treatment, but some had persistently elevated CPKs at end of treatment. None had renal failure.
- 24 patients randomized to reslizumab experienced a musculoskeletal adverse event within 24 hours of infusion. Of those, seven had elevations of CPK.
- Three patients discontinued reslizumab, two for muscle pain and one for CPK elevation to 1,247 U/L. A fourth patient in the reslizumab 0.3 mg/kg group had a CPK elevation to 2,353 U/L on his fourth, and final, infusion.

In summary, though there is an imbalance in CPK elevations among those randomized to reslizumab, none progressed to rhabdomyolysis with acute renal failure, and many experienced a return of their CPK to baseline with continued reslizumab therapy. CPK elevations were variably associated with muscle symptoms; most of the potentially life-threatening elevations were asymptomatic.

This reviewer explored the musculoskeletal and connective tissue disorders symptom organ class for high-level terms consistent with a muscle-related safety signal. In addition to the imbalance in myalgia reported by the Sponsor, it appears that some other forms of muscle pain were more common in the reslizumab arm, including pain in extremity.

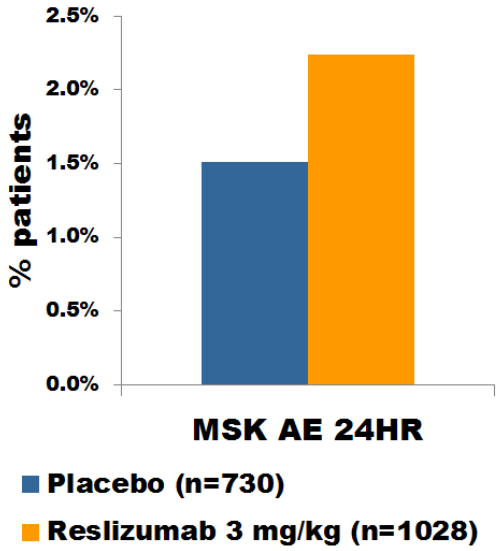
Table 36. Adverse events consistent with muscle pain, safety population

High Level Term	Dictionary-Derived Term	Placebo N=730		All Reslizumab N=1131	
		N	%	N	%
Musculoskeletal and connective tissue pain and discomfort	Back pain	25	3.4%	35	3.1%
	Pain in extremity	4	0.5%	9	0.8%
	Musculoskeletal chest pain	5	0.7%	8	0.7%
	Neck pain	2	0.3%	6	0.5%
	Musculoskeletal pain	4	0.5%	5	0.4%
Muscle pains	Myalgia	4	0.5%	10	0.9%
	Fibromyalgia	2	0.3%	1	0.1%
Muscle related signs and symptoms NEC	Muscle spasms	8	1.1%	10	0.9%
	Muscle swelling	0	0.0%	1	0.1%
	Muscle fatigue	0	0.0%	1	0.1%
Myopathies	Rhabdomyolysis	0	0.0%	1	0.1%

Source: ISS DDAE.XPT ISS ADSL.XPT, ISS Summary 7.1.3

In the Musculoskeletal and Connective Tissue Disorders System Organ Class, the incidence of adverse events occurring within 24 hours after infusion was higher in the reslizumab 3.0 mg/kg group (23[2.2%] patients) compared to placebo (11 [1.5%] patients). Preferred terms for which incidence was higher in the reslizumab arm included musculoskeletal chest pain, muscle spasms, myalgia, extremity pain, muscle fatigue, musculoskeletal pain, neck pain, and rhabdomyolysis.

Figure 19. Musculoskeletal adverse events within 24 hours of infusion

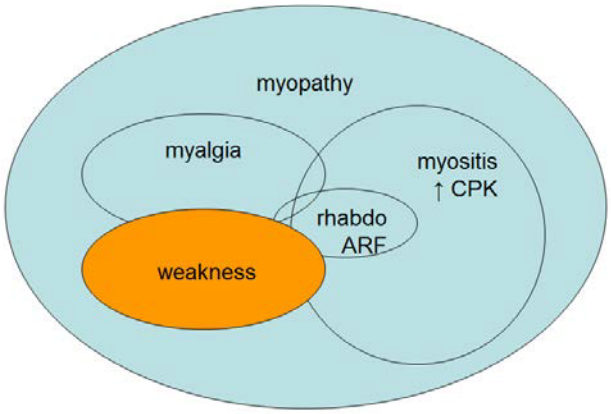


Source: K. Donohue

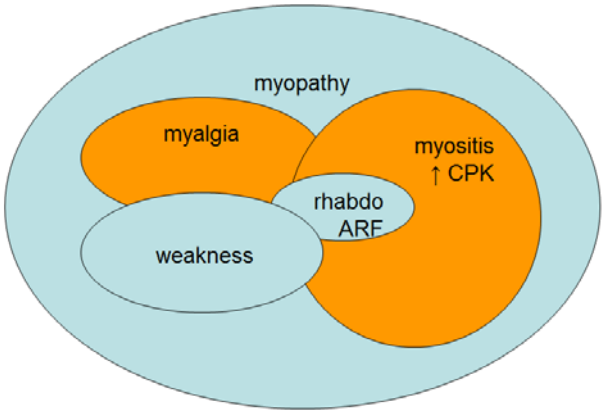
Many patients with severe asthma are treated with oral corticosteroids, and these too may cause muscle toxicity. Among patients taking oral corticosteroids at baseline, those randomized to reslizumab did have a higher incidence of musculoskeletal adverse events (19% for reslizumab vs. 15% for placebo, see Table 37). This was driven primarily by the preferred term of back pain (11% for reslizumab vs. 3% for placebo, see Table 38). No imbalance in musculoskeletal adverse events was observed among patients who were not taking oral corticosteroids at baseline (10% for reslizumab vs. 11% for placebo). However, the imbalance observed in CPK elevations does not appear to be due to concomitant corticosteroid use. The percentage of patients with CPK elevations and concomitant corticosteroid use was similar between treatment arms (13% for reslizumab vs. for 12% placebo among users of IV or oral corticosteroids).

Figure 20. Corticosteroid vs. reslizumab myopathy

a. corticosteroid myopathy



b. reslizumab myopathy



Source: K. Donohue

It is worth noting that steroid myopathy generally is marked by muscle weakness more so than muscle pain, and CPK values generally remain within the normal range (4). Thus, the muscle safety signal observed with reslizumab, marked by muscle pain and CPK elevations, may be distinct from that associated with corticosteroid treatment.

Teva has put forth a compelling counterargument. The heart of Teva's rationale is that the imbalance in CPK levels is due to an imbalance in baseline values, and is not related to reslizumab. This interpretation is supported by evidence that the medians did not increase over time, shift analyses of patients with normal baseline values show no imbalance between treatment arms, pharmacokinetic and pharmacodynamic analyses showed no relationship between CPK changes and reslizumab exposure, and no difference was observed between treatment arms in time to onset of CPK elevations. Lastly, most cases of CPK elevation were transient and returned to baseline while patients continued on treatment.

It is possible that Teva's view of the evidence is correct. However, interpretation of the muscle safety data must be tempered by the limitations in study conduct relevant for this safety signal. First, the inclusion of more patients on baseline oral corticosteroids in the placebo arm of the safety database would make it difficult to detect any muscle safety signal. Second, enrollment of patients with elevated baseline CPK values constituted a protocol violation. Third, the concurrent conduct of the pivotal trials for reslizumab was at Teva's discretion but precluded prospective evaluation of potential safety signals such as muscle adverse events and CPK elevations; failure to measure CPK during the open label extension is notable. Fourth, the timing of CPK measurements one month post-infusion likely failed to capture relevant CPK elevations concurrent with the spike in muscle adverse events that occurred in the 24 hours after reslizumab infusion. It will be important to consider these limitations when interpreting the available data and labeling for the muscle safety signal.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Due to the imbalance in baseline oral corticosteroid use and the potential for this to confound safety analyses, it is important to explore adverse events stratified by steroid use. Indeed, among patients taking oral steroids at baseline, those randomized to reslizumab had more adverse events than those in the placebo group for musculoskeletal and connective tissue disorders, injury, poisoning, and procedural complications, skin and subcutaneous tissue disorders, metabolism and nutrition disorders, psychiatric disorders, and vascular disorders.

Table 37. Adverse events (≥ 5%) by baseline oral corticosteroid use, system organ class

	Baseline OCS		No Baseline OCS	
	Placebo (N=73)	Reslizumab 3 mg/kg (N=73)	Placebo (N=657)	Reslizumab 3 mg/kg (N=955)
Patients with at least 1 event, N (%)	65 (89)	61 (84)	524 (80)	629 (66)
Infections and infestations	43 (59)	37 (51)	343 (52)	383 (40)
Respiratory thoracic and mediastinal disorders	50 (68)	36 (49)	302 (46)	284 (30)
Musculoskeletal and connective tissue disorders	11 (15)	14 (19)	72 (11)	92 (10)
Injury poisoning and procedural complications	9 (12)	11 (15)	53 (8)	58 (6)
Nervous system disorders	19 (26)	10 (14)	94 (14)	113 (12)
Skin and subcutaneous tissue disorders	6 (8)	9 (12)	64 (10)	62 (6)
Gastrointestinal disorders	10 (14)	8 (11)	98 (15)	101 (11)
Metabolism and nutrition disorders	5 (7)	8 (11)	28 (4)	29 (3)
General disorders and administration site conditions	17 (23)	7 (10)	63 (10)	70 (7)
Cardiac disorders	7 (10)	5 (7)	30 (5)	13 (1)
Psychiatric disorders	3 (4)	5 (7)	18 (3)	16 (2)
Vascular disorders	2 (3)	5 (7)	17 (3)	27 (3)
Investigations	7 (10)	3 (4)	52 (8)	70 (7)

Source: Integrated Summary of Safety Table 72
OCS = oral corticosteroid
System organ classes are sorted by descending order of incidence for the reslizumab 3.0 mg/kg treatment group of patients with OCS use at baseline. Patients are counted only once in each System Organ Class category.

Further exploration of this imbalance by preferred terms reveals that among patients taking oral corticosteroids at baseline, those randomized to reslizumab had a higher incidence of nasopharyngitis, back pain, oropharyngeal pain, sinusitis, pneumonia, dyspnea, hypercholesterolemia, and palpitations.

Table 38. Adverse events (≥ 5%) by baseline oral corticosteroid use, preferred terms

	Baseline OCS				No Baseline OCS			
	Placebo (N=73)		Reslizumab 3 mg/kg (N=73)		Placebo (N=657)		Reslizumab 3 mg/kg (N=955)	
Patients with at least 1 event, N (%)	65	(89)	61	(84)	524	(80)	629	(66)
Asthma	44	(60)	25	(34)	245	(37)	207	(22)
Nasopharyngitis	12	(16)	14	(19)	91	(14)	89	(9)
Back pain	2	(3)	8	(11)	23	(4)	25	(3)
Headache	10	(14)	6	(8)	52	(8)	72	(8)
Oropharyngeal pain	0		6	(8)	16	(2)	21	(2)
Sinusitis	5	(7)	6	(8)	46	(7)	51	(5)
Upper respiratory tract infection	5	(7)	6	(8)	64	(10)	90	(9)
Pneumonia	1	(1)	5	(7)	8	(1)	7	(<1)
Dyspnea	2	(3)	4	(5)	18	(3)	18	(2)
Hypercholesterolemia	2	(3)	4	(5)	6	(<1)	7	(<1)
Palpitations	1	(1)	4	(5)	9	(1)	6	(<1)
Urinary Tract Infection	4	(5)	4	(5)	20	(3)	30	(3)

Source: Integrated Summary of Safety Table 73
OCS = oral corticosteroid
Preferred terms are sorted by descending order of incidence for the reslizumab 3.0 mg/kg treatment group of patients with OCS use at baseline. Patients are counted only once in each preferred term category.

Oropharyngeal pain was more common in the reslizumab arm than the placebo arm. Other common adverse events were either evenly balanced or more frequent in the placebo arm.

Table 39. Common adverse events (≥ 2%), safety population

	Placebo (N=730)	Reslizumab 3 mg/kg (N=1028)
Patients with at least 1 AE, n (%)	589 (80.7)	690 (67.1)
Asthma	289 (39.6)	232 (22.6)
Nasopharyngitis	103 (14.1)	103 (10.0)
Upper respiratory tract infection	69 (9.5)	96 (9.3)
Headache	62 (8.5)	78 (7.6)
Sinusitis	51 (7.0)	57 (5.5)
Bronchitis	52 (7.1)	34 (3.3)
Urinary tract infection	24 (3.3)	34 (3.3)
Back pain	25 (3.4)	33 (3.2)
Influenza	37 (5.1)	33 (3.2)
Rhinitis allergic	22 (3.0)	28 (2.7)
Oropharyngeal pain	16 (2.2)	27 (2.6)
Pharyngitis	25 (3.4)	23 (2.2)
Cough	23 (3.2)	22 (2.1)
Dyspnea	20 (2.7)	22 (2.1)

Source: Integrated Summary of Safety Table 27

8.4.6. **Laboratory Findings**

A review of laboratory results from the placebo-controlled studies, 3081, 3082, 3083 and 3084, was notable for three findings.

First, a clinically significant imbalance in CPK elevations was observed. This is reviewed in detail in conjunction with a muscle safety signal in section 8.4.4. Significant Adverse Events.

Second, a higher percentage of patients treated with reslizumab had liver enzyme levels that shifted from normal to elevated over the course of the study, but these appear to be minor as shifts above the pre-specified potentially clinically significant threshold were balanced for placebo and reslizumab arms.

Table 40. Liver function shift table (%)

	Normal to High (%)		**Normal to Potentially Clinical Significant (%)**		
	Placebo (N=677)	Reslizumab (N=975)	Criterion	Placebo (N=677)	Reslizumab (N=975)
Alanine aminotransferase (U/L)	3	5	≥ 3 X ULN	2	1
Aspartate aminotransferase (U/L)	2	2	≥ 3 X ULN	<1	<1
Alkaline phosphatase (U/L)	1	2	≥ 3 X ULN	0	0
Gamma-glutamyltransferase (μ/L)	3	6	≥ 3 X ULN	4	3
Total bilirubin (μmol/L)	2	1	≥ 34.2	<1	<1

Source: Integrated Summary of Safety Tables 47 and 48
ULN = upper limit of normal

Third, decreased eosinophil counts are seen in the reslizumab treated groups; however, this is an expected pharmacologic effect. The reduction in eosinophils also resulted in a corresponding reduction in total white blood cell count in the reslizumab arm.

Apart from these three findings, there were no clinically significant laboratory abnormalities observed in a review of mean change from baseline and shift table analyses.

8.4.7. **Vital Signs**

Vital signs were measured prior to infusion. Post-infusion vital signs were not reported systematically in the safety database. The criteria used to identify potentially clinically significant vital signs were acceptable. No clinically significant differences between treatment groups are seen for sitting pulse, systolic and diastolic blood pressures, respiratory rate, or temperature as analyzed by absolute change, mean change from baseline, and shift tables.

Reviewer's Comment: The failure to capture and report frequent post-infusion vital sign data is notable in the setting of intravenous administration of an investigational monoclonal antibody in a severe asthma population known to be at increased risk of anaphylaxis. This deficiency in the application precluded an investigation of vital sign data for post-infusion hypotension,

tachycardia, and tachypnea consistent with anaphylaxis. However, given the investigator-reported cases of anaphylaxis, this safety concern will be communicated through labeling.

8.4.8. Electrocardiograms (ECGs)

ECGS were assessed at screening, and weeks 24, 36 and 52 (or early withdrawal visit) in Studies 3082 and 3083. They were assessed at screening and Week 16 for studies 3081 and 3084. ECGs were not assessed in Study 3085. ECGs were assessed by the investigator as either normal or abnormal; abnormal ECGs were further assessed for clinical significance. Overall, ECG data were available for 677 placebo patients and 975 reslizumab patients. A review of shifts from normal to abnormal and mean change from baseline in heart rate, PR, QRS, QT, QTc, and RR intervals showed no major treatment-related imbalances.

8.4.9. QT

No dedicated QT trials were performed. In general, monoclonal antibodies are not associated with QT prolongation. Thorough QT studies generally are not required for these clinical development programs.

8.4.10. Immunogenicity

The screening antibody assay has a sensitivity of 22 ng/ml, which is adequate to detect IgG, but insufficient to detect clinically relevant IgE. Typically, sensitivity below 5 ng/ml is required in order to detect clinically relevant IgE. Discussions between the Applicant and the Agency are ongoing at the time of this review regarding development of an anti-drug antibody assay with sufficient sensitivity to detect IgE.

For healthy volunteer studies C38072/1102 and C38072/1107, serum samples were analyzed for anti-drug IgG antibodies using a validated homogeneous solution based bridging enzyme-linked immunosorbent assay. A similar method with an additional confirmatory step to resolve IL-5 interference in asthma patient samples was used for anti-drug antibody analysis in the phase 3 studies 3081, 3082, 3083, 3084, and 3085. Alternative methodologies were used for studies I96-350, P00290, P01942, and Res-5-0010.

Immunogenicity as measured by the assay was low, with approximately 5% of patients developing at least one positive anti-drug IgG antibody during the treatment period. Anti-drug antibody responses were generally low titer and transient. The adverse event profile was similar in in anti-drug antibody positive vs. negative patients. There was no association of a positive anti-drug IgG antibody response with anaphylaxis or hypersensitivity reactions to reslizumab.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Infection

A priori, infection is a concern for any immunomodulator, including reslizumab. Among patients taking oral corticosteroids at baseline, reslizumab may confer increased risk of pneumonia. Overall, no imbalance is observed in the infections and infestations symptom organ class, and no opportunistic infections were reported. However, given the imbalance in baseline oral corticosteroid use, it is important to investigate this in a stratified fashion. Indeed, among patients taking oral corticosteroids at baseline, those randomized to reslizumab had a higher incidence of sinusitis, upper respiratory tract infection, and especially, pneumonia, compared to placebo.

Table 41. Infections stratified by baseline oral corticosteroid use, safety population

	Baseline OCS		No Baseline OCS	
	Placebo (N=73)	Reslizumab 3 mg/kg (N=73)	Placebo (N=657)	Reslizumab 3 mg/kg (N=955)
Infections and infestations	43 (59)	37 (51)	343 (52)	383 (40)
Sinusitis	5 (7)	6 (8)	46 (7)	51 (5)
Upper respiratory tract infection	5 (7)	6 (8)	64 (10)	90 (9)
Pneumonia	1 (1)	5 (7)	8 (1)	7 (<1)
Urinary Tract Infection	4 (5)	4 (5)	20 (3)	30 (3)

Source: Adapted from Integrated Summary of Safety Table 73

Eosinophils play a role in defense against helminthic parasitic infections, and thus these are a submission-specific safety issue. There were no reports of helminthic infections in the randomized safety population, which enrolled 392 patients (219 in the reslizumab group and 173 in the placebo group) from regions known to be endemic for helminthic parasites including South America (Argentina, Brazil, Colombia, Chile, and Peru), Central America (Mexico), Africa (South Africa), and Asia (Malaysia, Philippines, Thailand, Taiwan, Province of China, and Republic of Korea). However, patients with a history of exposure to parasites, diarrheal illness of undetermined etiology, or a history of diagnosed helminthic infection were excluded from the studies.

Eosinophils also may play a role in host defense from viral infections. In the safety analysis population, viral infections were more common in placebo patients (11%) than in reslizumab patients (7%). Consistent with this, herpes zoster was more common in the placebo arm (2 of 730 placebo patients vs. 1 of 1131 reslizumab patients).

8.6. Specific Safety Studies/Clinical Trials

The primary objective of Study 3085 was to obtain additional safety data. Study 3085 was a phase 3, 104-week, multicenter, open-label extension study in patients aged 12 through 75 years of age with moderate to severe asthma and blood eosinophils ≥400 cells/μL. Eligible patients enrolled in this study after completion of the end-of-treatment visit in Study 3081,

3082, or 3083, which served as the screening/baseline visit for participation in the open-label extension study. Patients received reslizumab by IV infusion at a dosage of 3 mg/kg after baseline procedures were completed, and every 4 weeks thereafter for up to 24 months. The study consisted of a screening/baseline visit followed by an open-label treatment period, an end-of-treatment visit conducted 4 weeks after the last dose of reslizumab, and a follow-up evaluation conducted 90 days after the end-of-treatment visit.

A total of 1052 patients were enrolled into the study; 481 patients were naïve to reslizumab at the time of enrollment (hereafter referred to as the reslizumab-naive group), and 571 patients had received reslizumab in the preceding study (hereafter referred to as the reslizumab-experienced group). Both groups were similar in terms of demographic characteristics. The majority of patients were female (61%), white (77%), and of non-Hispanic/Latino ethnicity (81%). The mean patient age was 47.2 years (range=12 to 77 years). As expected, baseline lung function and patient-reported measures of asthma control (ACQ, AQLQ, ASUI, and SABA use) were better on average in reslizumab-experienced patients compared to reslizumab-naïve patients.

Three deaths occurred during treatment, due to anal cancer, hemoptysis, and cardiac arrest (See Section 8.4.1 for details). The incidence of serious adverse events (7%) was similar in the reslizumab-naïve and reslizumab-experienced groups. Thirteen malignancies were diagnosed during the study, including breast cancer, melanoma, prostate cancer, and three diagnoses of skin basal cell carcinoma (See Section 8.7.1 for details). The overall rate of withdrawals from study due to adverse events was low (1% [n=5] and 2% [n=11] of patients in the reslizumab-naïve and reslizumab-experienced groups, respectively) and not predominated by a particular system organ class. The most common adverse events (>5%) occurring in all patients were asthma, nasopharyngitis, upper respiratory tract infection, sinusitis, headache, and bronchitis. The only treatment-related adverse event that occurred in more than 1% of patients was headache (2%). There were no reports of helminthic parasitic infections. As expected, at the onset of study 3085, eosinophil counts were higher in the reslizumab-naive group compared to the reslizumab-experienced group (0.5 versus 0.1 × 109 cells/L), but otherwise there were no clinically meaningful differences between the treatment groups in hematology variables at baseline. Eosinophil counts decreased for the placebo group with exposure to IV reslizumab 3.0 mg/kg in Study 3085, and eosinophil counts at the endpoint were similar between the treatment groups. There were no clinically meaningful differences between the reslizumab-naive vs. experienced groups with regard to vital signs or physical examination measures.

8.7. Additional Safety Explorations

8.7.1. Human Carcinogenicity or Tumor Development

Reslizumab is an immunomodulator, and thus malignancy is a safety issue of special concern. However, the role of IL-5 and eosinophils in tumor surveillance remains an open question.

Twenty-three cases of malignancy were observed in the reslizumab development program, eight in controlled trials, and fifteen in the open label extension trial. The eight cases of malignancy observed in controlled trials included six in the reslizumab arms (prostate, two lung cancers, squamous cell, keratocanthoma and plasmacytoma) and two in the placebo arms (bladder and colon). The fifteen cases in the open-label extension trial included five cases of basal cell carcinoma, three of breast cancer, two of malignant melanoma, and one each of anal cancer, lymphoma, malignant melanoma in situ, lung metastases and prostate cancer.

Overall, the incidence of malignancy was higher in the reslizumab group compared to placebo in controlled studies (0.6% vs. 0.3%), as well as in a comparison of malignancy rates in the reslizumab program vs. what has been observed in the National Cancer Institute's Surveillance, Epidemiology, and End Results Program database. However, a relative strength of the reslizumab program is that patients with a history of malignancy were not excluded, and 4 of the 19 reslizumab treated patients had a previous medical history of malignancy, 2 of whom had a reoccurrence of their previous malignancy. Plasmacytoma is a rare tumor, but otherwise the malignancies observed reflect a diverse range of common tissue types, and those reported in more than one patient were the more commonly occurring cancers.

Preclinical studies did not raise concern for mutagenicity or carcinogenicity. Agreement was reached on a Special Protocol Assessment for use of a transgenic mouse strain in a carcinogenicity study (Study DS-2012-005, see FDA Final Carcinogenicity Assessment Committee Report July 11, 2012 and FDA Response on Carcinogenicity Animal Model, February 25, 2014). In the study, reslizumab doses of up to 500 mg/kg/dose were given via IV injection every 2 weeks for up to 26 weeks. No mortality, macroscopic or microscopic findings concerning for carcinogenicity were observed.

8.7.2. **Human Reproduction and Pregnancy**

As of September 1, 2014, ten pregnancies were reported in the reslizumab development program, two during screening, and eight during treatment. One pregnancy each occurred in Study P00290 (reslizumab 0.3 mg/kg), Study 1102 (reslizumab 0.3 mg/kg), Study 3082 (reslizumab 3.0 mg/kg), and Study 3083 (reslizumab 3.0 mg/kg), three pregnancies in Study 3084 (reslizumab 3.0 mg/kg), and one pregnancy in Study 3085 (reslizumab 3.0 mg/kg). Information was available for seven of the eight pregnancies reported in reslizumab-treated female patients. Two ended in elective abortions, and five concluded with live births of infants with no malformations. One male baby had neonatal jaundice that was reported as an unrelated adverse event and was assessed as a physiologic jaundice. In preclinical studies, adverse genotoxic or reproductive effects were not observed. There is no clinical data on reslizumab and lactation. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for reslizumab and any potential adverse effects on the breast-fed child from reslizumab.

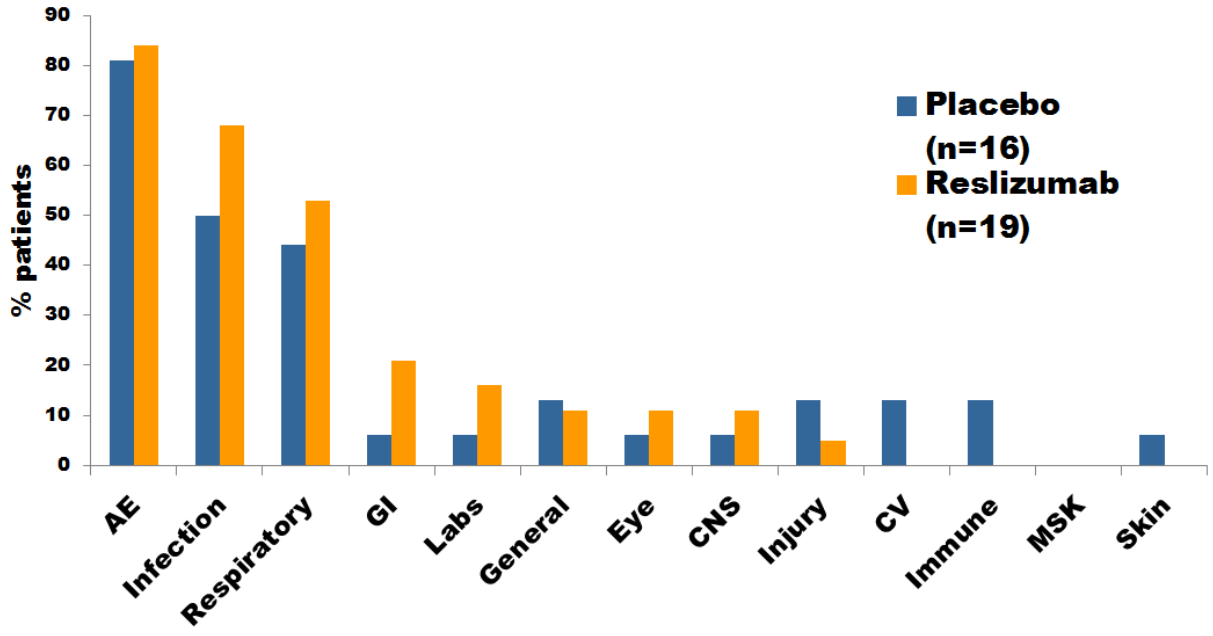
8.7.3. **Pediatrics**

The Applicant submitted a Pediatric Study Plan on August 7, 2014. The Division conveyed agreement to the Applicant on August 26, 2014. The agreed pediatric study plan includes a deferral of studies for the population of preschoolers (0 through 5 years of age) and children (6 through 11 years of age). The need for any additional studies in the preschool population (0 through 6 years) will be determined later.

The development program has enrolled a limited number of adolescents. This limits the interpretation of the safety data. Adolescents randomized to reslizumab were slightly more likely to report adverse events across a range of symptom organ classes than those randomized to placebo (See Figure 21). However, the nature of these adverse events was consistent with routine adolescent health problems, such as acne, broken wrist, upper respiratory tract infections, sinusitis, abdominal pain, or headache.

Given the known risks as presented here, and the divergent efficacy as described in Section X, this reviewer does not feel the risk benefit assessment supports approval of reslizumab in the adolescent pediatric population. As this group has been studied, the Pedatric Research Equity Act post marketing requirements might be considered fulfilled for this age group, with adequate information to be discussed in labeling. This is pending discussion with the Pediatric Review Committee.

Figure 21. Adverse events in adolescents



Integrated Summary of Safety Line Listings Section 7.14.3

8.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The highest administered dose of reslizumab studied in clinical trials was 12.1 mg/kg. Overall,

there were 56 instances in which 21 patients received a dose > 3.5 mg/kg. The applicant attests that review of adverse events reported in the month after these doses did not reveal a safety concern. A Controlled Substance Staff review was not indicated, as reslizumab is not anticipated to be a drug with abuse potential. This assessment was based on reslizumab's route of administration, mechanism of action, and lack of penetration of the blood-brain barrier due to large molecule size. Review of the adverse event data during the post-treatment follow-up period does not indicate any evidence of withdrawal or rebound effects, although it was observed that blood eosinophil levels returned towards the pretreatment baseline at the 90-day follow-up assessment.

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

At the time of this review, reslizumab is not approved for marketing in any country.

8.8.2. Expectations on Safety in the Postmarket Setting

Important subpopulations were not well represented in the safety database, including adolescents, those older than 65 years, and U.S. participants. With respect to older patients and U.S. participants, important differences in the safety profile are not anticipated in the postmarket setting for these subgroups. No potentially important differences are anticipated in how the drug was administered and used in the clinical trial versus its expected use in the postmarket setting that could lead to increased risk. However, adolescents are pediatric patients protected under Subpart D regulations as a vulnerable population. It is anticipated that off-label use would be infrequent and limited to rare disorders such as hypereosinophilic syndrome or eosinophilic esophagitis. Use in these populations would not raise specific safety concerns.

8.9. Integrated Assessment of Safety

The safety database included n=1028 patients treated with reslizumab at the to-be-marketed dose of 3mg/kg and n=730 patients randomized to placebo, and was consistent with international guidelines. There were four deaths in the program, three in patients randomized to reslizumab (anal cancer, hemoptysis secondary to tuberculosis, and a third death in a patient with a history of craniotomy for tumor), and one in the placebo arm (fentanyl overdose). Serious adverse events were more common, overall, in the placebo group. Exceptions that were more common in the reslizumab group included anaphylaxis, fall, chest pain and administration site events. Common adverse events generally were more frequent in the placebo arm. They included asthma, upper respiratory tract infections, nasopharyngitis, headache, and sinusitis.

Of note, more patients in the placebo arm were taking maintenance oral corticosteroids than in the reslizumab arm of the safety database; this could make it difficult to detect safety signals for which both oral corticosteroids and reslizumab may play a role, such as for infection or

myopathy. Two study sites in Study 3084 were terminated for violations of good clinical practice, but adverse event data from their fifteen participants were improperly excluded from safety analyses, including a muscle safety case with CPK elevations. There were several limitations in the collection of safety data, including failure to collect information regarding anaphylaxis events in a prospective manner, failure to capture post-infusion vital signs, infrequent measurement of serum chemistries, and so few details captured regarding adverse events that it was not possible to generate narratives retrospectively.

Despite these limitations, several safety signals have emerged from a review of the safety data, including anaphylaxis, muscle toxicity, malignancy, and infection. Anaphylaxis is a known safety risk for monoclonal antibodies, but it is rare to observe four cases of anaphylaxis in a clinical trials database as was seen in the reslizumab program. Patients randomized to reslizumab were more likely to experience moderate, severe or life-threatening elevations in CPK and more likely to report muscle pain. Further, there was evidence of time-dependence, as patients randomized to reslizumab were more likely to report musculoskeletal adverse events in the 24 hours following infusion. The incidence of malignancy was higher in the reslizumab group compared to placebo in controlled studies (0.6% vs. 0.3%), as well as in comparison to national cancer registries. Among patients taking oral corticosteroids at baseline, those randomized to reslizumab had a higher incidence of pneumonia compared to placebo. Adolescents randomized to reslizumab were slightly more likely to report adverse events across a range of symptom organ classes than those randomized to placebo, but the nature of these adverse events was consistent with routine adolescent health problems.

9 Advisory Committee Meeting and Other External Consultations

A Pulmonary-Allergy Drugs Advisory Committee meeting was held on December 9, 2015. The committee was asked to discuss the adequacy of the efficacy data, considering dose-ranging, the data in children age 12 to 17 years, in the US population, and the role of blood eosinophil counts in determining the target patient population.

There was broad agreement that the dose-ranging was suboptimal.

There was broad agreement that the safety and efficacy data for adolescents were insufficient to support approval. Several panel members speculated that the disease and/or response to treatment with reslizumab may in fact operate differently in this population compared to adults. Many called for additional study in this group.

Several panel members felt the adequacy of the data in the US population was problematic, especially for African American participants. Panel members speculated that the differential results observed in US patients, and especially African American patients, compared to the rest of the global development program, could be due to differences in access to care and background therapy. Another member speculated that some asthma patients have a

predominantly neutrophilic inflammatory response underpinning their asthma and thus would not be expected to respond to this therapy.

Several panel members expressed concerns about the adequacy of the safety data regarding malignancy. Panel members were more divided about whether the data collected were sufficient to adequately characterize the CPK safety signal.

Regarding the target patient population, it was suggested that labeling should reflect the populations who actually participated in the trials, not the inclusion and exclusion criteria. For example, the mean eosinophil value was higher than the inclusion criteria might suggest. Another panel member commented on the importance of noting the high degree of reversibility in airway obstruction required to enter the trial, that many severe asthma patients do not have this degree of reversibility, and that this distinction should be made clear in the labeling.

To summarize, the committee voted 13 "Yes" and 1 "No" that efficacy had been demonstrated in the adult population, with 0 voting "Yes" and 14 voting "No" for the demonstration of efficacy in the adolescent population. For Question 4, there were 11 "Yes" votes and 3 "No" votes that safety had been demonstrated in the adult population, with 0 "Yes votes" for the adolescent population and 14 "No" votes. For the final question asking if the risk benefit supported approval, there were 11 "Yes" votes for the adult population and 3 "No" votes, and 0 "Yes" votes for the adolescent population and 14 "No" votes.

10 Labeling Recommendations

10.1. Prescribing Information

Labeling negotiations are in process at the time this review was completed. Division recommendations included:

- A black box warning for anaphylaxis, consistent with labeling for omalizumab (Xolair)
- 1 INDICATIONS AND USAGE – consistent with mepolizumab (Nucala) but for adults age ≥ 18 years
- 2 DOSAGE AND ADMINISTRATION – consistent with omalizumab regarding monitoring and preparation to treat anaphylaxis
- 5 WARNINGS AND PRECAUTIONS - consistent with the mepolizumab label, although no need to mention herpes zoster under section 5.3 as this was not observed in the reslizumab program
- 6 ADVERSE REACTIONS - include muscle toxicity and CPK elevations, malignancy, and immunogenicity
- 8 USE IN SPECIFIC POPULATIONS – for section 8.1 a pregnancy registry is encouraged,

and for section 8.4 suggested labeling similar to fluticasone furoate and vilanterol (Breo Ellipta) for communicating pediatric findings

- 14 CLINICAL STUDIES – reported by exacerbation or lung function endpoints, include demographics table, symptom outcomes such as ACQ and AQLQ, and language regarding the relevant eosinophil threshold consistent with the mepolizumab label

10.2. Patient Labeling

At the time of this review, patient labeling materials were undergoing ongoing review by the patient labeling team.

10.3. Non-Prescription Labeling

Not applicable.

11 Risk Evaluation and Mitigation Strategies (REMS)

There are no additional risk management strategies required beyond the recommended labeling. Therefore, the subsequent subsections are not applicable for this review and have been omitted.

12 Postmarketing Requirements and Commitments

At the time of this review, no postmarketing requirements or commitments are recommended by the clinical team.

13 Appendices

13.1. References

1. Mepolizumab Pulmonary-Allergy Drugs Advisory Committee Meeting June 11, 2015. [cited 2015 November 4]. Available from: http://www.fda.gov/AdvisoryCommittees/Calendar/ucm446464.htm.
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13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): BLA 761033

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 433		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 5 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 1		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 417		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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/s/

KATHLEEN M DONOHUE
12/17/2015

BANU A KARIMI SHAH
12/17/2015

Medical Officer Memorandum
Division of Pulmonary, Allergy, and Rheumatology Products

Date: March 31, 2015
From: Kathleen M. Donohue, MD
Medical Officer, CDER/ODEII/DPARP
BLA: 761033, Reslizumab
Applicant: Teva
Subject: Filing Review
Materials: \\CDSESUB1\evsprod\BLA761033\0000
received March 30, 2015

Executive Summary

This is a medical officer review of BLA 761033 for Reslizumab, submitted on March 30, 2015. The submission is comprised of the final study reports for the initial development program. On the basis of these studies, the Applicant has proposed an indication to "reduce exacerbations, relieve symptoms and improve lung function in adults and adolescents (12 years of age and above) with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids."

Product Description

Reslizumab is a humanized IgG4κ monoclonal antibody that binds to human interleukin-5. It interferes with IL-5 binding to its cell-surface receptor. IL-5 is a key cytokine responsible for the differentiation, maturation, recruitment, and activation of human eosinophils. Reslizumab is supplied as a refrigerated, sterile, single-use, preservative-free solution for intravenous infusion. Each single-use vial is formulated with 100 mg of Reslizumab in a 10 ml glass vial as an aqueous solution containing 2.45 mg/mL sodium acetate trihydrate, 0.12 mg/mL anhydrous acetic acid, and 70 mg/mL sucrose. The proposed dose is 3mg/kg every 4 weeks.

Regulatory Background

August 18, 2010 – End of Phase II Meeting

- define treatment population using a clinically available test (not sputum eosinophilia)
- evaluate Reslizumab in both eosinophilic and non-eosinophilic asthma, and if not efficacious in non-eosinophilic asthma, this information may be included in labeling
- further dose ranging in the phase 3 efficacy studies was advised, the Applicant declined, the Agency acknowledged this was at the Applicant's discretion, and also at their risk, and would be a review issue
- replicate trials needed to support an asthma exacerbation claim
- Agency prefers FEV1 to percent predictedFEV1 as an endpoint

- validation of the asthma control questionnaire (ACQ) as an endpoint to support an indication
- adequacy of exacerbation endpoint and clinical relevance of treatment difference will be a review issue
- address target related safety issues such as immunoregulation, malignancy, parasitic infection, and ECG monitoring throughout phase III

Agreed Pediatric Study plan (see below), August 26, 2014

Pre-BLA Meeting, February 15, 2015

- Reslizumab does not appear to qualify for priority review because patients with asthma have many alternate therapies, including steroids.
- Adequacy of population PK analyses
- Anti-drug antibody assay validity
- Teva's intention to submit anti-drug antibody data, final study report for 3085 and case report forms at the 120 day safety update.
- Agency reiterated importance of evaluating risk of helminthic parasitic infection, suggested Xolair label as guidance
- Endotoxin levels

Development Program

The development program included four phase I studies, four phase II studies and six phase III studies. Overall, 13 studies are completed and one is ongoing. Reslizumab has been studied in several different patient populations, including asthma, eosinophilic esophagitis, nasal polyposis, hypereosinophilic syndrome, eosinophilic gastroenteritis, and PK studies in healthy volunteers. (b) (4)

For the asthma indication, the safety and efficacy of reslizumab were evaluated in four randomized, double-blind, placebo-controlled studies of 16 to 52 weeks duration involving 978 patients 12 years of age and older with moderate to severe asthma inadequately controlled on medium to high dose inhaled corticosteroids (ICS) (at least 440 mcg fluticasone propionate daily or equivalent) with or without other controllers. Additionally, an open-label, extension study (Study 3085) evaluated the long-term safety of reslizumab.

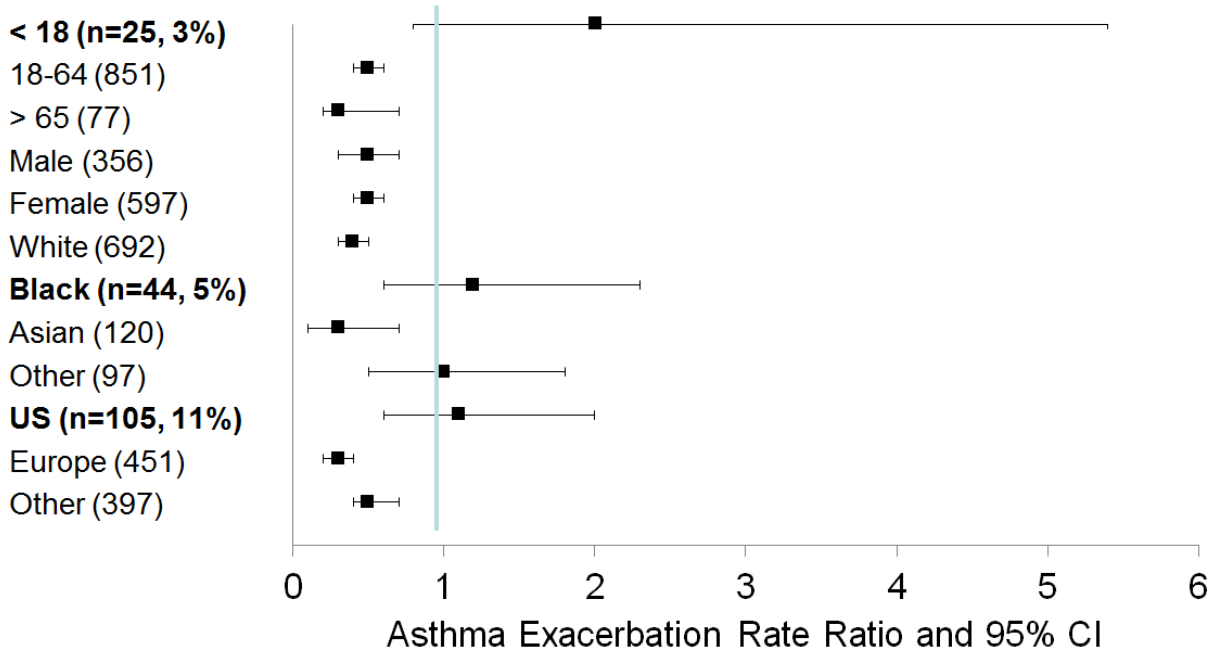
Trial	Population	N	Design	Dose	Wks	Endpoint
3081	Eosinophilic Asthma	311	P3 R DB PC PG	0.3-3mg/kg IV q4wks	16	FEV1
3082	Eosinophilic Asthma	488	P3 R DB PC PG	3mg/kg IV q4wks	52	50% ↓ CAE
3083	Eosinophilic Asthma	464	P3 R DB PC PG	3mg/kg IV q4wks	52	59% ↓CAE
3084	Mod to Sev Asthma	492	P3 R DB PC PG	3mg/kg IV q4wks	16	FEV1
3085	Eosinophilic Asthma	1008	P3 OLE	IV q4wks	104	Safety

Efficacy

Study 3081 observed a mean 160 ml increase in FEV1 compared to placebo at 16 weeks ($p=0.002$). Study 3082 observed a clinical asthma exacerbation (CAE) rate of 0.9 for reslizumab compared to 1.8 for placebo, a 50% reduction over 52 weeks ($p< 0.001$). Study 3083 observed a CAE rate of 0.9 for reslizumab compared to 2.1 for placebo, a 59% reduction over 52 weeks ($p< 0.001$). Study 3084 observed a mean increase in FEV1 of 260 ml for patients with eosinophil levels ≥ 400/µl compared to only a 33ml increase in FEV1 for those with an eosinophil level of < 400/µl at 16 weeks ($p=0.04$).

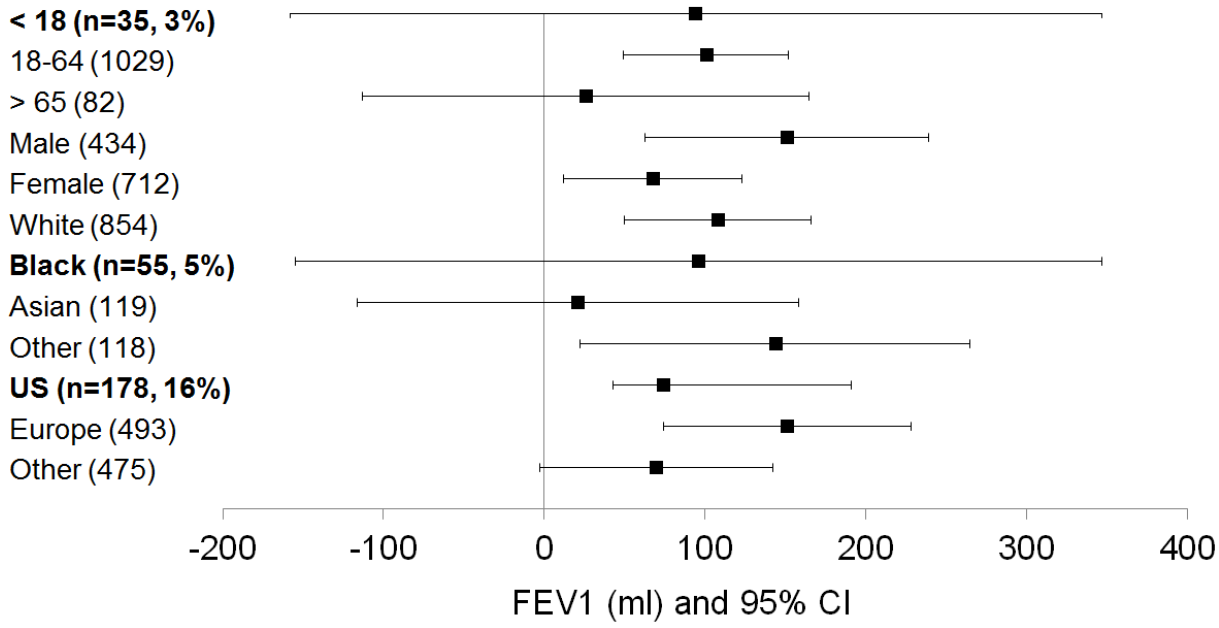
However, evidence of efficacy was less robust for key subgroups, with paradoxical findings for those under the age of 18 years, for Black patients, and for US participants (See Figure 1 below).

Figure 1. Clinical Asthma Exacerbation Rate for Reslizumab vs. Placebo by subgroup



It is reassuring that evidence of efficacy was more robust across subgroups for the FEV1 endpoint, with no paradoxical findings (See Figure 2).

Figure 2. Mean difference in FEV1 for Reslizumab vs. Placebo by subgroup



Safety

Exposure for the safety database was adequate. There were 2195 patients exposed to at least one dose. There were 1621 patients age ≥ 5 years exposed to the to-be-marketed dose. Overall there were four deaths in the development program, likely unrelated to study drug. Three occurred in patients treated with study drug, with cause of death attributed to anal cancer, hemoptysis, and cardiac arrest. One death occurred in the placebo arm, with cause of death attributed to narcotic overdose. Overall, serious adverse events were more frequent in the placebo arm (9%) compared to the Reslizumab arm (6%). However, three serious adverse events occurred more commonly in the Reslizumab arm. These included anaphylaxis (RR = 4.97; 95%CI 0.3 to 96; p = 0.3), malignancy (RR = 2.13; 95%CI 0.43 to 10.52; p = 0.4) and myalgia (RR 1.8; 95%CI 0.6 to 5.6; p = 0.3). Common adverse events were more common in the placebo arm (81%) vs. the Reslizumab arm (66%). Adverse events ocurring in ≥ 5% of participants included asthma, upper respiratory tract infections, nasopharyngitis, headahe and sinusitis.

Proposed Labeling

The applicant seeks an indication “to reduce exacerbations, relieve symptoms and improve lung function in adults and adolescents (12 years of age and above) with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids” Of note, the development program included only those on medium to high dose ICS, not any dose of ICS, and the threshold for elevated blood eosinophils is not specified in the indication statement.

(b) (4)

For safety, the label lists anaphylaxis and parasitic infections in the warnings and precautions. It lists anaphylaxis and myalgia in the adverse reactions section. (b) (4) the relative risk of malignancy was higher than that of myalgia and is a target related safety issue.

OSI Review/Audit

Initial review of the application raises the possibility of data integrity concerns given the somewhat paradoxical findings for the exacerbation endpoint in non-US regions. There was a strongly favorable point estimate and narrow confidence intervals suggesting efficacy from countries outside the United States vs. wide confidence intervals and a point estimate that suggests potential for harm from the patients studied in the United States (See Figure 1, above).

Also it is notable that Site No. (b) (6) had three investigators with disclosable financial information: (b) (6) received $257,675, $101,750, and $128,950 respectively for speaker and consulting honoraria. However, as the site enrolled (b) (6) patients for trial (b) (6) and (b) (6) screen failures it is unlikely to have biased the overall results of the study.

A sponsor-level inspection is planned.

Pediatric Development Plan

The Applicant submitted a Pediatric Study Plan on August 7, 2014. The Pediatric Review Committee (PeRC) concurred on August 20, 2014 and the Division conveyed agreement to the Applicant on August 26, 2014. The agreed PSP includes a deferral of studies for the population of preschoolers (0 through 5 years of age) and children (6 through 11 years of age). The need for any additional studies in the preschool population (0 through 6 years) will be determined at a later time. The agreed PSP includes the following (b) (4) :

(b) (4)

Recommendation

The application is fileable.

Comments for the Applicant

- The lack of evidence for a reduction in exacerbations is noted for key subgroups, including patients 12 to 17 years of age, black patients, and US patients, and will be a review issue.

- We note the lack of data supporting your recommendations for handling parasitic disease. This issue may require a PMR.

NDA/BLA Number: 761033 **Applicant:** Teva **Stamp Date:** March 30, 2015

Drug Name: Reslizumab **NDA/BLA Type:**BLA

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	✓			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	✓			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	✓			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	✓			
5.	Are all documents submitted in English or are English translations provided when necessary?	✓			
6.	Is the clinical section legible so that substantive review can begin?	✓			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	✓			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	✓			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	✓			
10	Has the applicant submitted the integrated summary of efficacy (ISE)?	✓			
11	Has the applicant submitted a benefit-risk analysis for the product?	✓			
12	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(1)
505(b)(2) Applications					
13	If appropriate, what is the reference drug?			✓	
14	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?			✓	
15	Describe the scientific bridge (e.g., BA/BE studies)			✓	
DOSE					

	Content Parameter	Yes	No	NA	Comment
16	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:	✓			Studies 1102, P00290 and 196-350 investigated doses from 0.03 to 3 mg/kg
EFFICACY					
17	Do there appear to be the requisite number of adequate and well-controlled studies in the application? 3082 and 3083 were randomized controlled 52 week studies of asthma exacerbation. 3081 and 3084 were randomized controlled 16 week studies of lung function.	✓			
18	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	✓			
19	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	✓			
20	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	✓			
SAFETY					
21	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	✓			
22	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			✓	
23	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			✓	
24	For chronically administered drugs, have an	✓			

	Content Parameter	Yes	No	NA	Comment
	adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?				
25	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			✓	
26	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	✓			
27	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	✓			Additional study may be needed for helminthic infections, malignancy
28	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?				
OTHER STUDIES					
29	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	✓			
30	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			✓	
PEDIATRIC USE					
31	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	✓			
ABUSE LIABILITY					
32	If relevant, has the applicant submitted information to assess the abuse liability of the product?			✓	
FOREIGN STUDIES					
33	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	✓			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
DATASETS					
34	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	✓			
35	Has the applicant submitted datasets in the format agreed to previously by the Division?	✓			
36	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	✓			
37	Are all datasets to support the critical safety analyses available and complete?	✓			
38	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	✓			
CASE REPORT FORMS					
39	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	✓			
40	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			✓	
FINANCIAL DISCLOSURE					
41	Has the applicant submitted the required Financial Disclosure information?	✓			
GOOD CLINICAL PRACTICE					
42	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	✓			Clinical overview, module 2, p. 8, yes to GCP, no mention of consent or IRB

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___YES___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Kathleen M. Donohue, MD	May 28, 2015
Reviewing Medical Officer	Date
Banu Karimi-Shah, MD	May 28, 2015
Clinical Team Leader	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KATHLEEN M DONOHUE
05/29/2015

BANU A KARIMI SHAH
05/29/2015