PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE (PADAC) MEETING

December 9, 2015

FDA Briefing Document

BLA 761033: Reslizumab for intravenous injection 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

Disclaimer Statement

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the biologics licensing application (BLA) 761033, reslizumab for intravenous injection 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, to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

FDA Briefing Package

DIVISION MEMORANDUM

Date: November 10, 2015

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To: Members, Pulmonary-Allergy Drugs Advisory Committee (PADAC)

Subject: Overview of the FDA background materials for the New Biologics License application (BLA) 761033, for Cinqair® (reslizumab) for intravenous injection for the proposed 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."

1. Introduction and Background

Thank you for your participation in the upcoming Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting to be held on December 9, 2015. As members of the FDA Advisory Committee, we consider your expert scientific advice and recommendations to the FDA very important to our regulatory decision-making processes. The objective of the upcoming meeting is to discuss the new biologics licensing application (BLA) 761033 from Teva for Cinqair® (reslizumab) for intravenous injection 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. The proposed dosage and administration is 3 mg/kg administered intravenously (IV) once every 4 weeks.

Reslizumab is a humanized monoclonal antibody (IgG4, Kappa, mAb) that binds to human interleukin 5 (IL-5). While several cytokines can affect eosinophils, IL-5 is the main cytokine involved in the regulation of blood and tissue eosinophils.[1] Cinqair® (reslizumab) for injection is not currently marketed in the United States or any other country in the world. However, another monoclonal antibody targeting IL-5 (mepolizumab, BLA 125526) was recently approved on November 4, 2015, and was discussed at a PADAC on June 11, 2015.[2] Mepolizumab is approved as add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. While the reslizumab program has also studied asthma patients with an eosinophilic phenotype, the proposed indication includes patients of a

[1] Tavernier J, Plaetinck G, Guisez Y, Van der Heyden J, Kips J, Peleman R, Devos R. The role of IL-5 in the production and function of eosinophils. In: Whetton AD, Gordon JR, editros. Cell biochemistry. Vol. 7: Hematopoietic cell growth factors and their receptors. New York: Plenum Press: 2000.p. 321-361.
[2] http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/ucm433815 htm

lesser disease severity (uncontrolled on inhaled corticosteroids (ICS)). The basis for approval for mepolizumab was a reduction in asthma exacerbations, oral corticosteroid (OCS) sparing, and a positive trend towards improvement in asthma symptoms. If approved, reslizumab would be another choice in the class of anti-IL-5 agents.

Asthma is a chronic inflammatory disorder of the airways affecting more than 22 million persons in the United States. Asthma remains the most common chronic disease of childhood and can have significant impact at the individual and societal level. In spite of the therapeutic advances in the management and treatment of asthma, challenges remain in many areas.[3] There are several classes of products available for use in patients with persistent asthma. These include ICS, inhaled long-acting beta-adrenergic agents (LABA), anticholinergic agents, leukotriene modifying drugs, methylxanthines, and omalizumab. With the appreciation that asthma is a chronic inflammatory disorder, inhaled corticosteroids have become the cornerstone of maintenance therapy for patients with persistent asthma. When an adequate dose of ICS has provided not asthma control, a second drug, such as a LABA if often added, preferably for a limited period of time with the intent of discontinuing the LABA once asthma control is achieved and maintained. Since some patients with persistent asthma use both an ICS and a LABA, these two drugs have been combined together and marketed as inhaled combination products. There are multiple such combination products in the market in the United States for patients with asthma. These are Advair Diskus and Advair HFA Inhalation Aerosol (combination of fluticasone propionate and salmeterol xinafoate), Symbicort (combination of budesonide and formoterol fumarate), Dulera (combination of mometasone furoate and formoterol fumarate), and Breo Ellipta (combination of fluticasone furoate and vilanterol).

The majority of patients with persistent asthma can be adequately controlled by following step-wise treatment recommendations noted above and described in US and global asthma treatment guidelines.[4, 5] However, some patients are not controlled despite step-wise treatments, e.g., high dose ICS plus additional controller medications, such as a LABA, and these would be the target patient population for IL-5 blocking agents. These patients often have asthma exacerbations requiring hospital or emergency department (ED) care, and may require treatment with high dose OCS. An American Thoracic Society (ATS) and European Respiratory Society (ERS) Task Force report from 2014 defines these patients as having "severe asthma" in that they have "asthma that requires treatment with high dose inhaled corticosteroids plus a second controlled and/or systemic corticosteroids to prevent it from becoming "uncontrolled" or that remains "uncontrolled" despite this therapy." [6] An ATS Workshop report from 2000 referred to patients with similar characteristics as those described above as having "refractory asthma." [7] Regular or periodic use of OCS may become necessary in patients with "severe asthma" or "refractory asthma" due to frequent exacerbations. Due to undesired effects of OCS, the aim of treatment is to utilize the lowest effective dose or avoid use of OCS when possible. The alternate therapeutic

[3] National Asthma Education and Prevention Report (NAEPP) Expert Panel Report 3- Guidelines for the Diagnosis and Management of Asthma. At: https://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines
[4] National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, 2007. At: http://www nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines
[5] Global Initiative for Asthma (GIINA): Global strategy for asthma management and prevention, Updated 2015. At: http://www.ginasthma.org/
[6] Task Force Report, ERS/ATS Guidelines on Severe Asthma. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. 2014. Eur Respir J 2014: 43:343-373.
[7] Proceedings of the ATS Workshop on Refractory Asthma. 2000. Am J Respir Crit Care Med 2000; 162:2341-2351.

options for these patients are limited. Recently approved mepolizumab also provides another option to OCS for patients with severe asthma and an eosinophilic phenotype. While reslizumab would similarly be an alternative to OCS, the proposed target patient population for reslizumab also includes a broader group of asthma patients with a lesser severity of asthma (i.e. those uncontrolled only on ICS) with evidence of eosinophilic inflammation, and therefore targets a broader patient population than that for whom mepolizumab is approved. As the committee considers the data presented, it will be important to consider the patient population in whom reslizumab was studied and in whom it should ultimately be indicated.

One challenge in the review of this application is the use of the qualifier "elevated blood eosinophil count" to describe a phenotype of asthma. Within this phenotype, elevated eosinophils have been variably defined with different cut-off numbers for eosinophil counts in blood, sputum, and/or BAL fluid. Defining an eosinophilic phenotype has been a challenge in the scientific and academic community, as eosinophil levels alone do not identify a particular patient subgroup or one that will benefit from treatment. The mepolizumab clinical development program used an eosinophil count of $\geq$ 150 cells/μL at screening together with criteria for severe persistent or refractory asthma to define their patient population. Committee members will note that Teva's patient selection criteria specified inclusion of a less severe population (those uncontrolled on ICS), however with an eosinophil count of $\geq$ 400 cells/μL. Given the similarities between the two development programs (mepolizumab and reslizumab), we analyzed the demographic characteristics of patients in the reslizumab development program to better understand the differences between patients studied versus those studied in the mepolizumab program. It is noteworthy that the patient populations were more similar than the inclusion criteria might indicate. For example, it appears that the inclusion criteria of requiring an eosinophil count greater than 400 cells/μL enrolled patients uncontrolled on both ICS and LABA, with a history of exacerbation, with some on OCS as well. This is discussed in more detail in Section 4.

In this BLA submission, Teva cites published studies conducted with reslizumab (Study P00290 and Study Res-5-0010),[8, 9] to indicate that asthma with elevated blood eosinophils can be characterized by a sputum eosinophil count of ≥3%, and these are the patients who can expect benefit from reslizumab. Teva selected elevated blood eosinophil as a practical surrogate of sputum eosinophilia because blood eosinophil counts are easily accessible to health care providers in clinical practice. Teva selected the ≥400 cells/ μL threshold informed by a secondary analysis of datasets from asthma patients unselected for sputum eosinophils from published studies.[10, 11] Results of the analysis indicated that blood eosinophil count of ≥400 cells/μL had a high positive predictive value for the presence of sputum eosinophils of ≥3%, and a count of <400 cells/μL identified the majority of patients without sputum eosinophilia. Teva's rationale for selecting a blood eosinophil threshold of ≥400 cells/μL will be an important issue for the committee's discussion.

[8] Green RH, Brightling CE, McKenna S, et al. Asthma exacerbations and sputum eosinophil counts: a randomized controlled trial. Lancet 2002; 360:1715-1721.
[9] Castro M, Mathur S, Hargreave F, et al. Reslizumab for poorly controlled, eosinopilic asthma: a randomized, placebo-controlled study. Am J Respir Crit Care Med 2011; 184:1125-1132.
[10] Farooqui N, Khan BQ, Wan JY, Lieberman P. Blood eosinophils as markers of inflammation in asthma [abstract]. Ann Allergy Asthma Immunol 2009; 103 (3 Suppl): A56-A57.
[11] Van Veen IH, Tem Brinke A, Gauw SA, et al. Consistency of sputum eosinophilia in difficult-to-treat asthma: A 5-year follow-up study. J Allergy Clin Immuol 2009: 124: 615-617.

The materials to be discussed in this meeting and the opinions we are seeking are primarily related to the clinical issues related to the efficacy and safety of reslizumab. Keep in mind that in the regulatory decision-making process to determine approvability of a product, the Agency takes into consideration various factors in addition to clinical issues, including manufacturing and controls of product, as well as preclinical considerations. These will not be the focus of this advisory committee meeting.

This memorandum summarizes the contents of the Agency background materials and the key issues and topics for discussion at the meeting. The content of this document and the materials prepared by the Agency reflect the preliminary findings and opinions based on review of the information submitted by Teva to support this BLA, but do not represent the Agency's final position. The feedback and insight you will provide to us at this advisory committee meeting will be an important factor in our decision-making. Attached are the background materials for this meeting. In addition to this memorandum, the FDA background materials include the following: Draft topics/issues for discussion, Clinical and Statistical Briefing Document, Clinical Pharmacology Briefing Document, and Chemistry Briefing Document.

Reslizumab is an anti-IL-5 monoclonal antibody which targets a subgroup of patients with asthma with an eosinophilic phenotype. There are several issues that we would like to focus your attention on for the purposes of this advisory committee meeting. From an efficacy standpoint, reslizumab demonstrated improvement in exacerbations and lung function when compared to placebo; however, the dose-ranging information was limited. The limitation in the dose-ranging may also have implications for the safety signals observed in the program: anaphylaxis and muscle toxicity.

2. Regulatory History of Reslizumab Development in Asthma

The Division and Teva (or predecessor company that owned reslizumab) had typical milestone meetings regarding reslizumab for asthma. Reslizumab was initially developed by Schering Plough. Ception acquired reslizumab from Schering Plough and continued its development. In 2010, Ception was acquired first by Cephalon, and Cephalon was then acquired by Teva in 2011.

The key interactions were as follows: End-of-Phase 2 (EOP2) meeting in September 2010 (held with Cephalon), Type C meeting in May 2013 (held with Teva), FDA feedback of statistical analysis plans of pivotal clinical studies (3081, 3082, 3083, and 3084) at various times in 2013 and 2014, and Pre-BLA meeting in February 2015. At the EOP2 meeting, the key discussion items were as follows: 1) The Division raised concerns regarding the use of sputum eosinophils to guide selection of patients for treatment with reslizumab; 2) The Division mentioned the need to study the whole spectrum of asthma patients, including patients who are predicted to respond and not to respond based on eosinophil phenotype; 3) The Division advised that more than one dose of reslizumab should be evaluated in phase 3 studies, however, Cephalon expressed their intent to proceed with evaluation of a single dose level; 4) There was general agreement that FEV_1 would be an acceptable primary endpoint for lung function studies, and asthma exacerbation would also be an acceptable endpoint noting that exacerbation events should be well- defined. At the Type C meeting, the key discussion items were as follows: 1) The Division restated the importance of studying patients across a spectrum of eosinophil counts; 2) The Division discussed the importance of Study 3084 (included patients irrespective of eosinophil counts) along with Studies 3081, 3082 and 3083 (included patients with eosinophil

count of ≥400 cells/μL) to support eosinophil threshold values for labeling; 3) The Division accepted the definition of asthma exacerbation proposed for the pivotal studies.

3. Product Information

Reslizumab is a humanized IgG4κ monoclonal antibody that binds to human interleukin-5. Reslizumab has a molecular weight of approximately 147 kDa. Reslizumab is produced by recombinant DNA technology in a mammalian cell expression system. Reslizumab is supplied as a refrigerated, sterile, single-use, preservative-free solution for intravenous infusion. Reslizumab is a clear to slightly hazy/opalescent, colorless to slightly yellow liquid. Reslizumab is supplied as 100 mg in a 10 mL glass vial. Each single use vial of reslizumab is formulated as 10 mg/mL reslizumab in an aqueous solution containing 2.45 mg/mL sodium acetate trihydrate, 0.12 mg/mL glacial acetic acid, and 70 mg/mL sucrose, with a pH of 5.5.

4. Clinical and Statistical - Efficacy

a. Overview of the clinical program

Teva submitted five principal efficacy and safety studies in support of the proposed asthma indication. They include a 16-week dose-ranging lung function study (Study 3081) and two 52 week exacerbation studies (Studies 3082 and 3083). These studies were conducted 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 definition of their chosen eosinophil threshold by examining FEV_1 response and blood eosinophil count interaction.

All eosinophil counts to determine patient eligibility for enrollment (in Studies 3081, 3082, 3083, and 3084) were measured at screening (3 to 4 weeks of beginning of treatment). All eosinophil counts were measured centrally on the same platform, with reference normal range of 0 to 800 cells/μL. Teva's threshold eosinophil count of ≥400 cells/μL would fall in the middle of the normal reference range.

All patients in the pivotal studies were receiving standard-of -care treatment optimized to asthma severity; either reslizumab or placebo was added on to the standard-of-care.

Table 1 outlines the pivotal studies that were submitted to support the efficacy and safety of reslizumab. Studies 3081, 3082, 3083, and 3084 will be the focus of the efficacy discussion. Study 5-0010 and Study 3085 will be included in the safety discussion in Section 5.

Table 1. Relevant controlled clinical studies with reslizumab in moderate and severe asthma

ID Year*	**Study Characteristics †** **- Patient age** **- Patient characteristics** **- Study design, objective** **- Study duration**	**Treatment groups ‡**	**N §**	**Efficacy Variables ¶**	**Regions and Countries //**
Phase 2 – Asthma with Sputum Eosinophilia					
Res 5-0010 [04/08- 03/10]	- 18 to 75 yr - FEV_1 50-<70%, - ICS required, LABA allowed, sputum eosinophil ≥3% at screening, no prior asthma exacerbation required - Parallel arm, DB - 15 weeks	Res 3 mg/kg IV Placebo	53 53	1^o: ΔACQ baseline to week 15 2^o: Δ FEV_1 baseline to week 15, sputum eosinophils	US, Canada
Dose Ranging Bronchodilator (lung function) study					
3081 [02/11- 12/13]	- 12 to 75 yr - ICS required, LABA, OCS allowed - blood eosinophil ≥400 cells/μL at screening - Parallel arm, DB - 16 weeks	Res 0.3 mg/kg IV Res 3 mg/kg IV Placebo	104 106 105	1^o: ΔFEV_1 baseline to over 16 weeks 2^o: ΔACQ baseline to over 16 weeks, ΔAQLQ baseline to week 16	US, North America, South America, Europe, Asia (37% US)
Exacerbation Studies					
3082 [04/11- 03/14]	- 12 to 75 yr - ICS required, LABA allowed - blood eosinophil ≥400 cells/μL at screening - ≥1 asthma exacerbation requiring systemic corticosteroid in past year, - Parallel arm, DB - 52 weeks	Res 3 mg/kg IV Placebo	245 244	1^o: Frequency of exacerbation ** 2^o: ΔFEV_1 baseline to over 16 weeks ΔACQ baseline to over 16 weeks, ΔAQLQ baseline to week 16	US, North America, South America, Europe, Asia, Others (15% US)
3083 [03/11- 04/14]	- Same as 3082	Res 3 mg/kg IV Placebo	232 232	1^o: Frequency of exacerbation ** 2^o: ΔFEV_1 baseline to over 16 weeks ΔACQ baseline to over 16 weeks, ΔAQLQ baseline to week 16	US, North America, South America, Europe (7% US)
Open Label Extension from Studies 3081, 3082, and 3083					
3085 [06/11-1/15]	- Same as 3082/3083	Res 3 mg/kg IV	1008	1^o: Safety 2^o: Asthma control	
Moderate to Severe Asthma – Bronchodilator (lung function) study					
3084 [02/12-08/13]	- 18 to 65 yr - ICS required, LABA allowed (≈80% used) - any blood eosinophil count - Parallel arm, DB - 16 weeks	Res 3 mg/kg IV Placebo	398 98	1^o: ΔFEV_1 baseline to week 16 2^o: ΔACQ baseline to over 16 weeks	US, (100% US)

* Study ID shown (top to bottom) as Teva's study number, [month/year study started-completed]† DB = double blind,
‡ Res = Reslizumab doses every 4 weeks; § Intent to treat (ITT)
¶ FEV_1 for Study 3081 was analyzed using mixed-model for repeated measures; frequency of asthma exacerbation for studies 3082 and 3083 were analyzed using negative-binomial regression model.
// North America countries: Canada, Mexico; South America countries: Argentina, Brazil, Chile, Columbia; Europe: Belgium, Czech Republic, Denmark, France, Germany, Greece, Hungary, Netherlands, Poland, Russia, Slovak Republic, Sweden; Asia:Israel, Malaysia, Philippines, Republic of Korea, Taiwan, Thailand; Others: Australia, New Zealand, S. Africa
** Asthma exacerbation: worsening of asthma that required the following medical intervention: 1) use of systemic, or an increase in the use of inhaled, corticosteroid treatment for 3 or more days, and/or 2) asthma-related emergency treatment including at least one of the following: an unscheduled visit to their healthcare professional for nebulizer treatment or other urgent treatment to prevent worsening of asthma symptoms; a visit to the emergency room for asthma-related treatment; or an asthma-related hospitalization. The medical intervention had to be corroborated with at least one of the following: 1) ↓ in FEV1 by 20% or more from baseline, 2) a ↓ in peak expiratory flow rate (PEFR) by 30% or more from baseline on 2 consecutive days, or 3) worsening of symptoms or other clinical signs per physician evaluation or the event.

b. Design and conduct of the studies

Study 3081: Lung function/dose ranging

Study 3081 was a 16-week, randomized, double-blind, placebo, controlled parallel group study to evaluate the efficacy and safety of two doses of reslizumab (0.3 or 3.0 mg/kg) in patients who were inadequately controlled on medium-to-high dose ICS (≥440 μg of fluticasone or similar) with or without another controller. The majority of patients (78%) were also taking a LABA as a second controller. Patients were required to have blood eosinophil count of ≥400 cells/μL, inadequate asthma control based on an Asthma Control Questionnaire (ACQ) score of ≥1.5, and airway reversibility of ≥12% to SABA during screening. The primary efficacy endpoint was overall change from baseline in trough $FEV_{1.}$

Studies 3082 and 3083: Exacerbations

Studies 3082 and 3083 were 52-week, randomized, double-blind, placebo-controlled, parallel-group studies to evaluate the efficacy of reslizumab, at a dosage of 3 mg/kg administered IV once every 4 weeks, in patients with asthma. Inclusion criteria were similar to Study 3081, with the additional requirement of ≥1 asthma exacerbation in the year prior to enrollment. OCS use (prednisone up to 10 mg per day or equivalent) was permitted during these studies. Randomization was stratified by maintenance OCS use. The primary endpoint in Studies 3082 and 3083 was the frequency of asthma exacerbation per patient during the 52-week treatment period. Asthma exacerbations were defined as: worsening of asthma that required the following medical intervention: 1) use of systemic, or an increase in the use of inhaled, corticosteroid treatment for 3 or more days, and/or 2) asthma-related emergency treatment including at least one of the following: an unscheduled visit to their healthcare professional for nebulizer treatment or other urgent treatment to prevent worsening of asthma symptoms; a visit to the emergency room for asthma-related treatment; or an asthma-related hospitalization. The medical intervention had to be corroborated with at least one of the following: 1) a decrease in FEV1 by 20% or more from baseline, 2) a decrease in PEFR by 30% or more from baseline on 2 consecutive days, or 3) worsening of symptoms or other clinical signs per physician evaluation or the event. Lung function (trough FEV1) and patient reported outcome measures (ACQ and Asthma Quality of Life Questionnaire (AQLQ)) were evaluated as secondary endpoints.

Study 3084: Lung function

The design and conduct of Study 3084 was similar to Study 3081, with the difference that patients were not required to have a specific blood eosinophil count. The intent of the study was to evaluate FEV_1 efficacy benefit and blood eosinophil count interaction. The primary endpoint was change from baseline to Week 16 in trough FEV_1.

c. Efficacy results

Characteristics of Enrolled Subjects

Some demographic and baseline characteristics of the subjects enrolled in the pivotal clinical studies are shown in Table 2. While the patient selection criteria allow for the inclusion of patients of those patients uncontrolled only on ICS (i.e. moderate persistent asthma), it is notable that the actual population enrolled in these studies tended to have more severe asthma, with the majority being uncontrolled despite a second controller (i.e. LABA), with 9 to 13% of patients in Studies 3082 and 3083 also taking OCS. It is also notable that the mean eosinophil counts of patients in studies 3081, 3082, and 3083 were ~600 cells/μl, when inclusion specified only that patients be ≥400 cells/μL. There did not appear to be any notable differences between the overall patient population and pediatric patients (12 to 17 years of age) with respect to disease characteristics. Careful examination of the disease characteristics of the enrolled subjects (Table 2) raises the important question as to whether the target population should extend to the broader patient population specified by the inclusion criteria (i.e. moderate-to-severe asthma) or should be limited to those patients who were actually studied (i.e. severe asthma).

Table 2. Selected characteristics for patients in the relevant controlled clinical studies

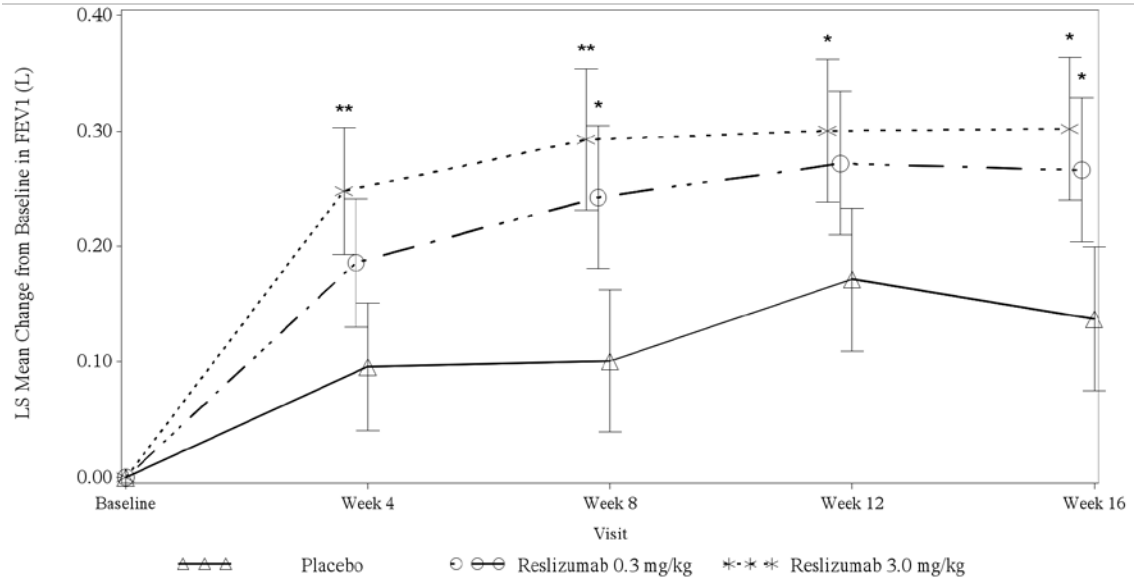
	3081	3084	3082	3083
All Patients: Adults + Pediatrics				
Demographics				
Age, mean in years	44	45	47	47
Asthma duration, mean in years	20.4	26.1	19.2	18.4
Pulmonary function tests				
Pre-bronchodilator FEV_1% predicted	70%	67%	64%	69%
Pre-bronchodilator FEV_1/FVC ratio, mean	0.67	0.69	0.64	0.67
Reversibility, mean % ΔFEV_1 post SABA	25%	26%	26%	28%
Eosinophil counts				
Baseline mean blood eosinophil count/μL	614	280	660	649
Exacerbation history				
Mean number of exacerbations in previous year	2	2	2	2
Percentage patients with ≥2 exacerbation in previous year	24%	17%	40%	42%
Percentage patients with ≥3 exacerbation in previous year	16%	9%	21%	20%
Background treatments for asthma[a]				
Medium dose inhaled corticosteroids (ICS)	67%	76%	56%	58%
High dose inhaled corticosteroids (ICS)	33%	24%	44%	42%
Non-ICS controller drug LABA at baseline	84%	80%	88%	83%
Oral corticosteroids (OCS)	NA	NA	13%	9%
Pediatric patients (12 to 17 yrs) only [Study 3081, n=15; Study 3082, n=13; Study 3083, n =12)				
Demographics				
Age, mean in years	14	-	14	15
Asthma duration, mean in years	11.4	-	8.3	10.1
Pulmonary function tests				
Pre-bronchodilator FEV_1, mean % predicted	74%	-	82%	92%
Post-bronchodilator FEV_1/FVC ratio, mean	0.75	-	0.71	0.75
Reversibility, mean % ΔFEV_1 post SABA	21%	-	31%	27%
Eosinophil counts				
Baseline mean blood eosinophil count/ μL	803		583	414
Exacerbation history				
Mean number of exacerbations in previous year	2.6	-	2.8	2.1
Percentage patients with ≥2 exacerbation in previous year	40%	-	54%	58%
Percentage patients with ≥3 exacerbation in previous year	40%	-	31%	25%
Background treatments for asthma				
Medium dose inhaled corticosteroids (ICS)	87%	-	69%	83%
High dose inhaled corticosteroids (ICS)	13%	-	31%	17%
Non-ICS controller drug (LABA)	93%	-	92%	58%
Oral corticosteroids (OCS)	NA	-	8%	0

NA = Information not collected
Current smokers were excluded from participation; smoking history was not collected in these studies
Post-bronchodilator spirometry was not performed in these studies
a. All patients had to be on ICS background therapy and could have been receiving any combination of background therapies (ICS with or without another controller [non-ICS and/or OCS]; therefore, some patients may be counted more than once in each category
Source: Teva Response to FDA Request for Information, August 21, 2015

Dose Ranging:

Study 3081 was the only study to investigate more than one dose of reslizumab (0.3 and 3 mg/kg IV). A total of 315 subjects were enrolled in this study. Approximately 15% of subjects discontinued study treatment, with slightly more discontinuing in the placebo group (19%) as compared with the two reslizumab treatment groups (11% and 15% in the 0.3 mg/kg and 3 mg/kg groups, respectively. 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. While the 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), both doses demonstrated efficacy with respect to lung function (See Figure 1). In addition to the primary endpoint, reslizumab treatment groups demonstrated improvements in both ACQ and AQLQ, when examined as mean treatment differences and as responder analyses.

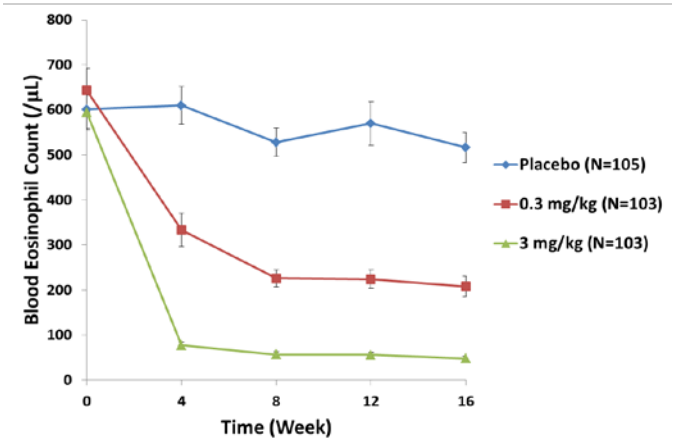
Figure 1. Mean change from baseline (±standard error) in FEV_1 to each visit and endpoint, Study 3081



* p≤0.05, ** p≤0.005 versus placebo. P-values are not adjusted to control for multiplicity. The only time point which has been controlled for multiplicity is week 16.

A dose-dependent reduction of blood eosinophil count was demonstrated. It appeared that the reduction plateau phase was reached at Week 4 and Week 8 for the 0.3 mg/kg, and 3 mg/kg treatment group, respectively. The absolute values of blood eosinophil counts reduced maximally to 517, 208, and 48 cells/μL (or reduced by 14%, 68%, and 92%) for placebo, 0.3 mg/kg, and 3 mg/kg treatment group, respectively.

Figure 2. Arithmetic mean (±SE) of absolute blood eosinophil counts-time profile in different groups: placebo (blue, N=105), 0.3 mg/kg reslizumab (red, N=103), and 3 mg/kg reslizumab (green, N=103)



Source: adapted from CSR 3081, page 351 - 355, Summary 15.24

Despite the Division's suggestion to study more than one dose in confirmatory studies, Teva decided to study a single dose of 3 mg/kg, based on the expected higher eosinophil reduction (which was corroborated in Study 3081). While the reduction in blood eosinophils is greater with the higher reslizumab dose (Figure 2), it is notable that efficacy with respect to lung function was statistically superior to placebo for both doses, although numerically higher (but not statistically different) in the reslizumab 3 mg/kg treatment group (Figure 1). As Study 3081 was conducted concurrently with the exacerbation studies, the results of this study did not inform the doses carried into the confirmatory studies. As the subsequent efficacy discussion will detail, reslizumab 3 mg/kg demonstrated efficacy with respect to exacerbations and lung function in Studies 3082 and 3083; however, based on the limited dose-ranging data available, it is unclear whether a lower dose might have been effective as well. While it is not required that the Applicant identify the lowest effective dose of reslizumab, study of lower doses is pertinent to the safety discussion, given the safety signals that were observed in this program. Because the mechanism behind these safety findings is unclear, and could be related to dose, it will be important for the committee to consider the limitations of the dose-ranging data when reviewing the safety findings (discussed below in Section 5), and whether additional dose-ranging data might be required to address the safety signals.

Exacerbation effects:

A total of 953 subjects were enrolled into Studies 3082 and 3083, of which 952 received at least one dose of study drug. Approximately 11-14% of patients discontinued study treatment prematurely, and this was balanced across treatment arms and studies. The primary endpoint for Studies 3082 and 3083 was the frequency of all asthma exacerbation per patient during the 52-week treatment period. Statistically significant reductions in all asthma exacerbation rates were seen in both exacerbation studies for reslizumab 3.0 mg/kg treatment groups compared to placebo (Table 3).

A secondary analysis was performed stratified by level of treatment needed for exacerbations (e.g. oral steroids, systemic steroids, and ED visit/hospitalization). The exacerbation rates and rate ratios compared to placebo for this secondary analysis are also shown in Table 3.

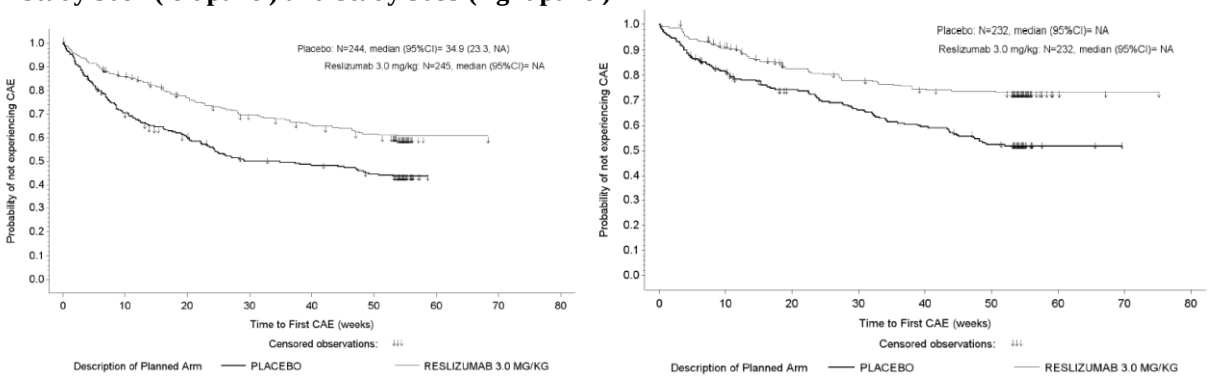
The majority of patients (>80%) who experienced at least 1 exacerbation in Studies 3082 and 3083 were treated with systemic corticosteroids for 3 or more days and would generally be classified as a moderate exacerbation. Statistically significant reduction in moderate exacerbation rate was also seen in both exacerbation studies for reslizumab 3.0 mg/kg treatment groups compared to placebo (Table 3). Patients who had exacerbations defined by ED visit or hospitalization, generally classified as severe exacerbations, also had numerical trend favoring reslizumab 3.0 mg/kg. While the rates of exacerbations leading to ED visit or hospitalization were low across treatment groups (approximate 1 in every 5 to 10 exacerbation required ED visit or hospitalization), the rate ratio of reductions of these severe events trended in the same direction as that of moderate exacerbations (Table 3). Kaplan-Meier analysis of time-to-first exacerbation also showed a beneficial response for reslizumab-treated groups compared to placebo in both the studies (Figure 3).

Table 3. Asthma exacerbation frequency by treatment group over 52 weeks, Studies 3082 and 3083

Study	Treatment	n	Adjusted exacerbation rate	Rate Ratio (95% CI), p-value
Exacerbation, All *				
3082	Reslizumab 3 mg/kg IV	244	0.90	0.50 (0.37, 0.67), <0.0001
	Placebo	245	1.80	
3083	Reslizumab 3 mg/kg IV	232	0.86	0.41 (0.28, 0.59), <0.0001
	Placebo	232	2.11	
Exacerbation, Requiring oral corticosteroid for ≥ 3 days				
3082	Reslizumab 3 mg/kg IV	244	0.70	0.44 (0.32, 0.61), <0.0001
	Placebo	245	1.59	
3083	Reslizumab 3 mg/kg IV	232	0.65	0.40 (0.27, 0.61), <0.0001
	Placebo	232	1.61	
Exacerbation, Requiring systemic corticosteroid for ≥ 3 days				
3082	Reslizumab 3 mg/kg IV	244	0.72	0.45 (0.33, 0.62), <0.0001
	Placebo	245	1.60	
3083	Reslizumab 3 mg/kg IV	232	0.65	0.39 (0.26, 0.58), <0.0001
	Placebo	232	1.66	
Exacerbation, Requiring ED visit or hospitalization				
3082	Reslizumab 3 mg/kg IV	244	0.14	0.66 (0.32, 1.36), 0.2572
	Placebo	245	0.21	
3083	Reslizumab 3 mg/kg IV	232	0.03	0.69 (0.29, 1.64), 0.4020
	Placebo	232	0.05	

* Asthma exacerbation defined as worsening of asthma that required the following medical intervention: 1) use of systemic, or an increase in the use of inhaled, corticosteroid treatment for 3 or more days, and/or 2) asthma-related emergency treatment including at least one of the following: an unscheduled visit to their healthcare professional for nebulizer treatment or other urgent treatment to prevent worsening of asthma symptoms; a visit to the emergency room for asthma-related treatment; or an asthma-related hospitalization. The medical intervention had to be corroborated with at least one of the following: 1) a decrease in FEV1 by 20% or more from baseline, 2) a decrease in PEFR by 30% or more from baseline on 2 consecutive days, or 3) worsening of symptoms or other clinical signs per physician evaluation or the event.
Analysis based on negative binomial regression model with adjustment for IVRS stratification factors (baseline use of OCS [yes or no] and geographical region [US or other]).
Analyses stratified by treatment were not controlled for multiplicity, therefore reported p-values are nominal.

Figure 3. Kaplan-Meier cumulative incidence curve for time to first asthma exacerbation (all exacerbations) in Study 3082 (left panel) and Study 3083 (right panel)



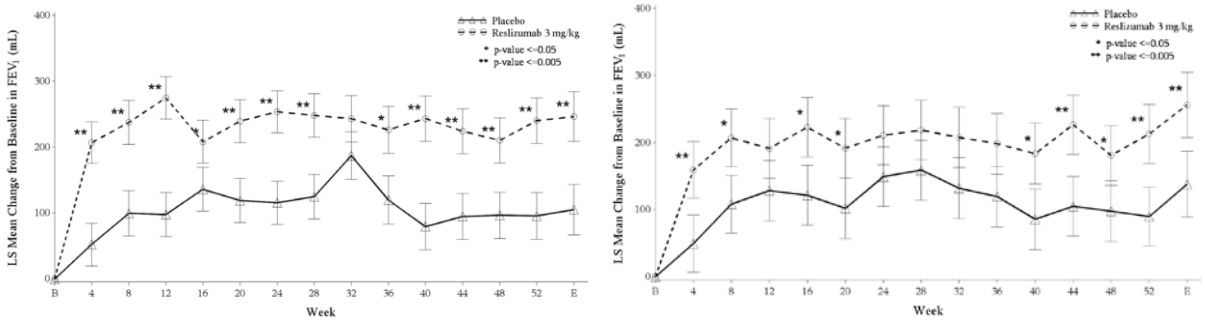
Bronchodilator (lung function) effects:

Spirometry was conducted in Studies 3081, 3084 (as the primary endpoint), and in 3082, 3083 as a secondary endpoint (Table 1). Trough FEV_1 was the measure of interest, which assesses sustained effect over time on lung function. Trough FEV_1 results for all four studies are shown in Table 4, and the time profile curves over study duration are shown from Study 3081 (Figure 1) and Study 3082 (Figure 4). Studies 3082 and 3083 (exacerbation studies) also showed statistically significant improvement with reslizumab over placebo with respect to lung function (Table 4, Figure 4).

Table 4. Change in FEV_1 (L) over placebo (treatment difference) at various time points, shown as mean (95% CI), Studies 3081 and 3084 (lung function studies), Studies 3082 and 3083 (exacerbation studies)

		Over 16 Weeks	At Week 16	Over 52 Weeks	At Week 52
Study 3081	Reslizumab 0.3 mg/kg IV	0.115 (0.016, 0.215)	0.125 (-0.003, 0.253)	Not Available	Not Available
	Reslizumab 3 mg/kg IV	0.160 (0.060, 0.259)	0.165 (0.037, 0.292)	Not Available	Not Available
Study 3082	Reslizumab 3 mg/kg IV	0.137 (0.076, 0.198)	0.072 (0.001, 0.144)	0.126 (0.064, 0.188)	0.145 (0.065, 0.224)
Study 3083	Reslizumab 3 mg/kg IV	0.093 (0.030, 0.155)	0.101 (0.023, 0.179)	0.090 (0.026, 0.153)	0.123 (0.047, 0.199)
Study 3084	Reslizumab 3 mg/kg IV	0.076 (-0.006, 0.158)	0.050 (-0.030, 0.165)	Not Available	Not Available

Figure 4. Mean change from baseline (± standard error) in FEV1 to each visit in Study 3082 (left panel) and Study 3083 (right panel).



* Week 16 was the only time point for which multiplicity was controlled

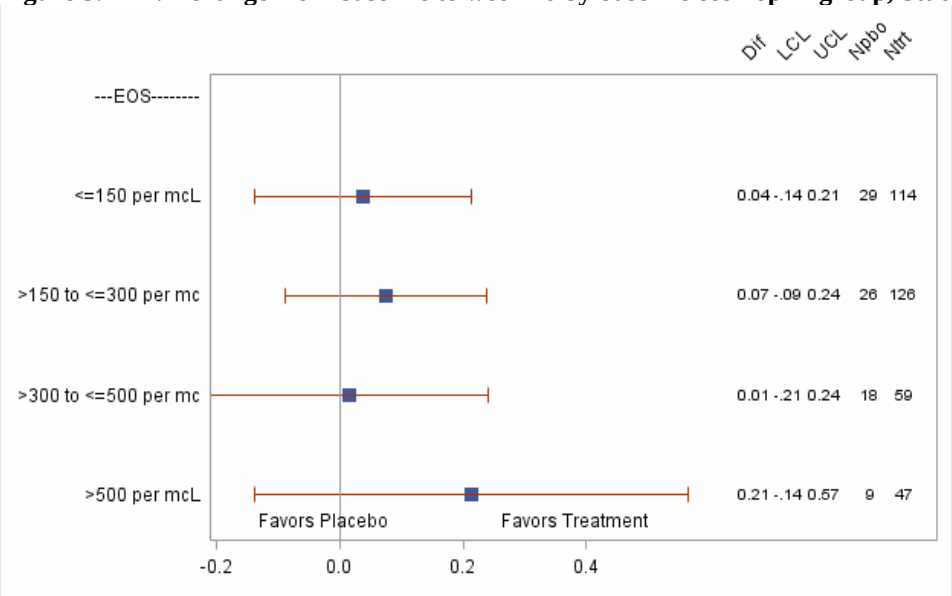
Study 3084 evaluated lung function (FEV_1) and included patients unselected for baseline blood eosinophil counts. This study was designed to test the interaction between FEV_1 change from baseline and the baseline eosinophil counts. The primary efficacy analysis, a linear regression model, failed to show a significant overall interaction between baseline eosinophil counts and FEV_1 change over 16 weeks or at week 16. When reslizumab treatment effect on FEV_1 was analyzed against various cutoffs of baseline eosinophil counts, it appeared that the treatment effect was only significant in patients with baseline counts ≥ 400 cells/μL (Table 5, Figure 5). However, this relatively large treatment effect was driven primarily by a differential response in the placebo patients meeting this criterion as compared with the placebo arms at other thresholds. Compared with the reslizumab group, baseline demography suggests that the small placebo group (N=13) may have entered the study with more severe asthma (median ACQ score 2.71 compared to 2.29 and FEV1 % predicted 65% compared to 67%, for the placebo and reslizumab groups, respectively). Given the failure of this pre-defined study to show an interaction between FEV_1 and eosinophil count, along with the inability to evaluate this interaction in other studies (where only patients who met the threshold of ≥ 400 cells/μL were enrolled), it will be important for the committee to consider the role of eosinophil counts in patients treated with reslizumab.

Table 5. Comparison of FEV_1 (L) Change from Baseline between Placebo group and Reslizumab group at week 16 by Various Cutoffs of Baseline Eosinophil Counts, Study 3084

Blood Eos (/μL)		Placebo[1]	Reslizumab 3.0 mg/kg[1]	Treatment Difference[2]	p Value
Cutoff					
100	< 100	0.207 (16, 0.0877)	0.252 (62, 0.0577)	0.045 (-0.155, 0.245)	0.1202
	≥ 100	0.170 (65, 0.052)	0.259 (282, 0.0259)	0.089 (-0.023, 0.202)	0.6537
200	< 200	0.193 (37, 0.0631)	0.239 (158, 0.0346)	0.046 (-0.092, 0.184)	0.2401
	≥ 200	0.169 (44, 0.0644)	0.253 (186, 0.0324)	0.084 (-0.057, 0.225)	0.5122
300	< 300	0.179 (54, 0.0539)	0.247 (239, 0.0277)	0.067 (-0.050, 0.184)	0.2818
	≥ 300	0.161 (27, 0.0826)	0.261 (105, 0.0433)	0.100 (-0.083, 0.283)	0.2579
400	< 400	0.215 (68, 0.0484)	0.247 (275, 0.0255)	0.033 (-0.073, 0.139)	0.0436
	≥ 400	0.002 (13, 0.1216)	0.272 (69, 0.0557)	0.270 (0.008, 0.532)	0.5422

[1] Least square mean (N, SE)
[2] Treatment difference (95% CI)

Figure 5. FEV1 change from baseline to week 16 by baseline eosinophil group, Study 3084



Source: Biostatistical Reviewer, Dr. Lan Zeng
EOS as categorical variable (EOS Group): Treatment interaction P-value= 0.4718
EOS as continuous variable: Treatment interaction P-value= 0.2291
EOS as continuous variable with Log transformation: Treatment interaction P-value= 0.5351

Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ),
ACQ and AQLQ are commonly used measurements tools for asthma with defined measurement properties,[12] and listed in common asthma treatment guidelines, [13, 14] and elsewhere.[15]

ACQ is a questionnaire to measure the adequacy of asthma control and change in asthma control that occurs either spontaneously or as a result of treatment. There are 7 items in ACQ: 5 items of self-administered questions (breathlessness, nocturnal waking due to asthma, asthma symptoms upon waking, activity limitation, and wheeze), 1 item of self-administered rescue bronchodilator use, and 1 item of FEV_1 completed by clinic staff. The 7 item complete ACQ is commonly used. There are shortened versions of ACQ, including a 5 item version that do not use rescue bronchodilator use and FEV_1. A change in score of 0.5 on the 7-point scale is the smallest difference that is considered clinically important, which is the minimal clinical important difference for ACQ. An ACQ score $\geq$1.0 indicates that asthma is not well-controlled.

AQLQ is a disease specific health-related instrument that measures physical and emotional impact of disease. There are 32 items in AQLQ that are in 4 domains – symptoms, activity limitation, emotional function, and environmental stimuli. A change in score of 0.5 on the 7-point scale is the smallest change that is considered clinically important, which is the minimal clinical important difference for AQLQ.

[12] Measurement of Health-Related Quality of Life & Asthma Control. At: https://qoltech.co.uk/index htm
[13] National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, 2007. At: http://www nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines
[14] Global Initiative for Asthma (GIINA): Global strategy for asthma management and prevention, Updated 2015. At: http://www.ginasthma.org/
[15] ATS website: http://www.thoracic.org/members/assemblies/assemblies/srn/questionaires/acq.php

ACQ and AQLQ were assessed in Studies 3081, 3082, and 3083. ACQ and AQLQ are important in Studies 3082 and 3083 (the exacerbation studies) as they provide other dimensions of benefit and at earlier time points. Results are shown in Table 6 and Table 7. Results of the responder analyses for ACQ and AQLQ support the exacerbation endpoint.

Table 6. ACQ responder analysis at ≥0.5 threshold at week 16 (primary time point) and week 52

	Reslizumab 0.3 mg/kg	**Reslizumab 3mg/kg**	**Placebo**
Study 3081 (lung function study)			
At Week 16	61%	64%	58%
Reslizumab 0.3 mg/kg vs Placebo, p-value			0.8
Reslizumab 3 mg/kg vs Placebo, p-value			0.5
Study 3082 (exacerbation study)			
At Week 16	-	69%	65%
Reslizumab 3 mg/kg vs Placebo, p-value			0.5
At Week 52	-	77%	64%
Reslizumab 3 mg/kg vs Placebo, p-value			0.002
Study 3083 (exacerbation study)			
At Week 16	-	70%	58%
Reslizumab 3 mg/kg vs Placebo, p-value			0.01
At Week 52	-	81%	62%
Reslizumab 3 mg/kg vs Placebo, p-value			< 0.0001
Source: Response to FDA Information Request, August 21, 2015			

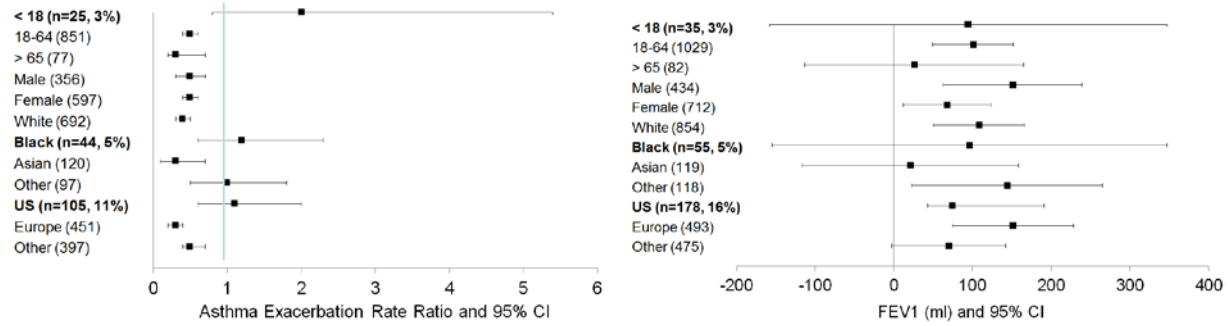
Table 7. AQLQ responder analysis at ≥0.5 threshold at week 16 (primary time point) and week 52

	Reslizumab 0.3 mg/kg	**Reslizumab 3 mg/kg**	**Placebo**
Study 3081 (lung function study)			
At Week 16	59%	64%	48%
Reslizumab 0.3 mg/kg vs Placebo, p-value			0.08
Reslizumab 3 mg/kg vs Placebo, p-value			0.02
Study 3082 (exacerbation study)			
At Week 16	-	66%	58%
Reslizumab 3 mg/kg vs Placebo, p-value			0.06
At Week 52	-	75%	65%
Reslizumab 3 mg/kg vs Placebo, p-value			0.03
Study 3083 (exacerbation study)			
At Week 16		67%	55%
Reslizumab 3 mg/kg vs Placebo, p-value			0.01
At Week 52		74%	64%
Reslizumab 3 mg/kg vs Placebo, p-value			0.03
Source: Response to FDA Information Request, August 21, 2015			

Subpopulations

Evidence of efficacy was less robust for certain 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 (Figure 5). While the paradoxical findings may be due to chance (driven by small sample size), it warrants further discussion whether the risk-benefit evaluation is favorable in these subgroups, which will be further addressed after the safety discussion below.

Figure 5. Efficacy analyses by subgroup, reslizumab vs. placebo, exacerbation rate ratios (left panel) and FEV1 (right panel)



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

5. Safety

a. Safety database

The safety assessment of reslizumab for asthma is based on the studies shown in Table 1. The most robust safety data are from placebo-controlled studies 5-0010, 3081, 3082, 3083, and 3084. Study 3085 provides longer-term, open label safety information, and will be discussed where relevant. The safety population included a total of 1870 patients of whom 1028 patients received reslizumab 3.0 mg/kg every 4 weeks.

b. Safety findings

Deaths, SAEs, dropouts, and discontinuations

Four deaths were reported during the asthma clinical studies, three of the four deaths occurred in Study 3085. Three of the four deaths occurred in a reslizumab treatment arm. None were considered to be related to study drug. The deaths were due to the following causes: one patient died of progressive anal cancer; one patient died due to hemoptysis, aspiration pneumonia, and cardiac arrest; one patient died due to cardiac arrest, and one patient (placebo treatment group) died probably due to accidental combined drug intoxication with fentanyl and diphenhydramine.

Serious adverse events (SAEs)[16] occurred with comparable frequencies between reslizumab and placebo treatment groups. The majority of the events were related to asthma (2% in reslizumab 3 mg/kg treatment groups and 3% in placebo treatment group). Anaphylaxis as a treatment-related SAE was reported in 4 patients in the reslizumab 3 mg/kg treatment group. These were considered to be related to reslizumab by the investigators and by Teva. Anaphylaxis as a safety signal will be discussed in further detail below.

Dropouts and discontinuations were low (approximately 5% in reslizumab and placebo treatment groups) in the controlled clinical studies. There were no trends in events leading to discontinuations. The most common event leading to discontinuation in all groups was asthma.

[16] Serious Adverse Drug Experience is defined in 21 CFR 312.32 as any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience (defined in the same regulation as any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Common Adverse Events

Common adverse events seen were typical of an asthma program. Common adverse events reported were asthma (23% in reslizumab vs 40% in placebo), nasopharyngitis (10% in reslizumab vs 14% in placebo), upper respiratory tract infections (9% in reslizumab vs 10% in placebo), headache (8% in reslizumab vs 9% in placebo), and sinusitis (6% in reslizumab vs 7% in placebo). There were no adverse events for reslizumab that occurred with a frequency greater than 1% higher than that of corresponding placebo frequency

Adverse Events of Special Interest

1) Anaphylaxis

Allergic reactions including anaphylaxis are a known risk with biologic drug products. It is notable that in the development program, potential anaphylaxis events were not prospectively assessed by investigators using accepted criteria, such as those developed by the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network (NIAID/FAAN).[17] Anaphylaxis was identified by investigators and reported as an adverse event; this prompted a search of the safety database using standard queries to ascertain the scope of the safety signal. Of the 1311 patients in the placebo-controlled asthma studies (3081, 3082, 3083, 3084, 5-0010), there were 5 cases of anaphylaxis in the reslizumab group, 3 of which appear to be related to reslizumab, and no cases of anaphylaxis in the placebo group. The narratives for these patients are detailed in the Clinical and Statistical Briefing Document. At the time of finalization of this memorandum, the Applicant has agreed to the Agency's request to conduct a search for potential anaphylaxis cases in the whole database and have these cases independently adjudicated according to the NIAID/FAAN criteria.[17] We anticipate that during the meeting, an updated and complete analysis of anaphylaxis cases will be presented. However, the ability to adjudicate these cases definitively will be limited, as necessary data (such as post-infusion vital signs) were not captured in a prospective manner in all patients. The lack of detailed data post-infusion may preclude our ability to identify additional cases of anaphylaxis. Nevertheless, given the identified cases of anaphylaxis cases so far, it seems reasonable to conclude that reslizumab is associated with anaphylaxis. Further analyses of the database may better quantify the risk.

The presence of an anaphylaxis safety signal in the reslizumab development program may tie into another important product-related issue as summarized below and discussed in more detail in the CMC portion of the briefing document. Reslizumab is a monoclonal antibody manufactured in a murine cell line (NS0). Murine cell lines synthesize a blood group oligosaccharide, glactose-alpha-1,3-galactose, known as alpha-gal.[18] Reslizumab drug product does contain alpha-gal. In the literature, an increased risk of anaphylaxis has also been observed with another monoclonal antibody, cetuximab, which was manufactured in another murine cell line. Anaphylaxis with cetuximab was noted with first-time infusions (suggesting pre-existing sensitization). Indeed, IgE antibodies specific for alpha-gal were identified in pre-treatment

[17] Sampson HA, Munoz-Furlong A, Campbell RL et al. Second symposium on the definition and management of anaphylaxis: summary report – second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006; 117:391-397.

[18] Li F, Vijayasankaran N, Shen AY, Kiss R, Amanullah A. Cell culture processes for monoclonal antibody production. *MAbs* 2010; 2: 466-479.

serum samples from patients who later experienced anaphylaxis to cetuximab,[19] and alpha-gal was identified on cetuximab via mass spectrometry.[20] In addition, cetuximab anaphylaxis cases exhibited significant regional variability, with the highest number of US cases observed in the Southeast. This led to the hypothesis that tick bites may cause patients to develop IgE antibodies specific for alpha-gal. Evidence for the tick bite hypothesis comes from ecological data showing an increase in prevalence of cetuximab anaphylaxis in a geographic region matching 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.[21] While the mechanism by which this sensitization occurs remains an open question, it is notable that the three reslizumab-related cases of anaphylaxis in the asthma program occurred in locations consistent with the tick bite hypothesis.

Whether and to what extent alpha-gal is playing a role in the observed anaphylaxis safety signal is unclear. Given the relatively high frequency of anaphylaxis observed in the clinical development program, along with the proposed clinical use in a patient population at higher risk of anaphylaxis, we feel that the product issues merit your consideration, as you consider the risk-benefit evaluation of reslizumab for the proposed indication. Lack of a clear mechanism also ties back to the limitations in the dose-ranging data, as it is unclear if the risk-benefit assessment of a lower dose might have been more favorable.

2) Creatine Phosphokinase (CPK) Elevation/Muscle Safety Signal
CPK elevations occurred more often in the reslizumab arm for moderate, severe, and potentially life-threatening categories of severity. Indeed, the prevalence of potentially life-threatening CPK elevations (> 10 x ULN) was double in the reslizumab arm (0.8%) compared to the placebo arm (0.4%). The mechanism by which reslizumab could lead to CPK elevation is unknown; however examination of other adverse event data is also consistent with a muscle safety signal. Although the differences are small, musculoskeletal chest pain, muscle spasms, myalgia, extremity pain, muscle fatigue, musculoskeletal pain, neck pain, and rhabdomyolysis occurred with higher incidence 24-hours after infusion in the reslizumab group as compared to placebo. While we acknowledge the Applicant's rationale that the CPK imbalance is due to an imbalance in the baseline values, the evaluation of this signal is marked by several limitations, most notable of which includes the lack of CPK measurement in the 24 hours after reslizumab infusion, at which time the muscle adverse events were being reported. Whether this safety signal has been adequately characterized, or requires further investigation, will be another important topic for discussion.

6. Risk-benefit evaluation of reslizumab and issues for consideration

Reslizumab, another member of the anti-IL-5 class of monoclonal antibodies, is being proposed to reduce exacerbation, relieve symptoms, and improve lung function in adults and adolescents

[19] Chung CH, Mirakhur B, Chan E, Le QT, Berlin J, Morse M, Murphy BA, Satinover SM, Hosen J, Mauro D, Slebos RJ, Zhou Q, Gold D, Hatley T, Hicklin DJ, Platts-Mills TA. Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1,3-galactose. *N Engl J Med* 2008; 358: 1109-1117.
[20] Qian J, Liu T, Yang L, Daus A, Crowley R, Zhou Q. Structural characterization of N-linked oligosaccharides on monoclonal antibody cetuximab by the combination of orthogonal matrix-assisted laser desorption/ionization hybrid quadrupole-quadrupole time-of-flight tandem mass spectrometry and sequential enzymatic digestion. *Anal Biochem* 2007; 364: 8-18.
[21] Steinke JW, Platts-Mills TA, Commins SP. The alpha-gal story: lessons learned from connecting the dots. *J Allergy Clin Immunol* 2015; 135: 589-596; quiz 597.

(12 years of age and above) with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids. While the patient selection criteria in the reslizumab clinical program allowed for inclusion of patients with moderate to severe asthma, the patients who were actually enrolled in the clinical program had more severe asthma (majority also on LABA as a second controller, and some on OCS). As the committee considers the data presented, it will be important to consider the appropriate target population for reslizumab, and whether the proposed indication should extend to the broader patient population specified by the inclusion criteria or should be limited to those patients who were actually studied (i.e. severe asthma).

While the dose-ranging data was limited, Teva has provided some rationale for their choice of dose, and the submitted data show a consistent effect for reduction in exacerbations and improvement in lung function in the studied asthma population, with a history of exacerbation despite ICS and other controller therapies. Evidence for efficacy with respect to exacerbations was less robust in adolescent and US patients, although improvement in lung function in these patients was generally supportive.

Evaluation of the submitted safety database revealed two important safety signals: anaphylaxis and muscle enzyme (CPK) elevation. It will be important for the committee to consider each of these in the risk-benefit evaluation of reslizumab for the proposed indication. Anaphylaxis is a known risk with biologic products, and the patient population in whom reslizumab would be indicated is at increased risk by virtue of their underlying disease. While analysis of this safety signal is ongoing, it is notable that events were not prospectively collected or adjudicated according to accepted criteria. Further, there is the product-related issue of the presence of alpha-gal, which may tie in with this safety signal, although this remains an open question.

An increased incidence of muscle adverse events in the reslizumab treatment arms was noted 24-hours post-infusion. In addition, there is evidence for elevated CPK enzymes, indicating some type of muscle toxicity. It is difficult to characterize the true magnitude of this safety signal, as we do not have data for CPK following infusion that correspond temporally to the clinical complaints. Whether these safety signals have been adequately characterized to support the risk-benefit evaluation of reslizumab in the proposed patient population will be an important issue for your discussion.

Draft Topics/Issues for Discussion

1. **DISCUSSION**: Discuss the efficacy data for reslizumab 3 mg/kg IV administered once every 4 weeks to support its use in the treatment of asthma. Consider the following issues in the discussion:

a) asthma severity of the target patient population to be treated with reslizumab, noting that while the patient selection criteria allowed for a broader severity of asthma patients to be enrolled, those patients actually enrolled and studied were those with severe asthma.
b) adequacy of the dose ranging data
c) adequacy of the efficacy data in children 12 to 17 years of age
d) adequacy of the data in the US population
e) the role of blood eosinophil counts in determining the target patient population

2. **VOTE:** Do the efficacy data provide substantial evidence of a clinically meaningful benefit of reslizumab 3 mg/kg IV once every 4 weeks for the treatment of asthma?

a) in adults, 18 years of age and older?
If not, what further data should be obtained?

b) in children 12 – 17 years of age?
If not, what further data should be obtained?

3. **DISCUSSION:** Discuss the safety data for reslizumab 3 mg/kg administered once every 4 weeks with consideration of the findings of anaphylaxis and muscle enzyme elevation. Comment on the potential impact of additional dose-ranging data or product attributes (e.g alpha gal) when discussing the anaphylaxis safety signal.

4. **VOTE:** Is the safety profile of reslizumab 3 mg/kg IV administered once every 4 weeks adequate to support approval for patients with asthma?

5. **VOTE:** Do the available efficacy and safety data support approval of reslizumab 3 mg/kg IV every 4 weeks for the treatment of patients with asthma?

a) in adults 18 years of age and older?
If not what further data should be obtained?

b) in children 12 – 17 years of age?
If not what further data should be obtained?

Joint Clinical and Statistical Briefing Document for the Pulmonary—Allergy Drugs Advisory Committee Meeting

December 9, 2015

Cinqair® (reslizumab for injection) BLA 761033

Dose: 3 mg/kg intravenous injection every 4 weeks

Proposed 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."

Reviewers: Kathleen M. Donohue, M.D., Medical Officer
Lan Zeng, M.S., Statistical Reviewer

Department of Health & Human Services
Food & Drug Administration
Center for Drug Evaluation & Research
Division of Pulmonary, Allergy and Rheumatology Products
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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. 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 dose-ranging 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 of 2012. Study 3085 was an open-label extension study that began in June of 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 0.16 L with 95%CI (0.06, 0.26), p=0.002). Study 3082 observed a clinical 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 0.38, 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, which may be due to a contaminant known as alpha-gal. 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). 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 notable limitations. First, dose-ranging data are limited. Second, the exacerbation studies (3082, 3083) were stratified by oral corticosteroid use and the lung function studies by history of exacerbation. The stratification variable was misclassified in 2-4% of patients in lung function studies and in 6-9% of patients in exacerbation studies. There also were more patients taking baseline oral corticosteroids in the placebo arm of Study 3082 and in the placebo arm of the safety database as a whole. This imbalance could increase the chance of falsely concluding efficacy in Study 3082, and decrease the chance of detecting safety signals for which both steroids and reslizumab could play a role, such as infections or myopathy. Third, protocol violations were frequent, affecting up to one quarter of study participants. Fourth, although the changes appear minor, it is noteworthy that the definition of the primary exacerbation endpoint was changed after enrollment was completed for studies 3082 and 3083, and the databases for both trials were unlocked for editing after unblinding. Fifth, 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.

It will be important for committee members to consider the safety and efficacy issues raised in this review during discussion of the overall risk-benefit evaluation of reslizumab for the proposed indication.

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-Imunoglobulin 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
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 under investigational new drug application number 101399.

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.

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.

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 III

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

May 2013: Type C Meeting

- Agreement was reached regarding the definition for an asthma exacerbation in Studies 3082 and 3083.

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. Product Quality

Refer to the attached product quality briefing document for further details.

4.2. Clinical Pharmacology

4.2.1. 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.

4.2.2. 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.

4.2.3. **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.

4.2.4. **Blood Eosinophil Count**

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.

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	15	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	FEV_1
(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	1008	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

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 a safety endpoint. 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 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 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

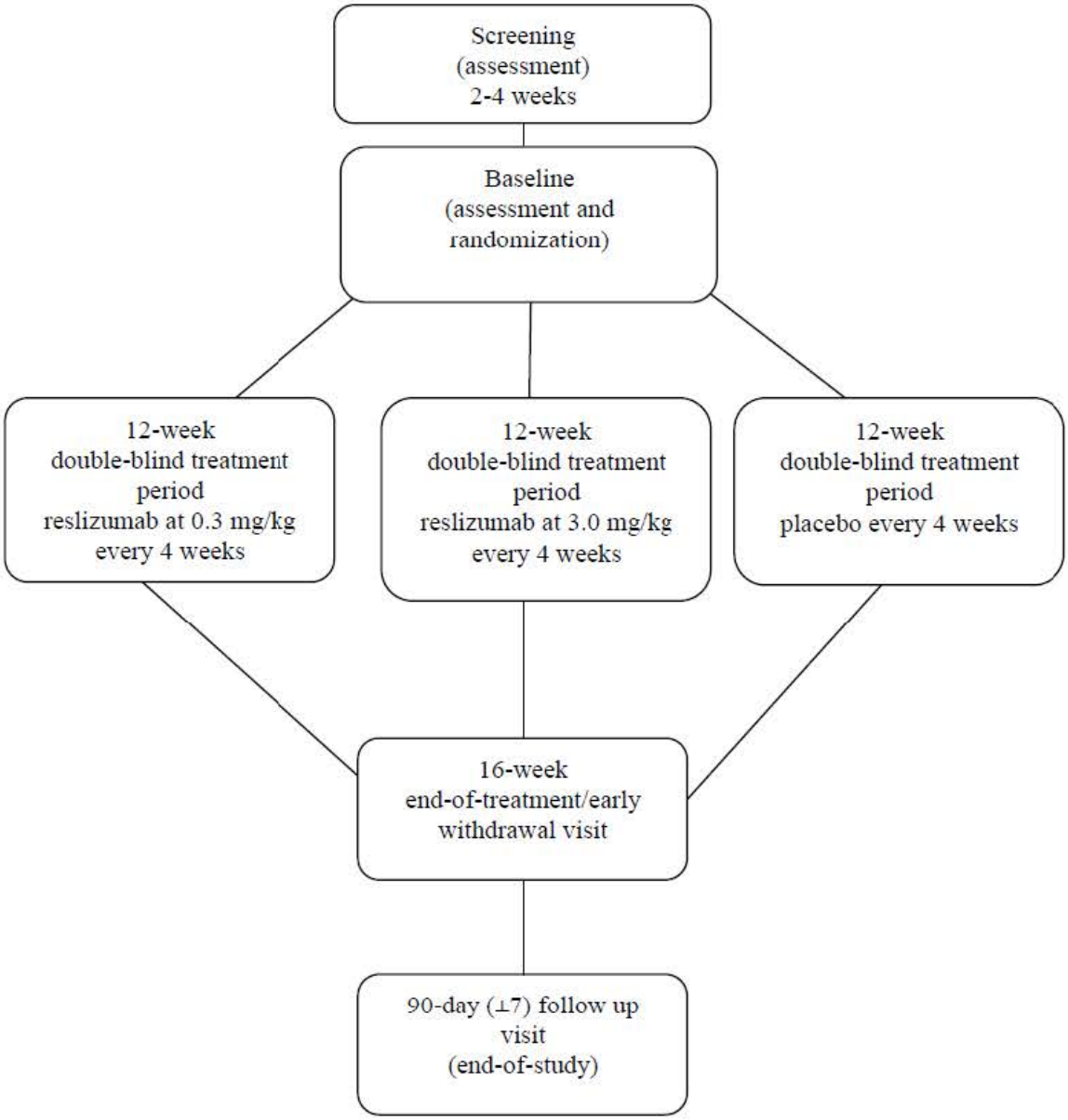
6.1.1. Study Design

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 1. 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 monoclonoal antibody, methotrexate, cyclosporin, interferon-α, or anti-tumor necrosis factor monoclonoal 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 20 mM sodium acetate, 7% sucrose, pH 5.5 buffer

Placebo: sterile solution for infusion presented as 10 mL per vial, formulated in 20 mM sodium acetate, 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.

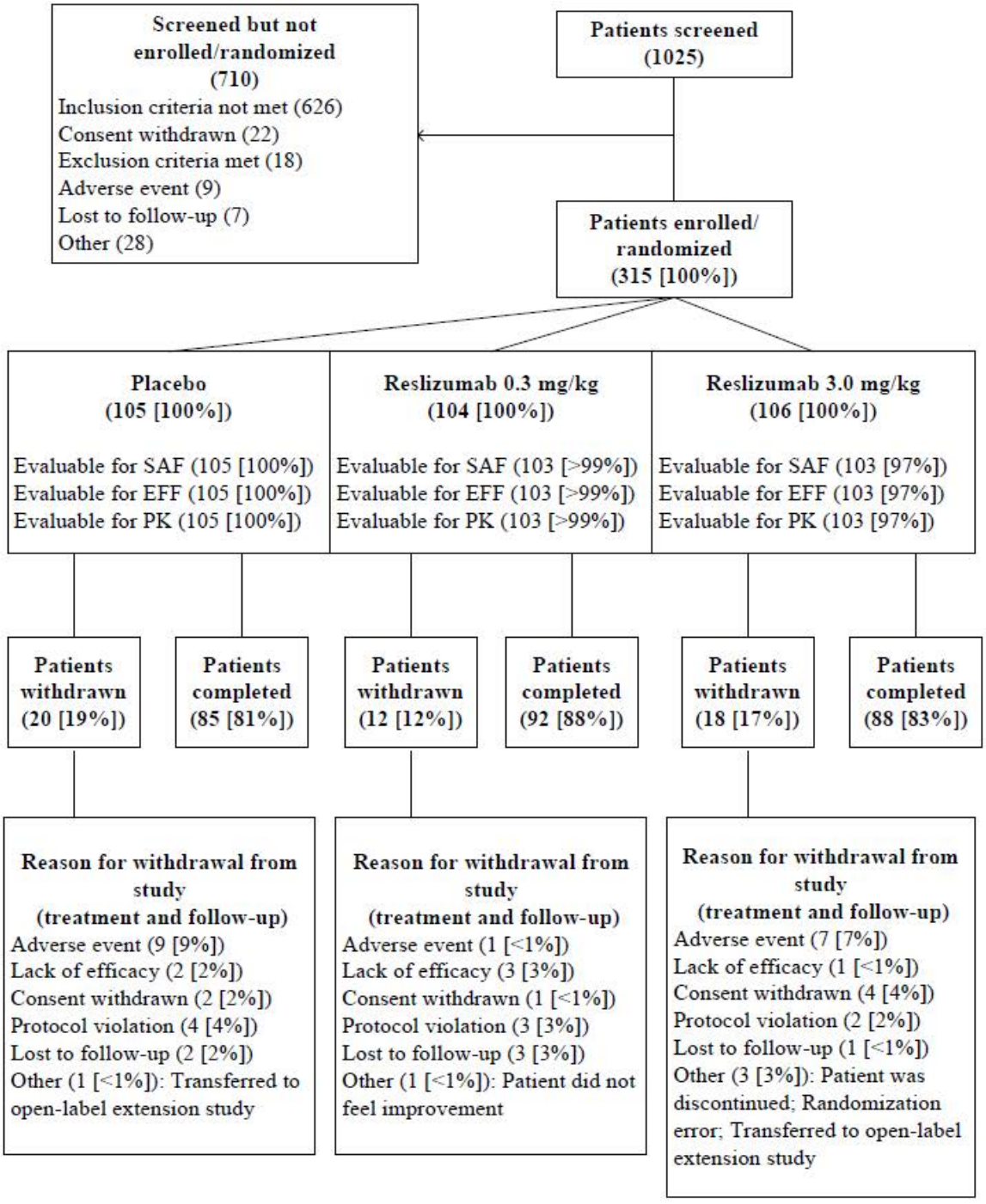
6.1.2. Study Results

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 2. 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.

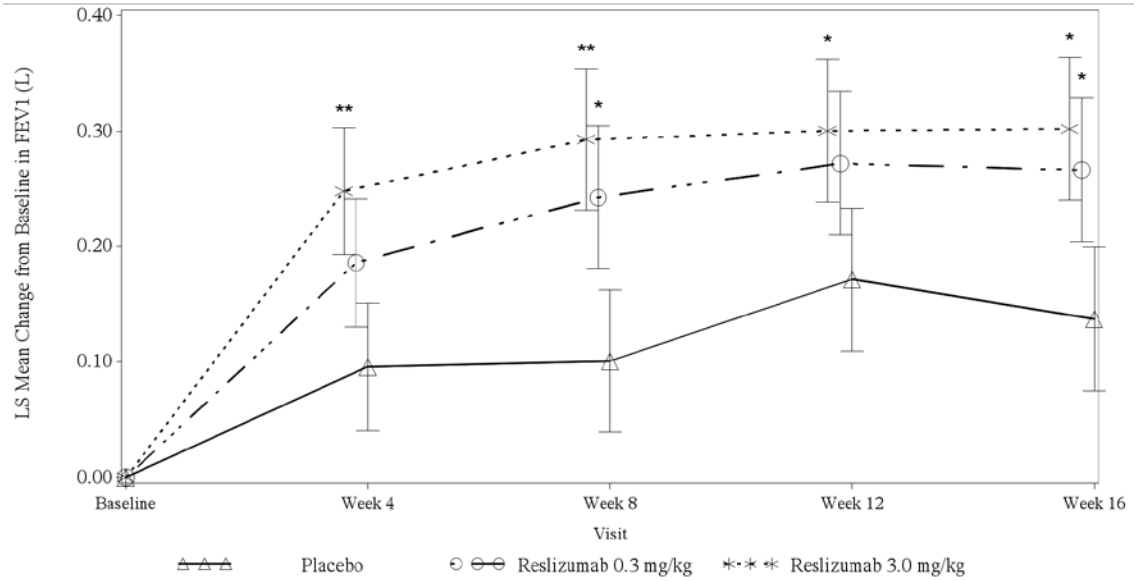
Efficacy Results – Primary Endpoint

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 3. 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. However, it is notable that there were protocol violations for more than 20% of participants in Study 3081.

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

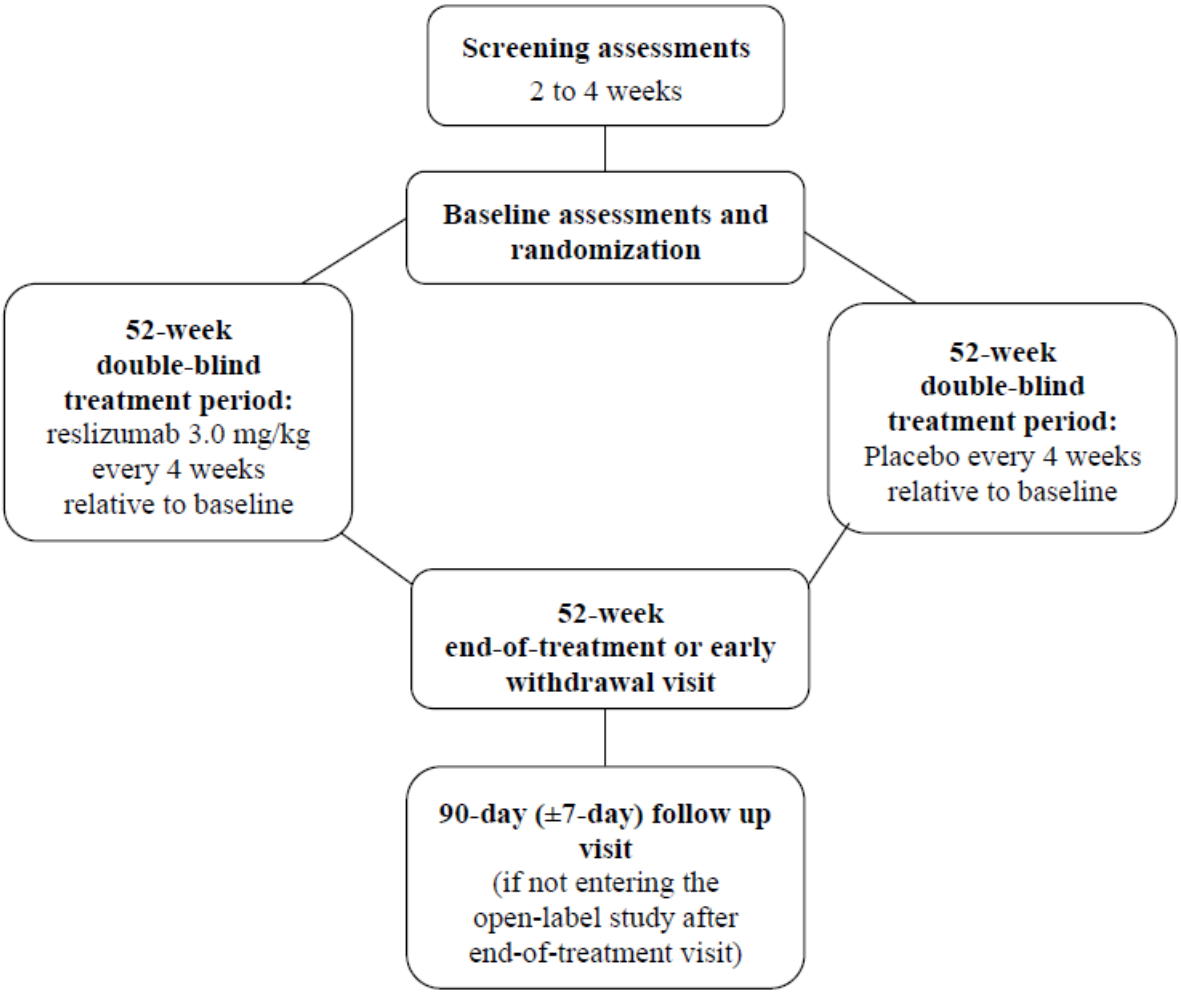
Studies 3082 and 3083 were conducted concurrently with each other and with Study 3081, the dose-ranging study. As noted earlier, this timeline precluded use of dose-ranging data from 3081 to inform dose selection for Studies 3082 and 3083. Since Studies 3082 and 3083 were nearly identical, their design 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 4. 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 monoclonoal antibody, methotrexate, cyclosporin, interferon-α, or anti-tumor necrosis factor monoclonoal 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 20 mM sodium acetate, 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 20 mM sodium acetate, 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 9.0% for placebo patients and 6.5% 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.

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 marked a change in sponsorship from Cephalon to Teva, and sample size was increased from n=440 to n=800, citing papers showing a lower-than-expected exacerbation rate (26, 27). Power was increased to 90%, with no rationale offered. 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). No rationale was offered for reducing power back to 80%. Amendment 6 altered the definition of an exacerbation 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 the 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.

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, and while a priori it does not discredit the data, it does merit further consideration.

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 (Study report p. 17).

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, Concomitant Medications, and Rescue Medication Use

Compliance was excellent (approximately 100%) in both arms in both studies. Concomitant 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

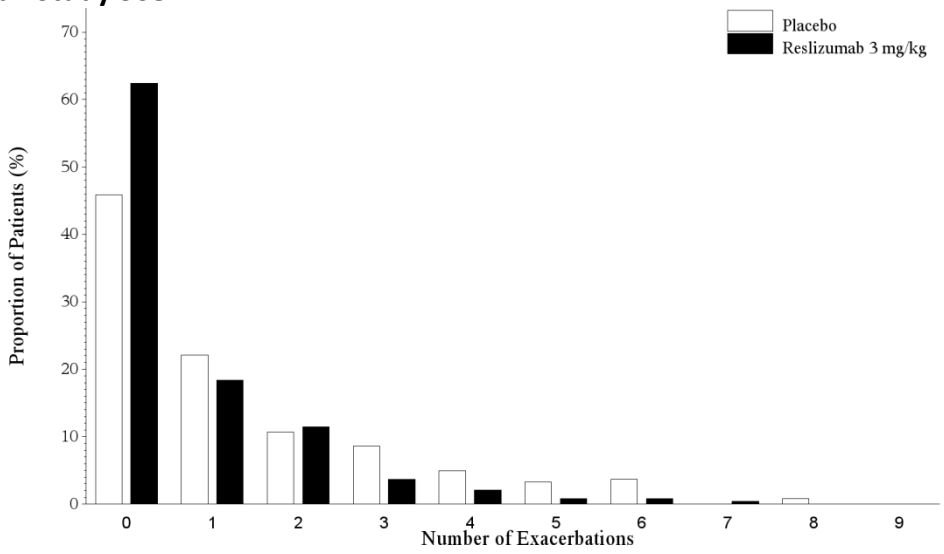
Parameter	Study 3082		Study 3083	
	Placebo (N=244)	Reslizumab (N=245)	Placebo (N=232)	Reslizumab (N=232)
Patients with ≥1 exacerbation, n (%)	132 (54.1)	92 (37.6)	105 (45.3)	59 (25.4)
Sponsor's Analysis*				
Adjusted exacerbation rate	1.80	0.90	2.11	0.86
(95% CI)	(1.37, 2.37)	(0.68, 1.20)	(1.33, 3.36)	(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

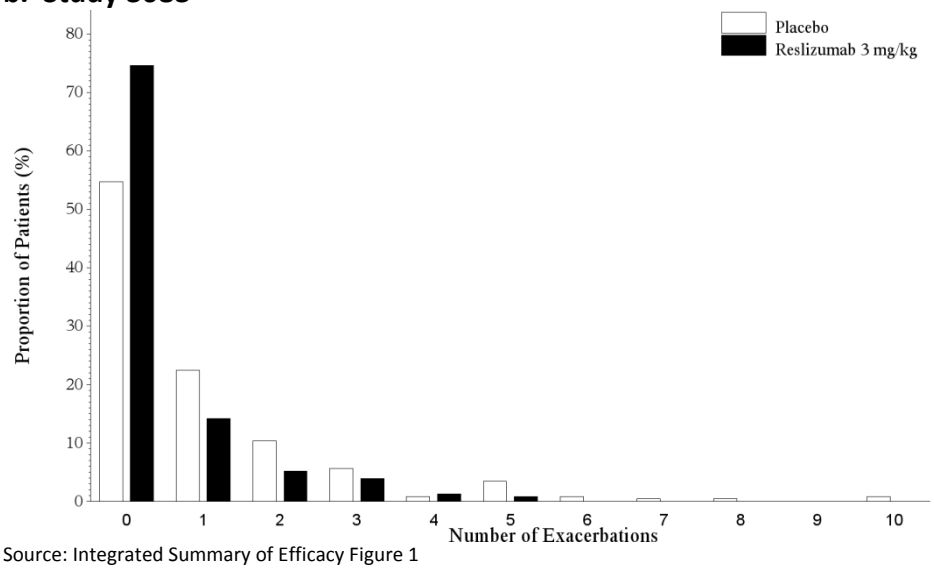
The frequency distribution of exacerbations during the 52-week treatment period is shown in Figure 5. The proportion of patients who did not experience an asthma exacerbation during the entire treatment period was higher in the reslizumab group (62% and 75%) compared with the placebo group (46% and 55%), in Studies 3082 and 3083, respectively.

Figure 5. 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 OCS 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 OCS use				
exacerbation rate (95% CI)	1.59 (1.18, 2.14)	0.6974 (0.509, 0.956)	1.61 (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. This reviewer does not agree with the sponsor's assertion that this is unlikely to affect the overall results or conclusions. This is a large imbalance, and the effect on the outcome even from a relatively small imbalance in this baseline characteristic could be profound. The patients in the placebo arm of Study 3082 were considerably sicker than those in the treatment arm. This has implications for drawing conclusions about both efficacy and safety. Results from sensitivity analyses are reassuring and are discussed in detail above. Whether they are sufficient to overcome this limitation and conclude efficacy is an important question for the committee's consideration. The direction of misclassification of baseline oral corticosteroid use in Study 3083 was such that the reslizumab arm had more severe asthma patients than the placebo arm, and thus the bias would be towards the null. However, as the magnitude of the misclassification was greater in Study 3082 than in 3083, the implications for interpreting pooled safety data remain a concern. More patients in the pooled placebo arm were taking baseline oral corticosteroids, which could obscure safety signals such as muscle toxicity or infections. This is discussed further in Section 8.

Three additional features of study conduct were notable. First, there was a high rate of protocol violations. Second, the primary endpoint definition was changed after enrollment was complete. Third, the database was edited after unblinding, although these changes were reported to be minor.

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

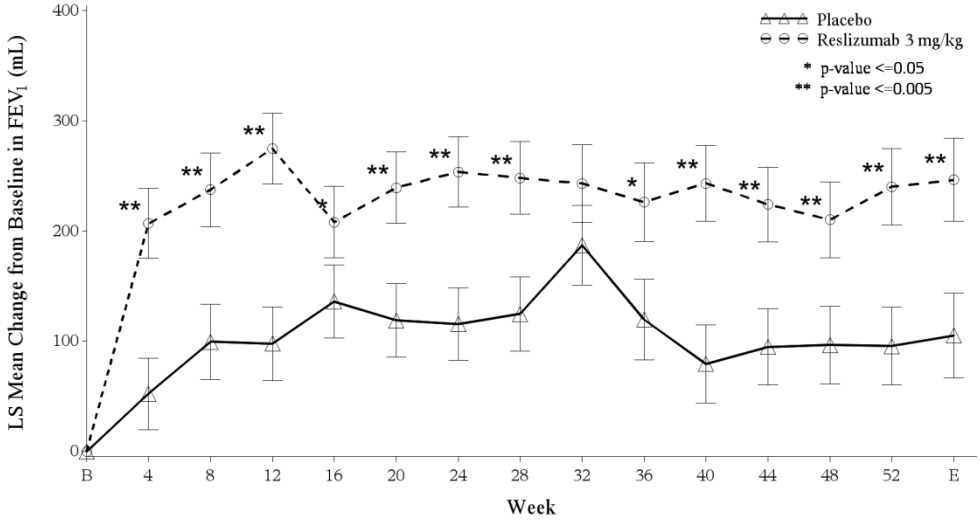
		Study 3082			Study 3083		
	Statistic	Placebo	Res	Res - Pbo (95% CI) p-value	Placebo	Res	Res - Pbo (95% CI) p-value
FEV_1 Δ to Week 16	LS mean (SE)	0.136 (0.033)	0.208 (0.032)	0.072 (0.001, 0.144) 0.0483	0.122 (0.045)	0.223 (0.045)	0.101 (0.023, 0.179) 0.0109
FEV_1 Δ over 16 weeks	LS mean (SE)	0.110 (0.031)	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

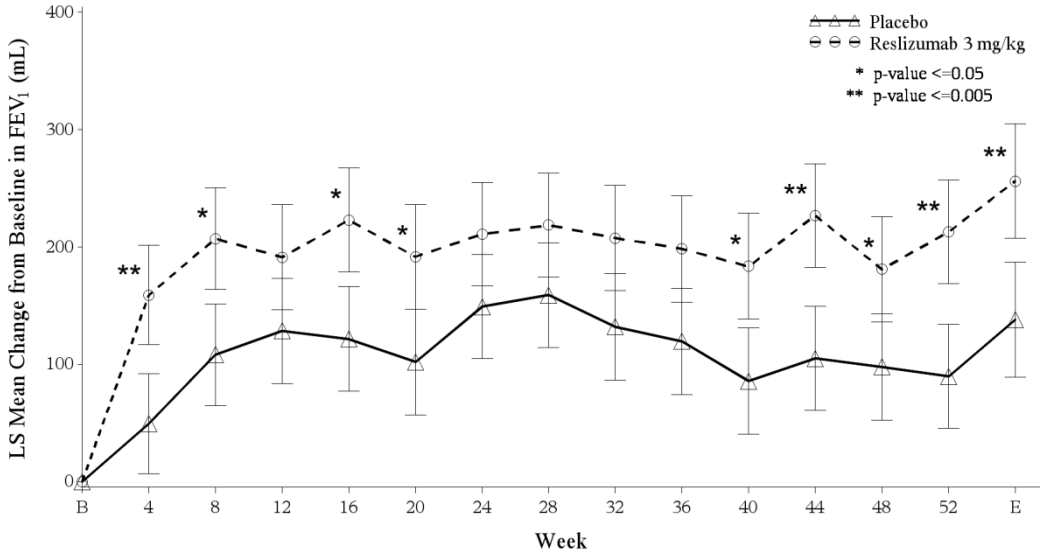
Figure 6 illustrates the mean change from baseline in FEV_1 to each visit. In both studies, statistically significant improvement (increase) was observed for both the change from baseline to week 16 and overall change over 16 weeks in the reslizumab group compared with placebo. Based on the hierarchical testing procedure, the other secondary endpoints were tested sequentially.

Figure 6. 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

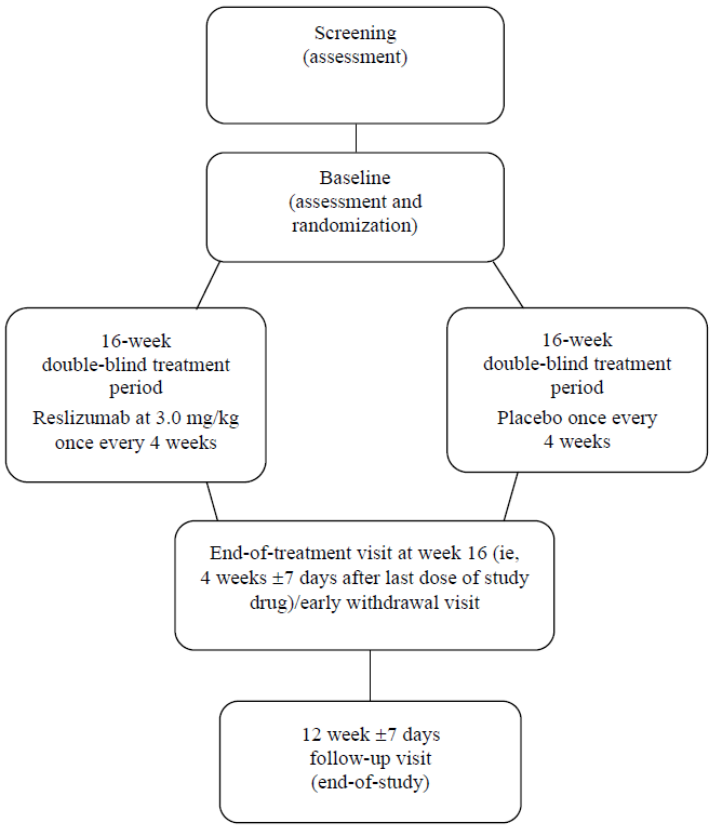
Study 3084 was titled "A 16-Week, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Reslizumab (3.0 mg/kg) Treatment in Patients With Moderate to Severe Asthma." The primary objective was to characterize the efficacy of reslizumab treatment compared with placebo 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 7. 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 monoclonoal antibody, methotrexate, cyclosporin, interferon-α, or anti-tumor necrosis factor monoclonoal 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 monoclonoal antibody, methotrexate, cyclosporin, and interferon-α - 6 months
- Anti-TNF monoclonoal antibody - 6 months
- All other biologic therapies including omalizumab (XOLAIR®) - 6 months
- Anti-IL-5 monoclonoal 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 20 mM sodium acetate, 7% sucrose, pH 5.5 buffer.

Placebo: Placebo was provided as a sterile solution for infusion presented as 10 mL per vial, formulated in 20 mM sodium acetate, 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

As the primary analysis for the primary endpoint, a linear regression model was used 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

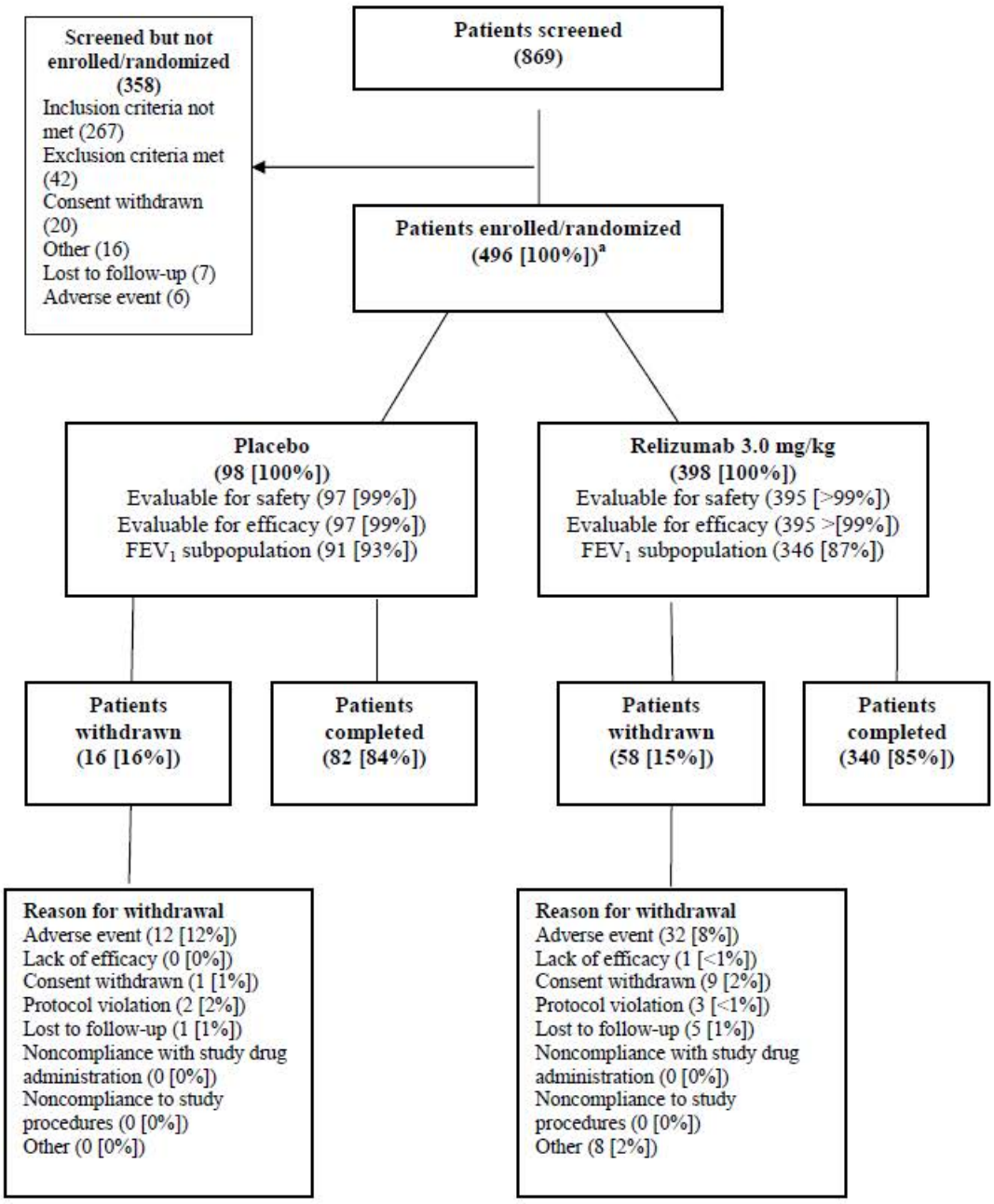
Compliance with Good Clinical Practices

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 8. 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.

This failure to show an interaction between lung function and blood eosinophil counts will be an important discussion point for the committee to consider when thinking about the role of blood eosinophil counts in making treatment decisions about reslizumab.

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

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. However, protocol violations occurred for nearly a quarter of participants 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)

	Overall population		Baseline blood eosinophils (<400 cells/µL)		Baseline blood eosinophils (≥400 cells/µL)	
Variable (unit) Statistic	**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

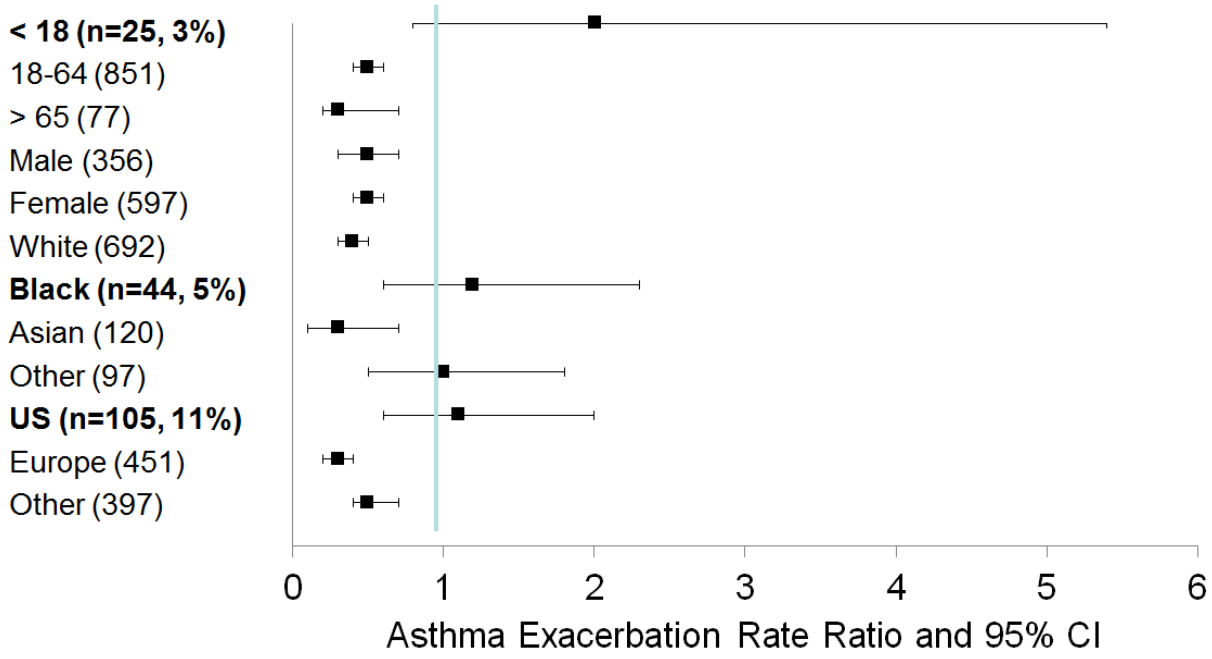
	3081	3082	3083
FEV_1 Δ to Week 16	0.165 (0.037, 0.292) 0.0118	0.072 (0.001, 0.144) 0.0483	0.101 (0.023, 0.179) 0.0109
FEV_1 Δ over 16 weeks	Primary endpoint	0.137 (0.076, 0.198) <0.0001	0.093 (0.030, 0.155) 0.0037
AQLQ Δ to Week 16	0.358 (0.047, 0.670) 0.0241	0.238 (0.048, 0.428) 0.0143	0.209 (0.025, 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**

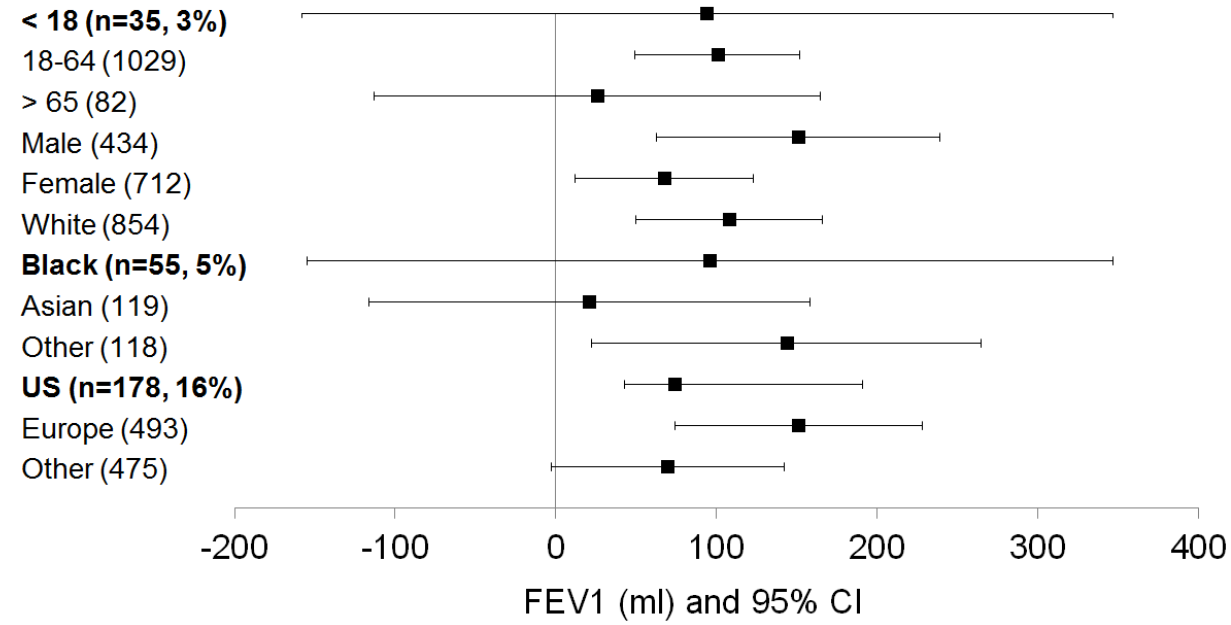
Evidence of efficacy was less robust for some subgroups with low enrollment. A paradoxical increase in asthma exacerbation rates was observed for adolescent, African American, and U.S. patients, though evidence for improvement in lung function generally was supportive.

Figure 9. 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. 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. Had it been studied further in phase 3, this lower dose could have demonstrated a more favorable risk-benefit profile.

7.2. Additional Efficacy Considerations

7.2.1. Risk-Benefit Considerations in Subgroups

A paradoxical increased risk of exacerbation was observed in three subgroups: patients 12 to 17 years of age, black patients, and U.S. patients. *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, it warrants further discussion whether the risk-benefit evaluation is favorable in these subgroups. Evidence of efficacy is derived largely from participants at foreign study sites. Despite the paradoxical findings observed for U.S. patients, we ask the committee to discuss whether it is reasonable to extrapolate this efficacy to U.S. patients.

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 0.16 L 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 0.38, 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 31 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, though evidence for improvement in lung function generally was supportive. 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.

Due to errors in study conduct, more patients in the placebo arm of the safety population were taking oral corticosteroids at baseline. 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.

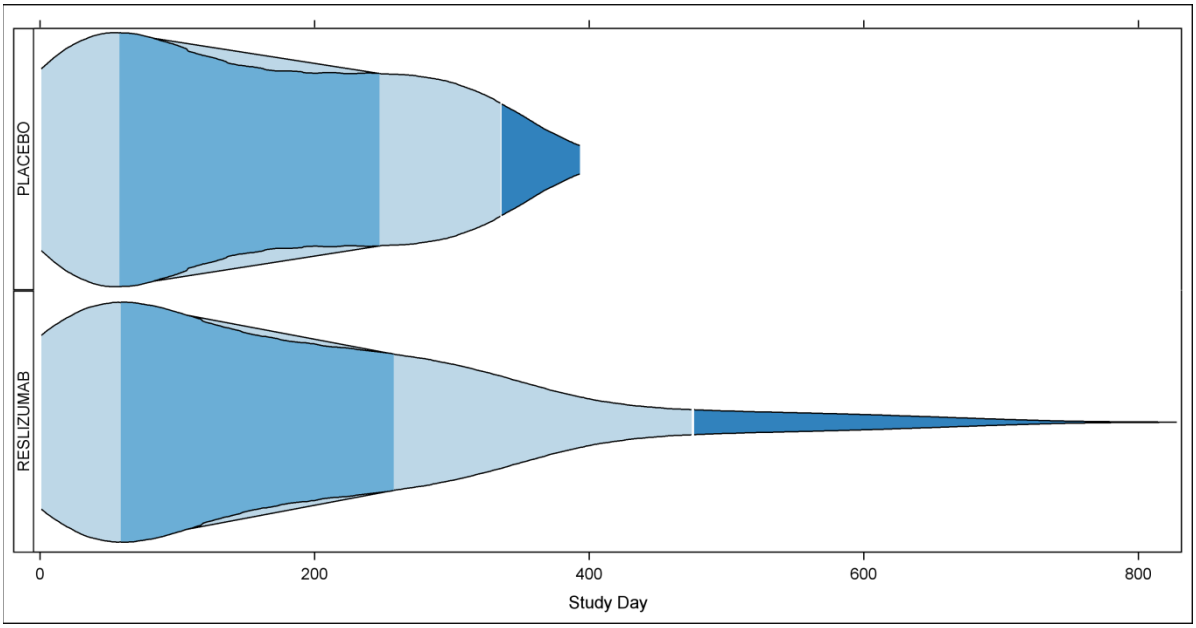
Reviewer Comment: The longer average duration of treatment in the placebo arm in controlled trials could obscure detection of a safety signal for which duration is important, such as malignancy.

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 ± 131
Duration of treatment n (%)		
≥ 6 months	436 (60)	440 (39)
≥ 12 months	388 (53)	389 (34)

Source: Integrated Summary of Safety table 11

Figure 10. 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. Whether this introduces questions into the quality of the safety database is an important issue for the committee's discussion.

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 was 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 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.

Several deficiencies were noted in the integrated summary of safety. The broad anaphylaxis standard MedDRA query incorrectly excluded narrow terms, thus underreporting the frequency of this clinically significant adverse event. The Applicant was asked to correct this issue, and their response is outlined below. Two study sites were discontinued for GCP violations, but adverse event data from fifteen participants at these sites was improperly excluded from the safety database, including cases of acute urticaria and a possible case of rhabdomyolysis. Latency times to malignancy were calculated incorrectly until corrected in a subsequent communication. Twenty-five adverse events from patients treated with reslizumab in study 3085 were not coded into MedDRA terms, and thus were not reported in safety analyses. These included a case of respiratory failure, ten asthma exacerbations, and a case of tendonitis.

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

[1] 21 CFR 312.32(a) and 314.80

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 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.

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)	2 (<1)
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, though the data supporting these analyses are problematic. 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. It was not possible to verify this point with independent analysis of the submitted data. Even after reviewing the submitted syntax , it is unclear to this reviewer how the summary safety tables were generated from these datasets.

8.4.4. Significant Adverse Events

Reslizumab was associated with two significant adverse events, anaphylaxis and a muscle safety signal. Both were the subject of ongoing discussion between the Agency and the Applicant, with late breaking responses to information requests undergoing further evaluation at the time of this review. In response to an Agency request, Teva agreed to perform independent adjudication of all anaphylaxis cases identified by a standard MedDRA query that occurred within 24 hours of study drug administration. The results of this analysis are expected in mid-November, after release of this document to committee members.

Anaphylaxis

A higher rate of anaphylaxis was observed in patients treated with reslizumab, compared to those treated with placebo. A narrow standard query of the Medical Dictionary for Regulatory Activities was performed for anaphylaxis. Search terms included anaphylactic reaction/shock/transfusion reaction, anaphylactoid reaction/shock, circulatory collapse, first use syndrome, Kounis syndrome, shock, and type I hypersensitivity. Of the 1131 patients in the placebo controlled asthma trials (Studies 3081, 3082, 3083, 3084, and Res-5-0010), there were

5 cases of anaphylaxis in the reslizumab group, 3 of which appear related to reslizumab, and no cases of anaphylaxis in the placebo group.

- The first, patient 370307, 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, and flushing. 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, patient 370312, 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, patient 831404, 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, flushing, and saturation of 89%). 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.

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, patient 064203, 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, patient 904405, 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 "All 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, both from study Res-5-0004:

- Patient 10404 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.
- Patient 12716 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:

- Patient 104-12 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.

- Patient 10602 was 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.
- Patient 12124 was 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.

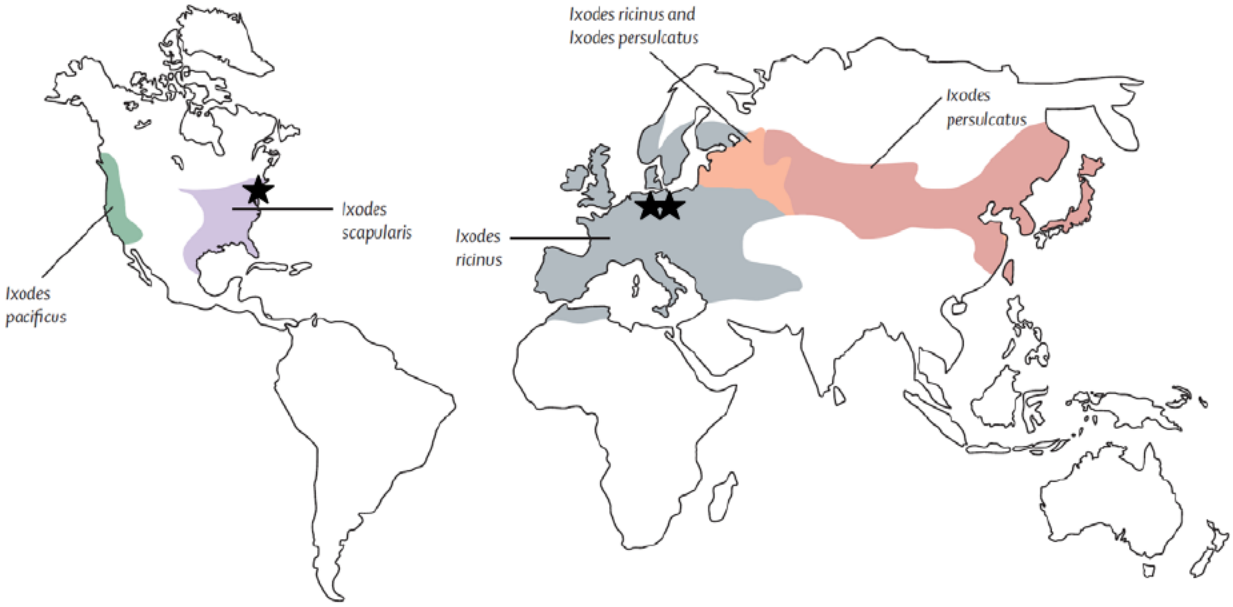
- Patient 13001 was an 11-year-old boy who had three events of anaphylactic reaction on day 682, day 756, and day 896 of the study (ranging from 13 to 16 days after administration of reslizumab at 1.0 mg/kg). Each event was described as due to nuts. After each occurrence, reslizumab administration was continued with no dose change. The patient had known allergies to eggs, many other foods, and nuts.
- Patient 119-08 was 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.
- Subject 104-15 ((b) (6)) was a 16 year-old Caucasian male with known peanut allergy who 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, adding to the evidence that the assay likely may be too insensitive to be clinically useful (see section 8.4.10 Immunogenicity).

The higher rate of anaphylaxis observed in the reslizumab arm of the asthma program may be due to a contaminant 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. 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).

All 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 (370307 and 370312), in the distribution of the *Ixodes ricinus* tick, and one in New York (831404), in the distribution of the *Ixodes scapularis* tick.

Figure 11. Distribution of reslizumab anaphylaxis cases relative to tick species



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

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.

CPK elevations occurred more often in the reslizumab arm for moderate, severe, and potentially life-threatening categories of severity. 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%).

The reslizumab treatment group had three cases for which additional detail was provided. One young male patient (828411) had an adverse event of rhabdomyolysis with CPK elevation thought secondary to recent intense weightlifting. A second patient (630319) had an adverse event of toxic myocardiopathy. A third patient from Study 3084 (No. 864405) was a 35-year old white male who 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. This adverse event was noted only in a footnote in the report for study 3084; his data were improperly excluded from safety analyses, including the table above, as he was one of the 15 patients recruited at study sites terminated for GCP violations. All three patients continued on reslizumab treatment.

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 other forms of muscle pain were more common in the reslizumab arm.

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

		Placebo N=730		All Reslizumab N=1131	
High Level Term	**Dictionary-Derived Term**	**N**	**(%)**	**N**	**(%)**
Musculoskeletal and connective tissue pain and discomfort	Back pain	8	1.1%	20	1.8%
	Pain in extremity	3	0.4%	8	0.7%
	Musculoskeletal chest pain	2	0.3%	7	0.6%
	Neck pain	.	.	4	0.4%
	Musculoskeletal pain	2	0.3%	2	0.2%
Muscle pains	Myalgia	2	0.3%	5	0.4%
	Fibromyalgia	1	0.1%	1	0.1%
Muscle related signs and symptoms NEC	Muscle spasms	.	.	5	0.4%
	Muscle swelling	.	.	1	0.1%
	Muscle fatigue	.	.	1	0.1%
Myopathies	Rhabdomyolysis	.	.	1	0.1%

Source: ISS DDAE.XPT ISS ADSL.XPT

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.

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).

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 that is important for the committee's consideration. 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 numerous limitations in study conduct relevant for this safety signal. Deficiencies in study conduct tend to bias safety analyses toward failing to detect a signal when one is in fact present. 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, reasonable baseline chemistry values were an inclusion criterion for all of the controlled safety studies. Violations of inclusion criteria were a major factor contributing to the exceptionally high rate of protocol violations observed in the reslizumab program. Better trial conduct could have mitigated a baseline imbalance in CPK values. 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 for the committee to consider these limitations in interpreting the available data about 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 46 and 47
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.

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 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.

For healthy volunteer studies C38072/1102 and C38072/1107, serum samples were analyzed for anti-drug 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 insensitive assay was low, with approximately 7% of patients developing at least one positive anti-drug 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 antibody response with anaphylaxis or hypersensitivity reactions to reslizumab.

Reviewer Comment: These findings should be interpreted with caution given the insensitivity of the assay. Please see Dr. Joao Pedras-Vasconcelos' review for details.

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 731 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**

Teva does not propose a pregnancy registry. 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, but no major differences in safety are observed when adverse events are evaluated. Given the potential muscle safety signals and anaphylaxis, along with the limited efficacy findings, whether reslizumab should be approved in adolescents is a key issue for the committee's discussion.

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. Whether the potential risk-benefit assessment supports approval in this population will be an important issue for the committee's discussion. 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.

9 Appendices

9.1. References

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Clinical Pharmacology Briefing Document for the Pulmonary—Allergy Drugs Advisory Committee Meeting

December 9, 2015

Cinqair (reslizumab for intravenous infusion) BLA 761033

Dose: 3 mg/kg intravenous infusion once every 4 weeks

Proposed 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"

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2.2 Clinical Pharmacology

2.2.1 Background

Cinqair (reslizumab) is a humanized monoclonal IgG4 anti-IL5 antibody. IL-5 is a cytokine important in the growth, differentiation, activation and survival of eosinophils. Reslizumab is proposed 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 is supplied as 10 mL 10 mg/mL solution in a single-use vial for IV infusion only. Reslizumab should be diluted with 50 mL saline prior to IV infusion and the infusion time is 20 – 50 minute. The proposed dosing regimen is 3 mg/kg once every 4 weeks.

2.2.2 Biopharmaceutics

Throughout the clinical development program, the drug product formulation of reslizumab (10 mg/mL reslizumab in 20mM sodium acetate, 7% sucrose, pH 5.5 buffer) has remained the same, and various Type 1 glass vials have been used as the primary container, ranging in size from 2 mL to 10 mL.

2.2.3 Pharmacokinetics

Pharmacokinetics in Healthy Subjects

Reslizumab PK in healthy subjects was evaluated in Study 1102. Four parallel groups of healthy subjects received five Q4w IV doses of 0.3, 1.0, 2.0, or 3.0 mg/kg reslizumab. 100 subjects completed the study. Following the single dose, peak concentrations were observed in the majority of profiles at the end of infusion (50 minutes). After that, reslizumab plasma concentrations declined in a bi-exponential manner. The mean observed accumulation ratio ranged from 1.5 to 1.9. The mean terminal-phase elimination half-life ranged from 25 to 32 days. The exposures were comparable between Japanese and non-Japanese. There was no consistent or notable trend toward a deviation from proportionality following either a single dose or multiple doses.

Pharmacokinetics in Patients

Reslizumab serum concentrations in asthma patients from five studies (350, 290, 10, 3081, and 3082) were pooled with other studies in a population PK analysis. The PK parameters were comparable between healthy subjects and asthma patients.

Reslizumab clearance is approximately 7 mL/hour. The volume of distribution of reslizumab is approximately 5 L. The terminal elimination half-life of reslizumab is approximately 24 days.

Pharmacokinetics in Special Populations

The effect of sex, age, race, and body weight on the PK of reslizumab was assessed using the population approach.

Race, Gender, Age, and Weight
Race, ethnicity, age and gender did not significantly impact the PK of mepolizumab. Reslizumab clearance increases with body weight.

Immunogenicity

The same homogenous bridging ELISA assay was applied in all the Phase 3 studies for detecting anti-reslizumab antibody. Following 3 mg/kg reslizumab treatment, the rate of treatment-emergent anti-drug-antibody incidence (ADA) is 5.4%. Among treatment-emergent ADA positive patients, 43% was transient (only positive in one post-dose sample). The geometric mean titers of ADA was 1:7.6 (CV=121%). There is no apparent impact of ADA on reslizumab PK, efficacy, and safety. The Sponsor did not develop an assay to detect the neutralizing capacity of reslizumab ADA.

2.2.4 Pharmacodynamics and Drug Development

Study 290, initiated in 1997, was the only dose-ranging (0.3 mg/kg and 1 mg/kg) Phase 2 study that evaluated clinical efficacy upon two doses administered 12 weeks apart. Total 211 patients enrolled in the study. However, there were no statistical significant differences on FEV1 change from baseline between reslizumab treatment groups and placebo groups.

Study 10, initiated in 2008, was the only Phase 1/2 study that listed eosinophil count as an inclusion criterion. The enrolled asthma patients were required to have eosinophils in an induced sputum sample of no less than 3%. 106 patients were randomly assigned by a 1:1 ratio to 3.0 mg/kg reslizumab treatment group or placebo group for a 15-week q4w treatment. Approximately half of the patients had baseline blood eosinophil count ≥ 500 cells/μL. An exploratory analysis showed that FEV1 improvement from baseline was significantly higher in reslizumab treatment group than the placebo group in the ≥ 500 cells/μL population (0.25 L), but not in the < 500 cells/μL population (0.19 L) (Table 4.9). Therefore, blood eosinophil count ≥ 400 cells/ μL was selected as an inclusion criteria in all the subsequent Phase 3 trials.

Table 1 FEV1 Change from Baseline to the End-of-Therapy by Baseline Blood Eosinophil Counts[1]

	Baseline Eosinophil Counts < 500 cells/μL		**Baseline Eosinophil Counts < 500 cells/μL**	
	Placebo (N=25)	Reslizumab (N=24)	Placebo (N=27)	Reslizumab (N=28)
FEV1 Change from Baseline (L)[2]	-0.12 (0.067)	0.08 (0.073)	-0.05 (0.092)	0.27 (0.069)
Difference from Placebo (L)[3]		0.19 (-0.02, 0.39)		0.25 (0.01, 0.50)
p Value		0.0737		0.0419

[1] Asthma patients in this study were enrolled by inclusion criterion of ≥ 3% sputum eosinophil
[2] Mean (SE)
[3] Adjusted mean difference (95% CI)
Source: adapted from CSR 0010, page 83, Table 19

The change in sputum eosinophil counts from baseline to the end of therapy was statistically different comparing the reslizumab treatment group with the placebo group (Figure 1). The arithmetic mean of

sputum eosinophil counts reduced to 2-3% at Week 4 following the first dose reslizumab 3 mg/kg treatment and was maintained at that level till the end of therapy.

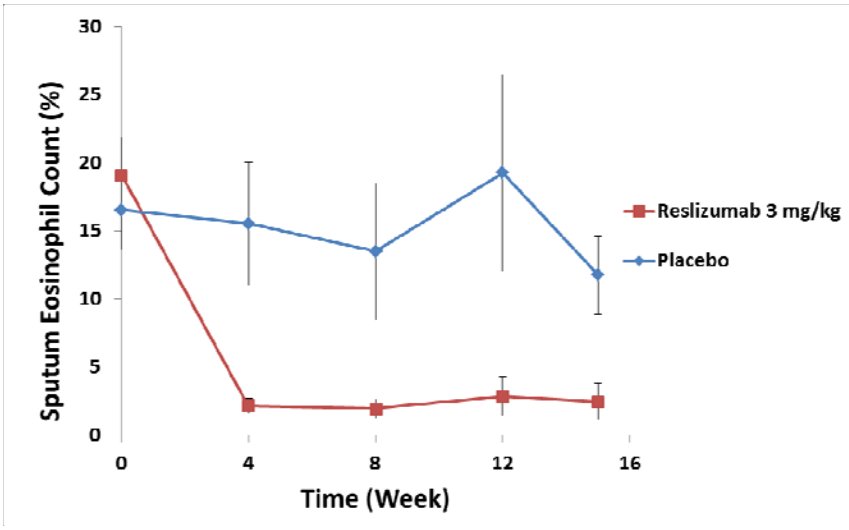

Figure 1 Arithmetic mean (SE) of sputum eosinophil counts (%) time profile following placebo (N=52) and 3 mg/kg reslizumab (N=53) treatment. Some subjects had more than one sputum eosinophil record per scheduled visit. (Source: reviewer's analysis)

Study 3081 was a dose-ranging (0.3 mg/kg and 3 mg/kg) Phase 3 study evaluating the dose effect on clinical efficacy endpoint FEV1 change from baseline. A clear trend of dose-dependent reduction of blood eosinophil count was demonstrated (Figure 2). It appeared that the reduction plateau phase was reached at Week 4 and Week 8 for 0.3 mg/kg, and 3 mg/kg treatment group, respectively. The absolute values of blood eosinophil counts reduced maximally to 517, 208, and 48 cells/μL (or reduced by 14%, 68%, and 92%) for placebo, 0.3 mg/kg, and 3 mg/kg treatment group, respectively.

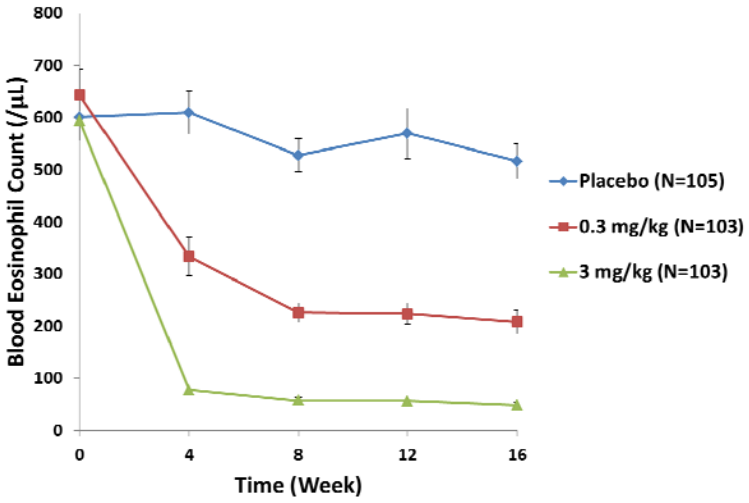

Figure 2 Arithmetic mean (±SE) of absolute blood eosinophil counts-time profile in different groups: placebo (blue, N=105), 0.3 mg/kg reslizumab (brown, N=103), and 3 mg/kg reslizumab (green, N=103). (Source: adapted from CSR 3081, page 351 - 355, Summary 15.24)

A pooled data (Studies 350, 290, 10, 3081 and 3082) was used for an exposure-response analysis for blood eosinophil count. The IC_{50} and IC_{90} values of reslizumab concentration that are required for 50% and 90% reduction of blood eosinophils were estimated as 0.77 and 6.96 µg/mL, respectively. For comparison, the estimated reslizumab average concentration at steady state ($C_{av,ss}$) values following 0.3 mg/kg and 3mg/kg reslizumab treatment was 4.8 and 44.2 µg/mL, respectively.

Exposure-response relationship was established between FEV1 improvement from baseline and reslizumab average concentration at steady state ($C_{av,ss}$) . A time-dependent E_{max} model estimated an approximately 70 mL of more FEV1 improvement at Week 16 from 0.3 mg/kg to 3 mg/kg reslizumab treatment. There is no apparent trend for change in the rate of clinical asthma exacerbation with reslizumab $C_{av,ss}$. There is no significant trend of increase of muscle disorder adverse events with reslizumab $C_{av,ss}$. There is no apparent dose-response trend for serum creatine phosphokinase (CPK) concentration.

Product and Immunogenicity Briefing Document for the

Pulmonary—Allergy Drugs Advisory Committee Meeting

December 9, 2015

Cinqair® (reslizumab for injection)

BLA 761033

Reviewers:

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Product Information for Reslizumab:

Cinqair® (reslizumab) is a humanized IgG4κ antibody that binds to human interleukin-5 (IL-5). IL-5 plays an important role in the differentiation, maturation, recruitment and activation of human eosinophils. The mechanism of action for reslizumab includes its specific binding to IL-5, thereby preventing IL-5 binding to its cell-surface receptor on target cells. The exact epitope recognized by reslizumab on IL-5 has not been revealed in the submission. IL-5 receptor is primarily found on the surface of cells involved in the etiology of asthma such as eosinophils, basophils, mast cells, and airway smooth muscle cells. Reslizumab is produced by recombinant DNA technology in murine myeloma Non-Secreting 0 (NS0) cells and is purified from the culture supernatant. Reslizumab is a glycoprotein with an approximate a molecular weight of 147 kDa. Cinqair® (reslizumab) injection is supplied as a sterile, single-use, preservative-free solution for intravenous infusion. Cinqair® (reslizumab) is supplied as 100 mg in a 10 mL glass vial. Each single-use vial contains 10 mg/mL reslizumab in an aqueous solution with a pH of 5.5 containing 2.45 mg/mL sodium acetate trihydrate, 0.12 mg/mL glacial acetic acid as buffering agents and 70 mg/mL Sucrose as a protein stabilizing agent.

Immunogenicity Information for Reslizumab

Although reslizumab is a humanized IgG4 monoclonal antibody, therapeutic administration of the product induces treatment-emergent anti-drug antibodies (ADA) in clinical studies. Subjects were classified as having a treatment-emergent ADA response if a sample tested positive in the assay at any of the postdose time points but not at the predose time point, or postdose ADA titer increased 4-fold or greater from a positive baseline ADA sample. Immunogenicity rates were determined using validated screening, confirmatory, and titering assays. Data obtained from cohort 3 patients, which include patients enrolled in placebo controlled studies C38072/3081, 3082, 3083, and 3084 dosed with 3.0 mg/kg, showed that 53/983 patients (5.4%) were positive for treatment-emergent ADA with titers ranging from 1:1 to 1:106. Fifty one percent of these patients (27) had transient responses. Transient responses are those that are positive at only one time point. In the long-term, open-label cohort 4 study, C38072/3085, using the 3.0 mg/kg dose, 49/1014 (4.8%) patients developed ADA with titers ranging from 1:2 to 1:33. ADA were transient in 20 (41%) patients. The incidence of hypersensitivity reactions that occurred during infusion and subsequent administration site reactions in reslizumab treated patients (30%) is similar to that seen with placebo-treated patients (39%). The basis for such hypersensitivity reactions is not known, but the eosinophilic asthmatic study population as a whole appears to experience them at a fairly high rate. Overall, the reported rate of adverse events for phase 3 studies was similar between the ADA positive (65%) and ADA negative (67%) patients. Except for treatment-associated anaphylaxis, there appears to be no association between the presence of anti-drug antibodies and either loss of efficacy or increased levels of adverse events.

The sponsor reported five anaphylactic reactions in the asthma clinical program. Of these, three cases had a temporal link to infusion of 3mg/kg of reslizumab. These were observed in three ADA-negative female patients, two from study C38072/3083 and one from study 3082. Two of the patients had medical histories of hypersensitivity/anaphylaxis to multiple allergens, and the third had a history of drug sensitivities. Thus, these patients can be considered to have a predisposition to hypersensitivity reactions. While it is possible that the cohort of eosinophilic asthmatics as whole may be more predisposed to develop anaphylaxis, the sponsor reports no other drug-related anaphylaxis in either the long-term extension of the 3.0 mg/kg-dose or the overall reslizumab program. The validity of these data is currently uncertain as additional drug-related anaphylaxis events may have taken place, which were not appropriately documented.

Product-related factors in reslizumab may impact immunogenicity and affect the incidence of anaphylaxis. These factors include glycosylation, and residual nucleic acids and host cell proteins from the cell substrate used to manufacture reslizumab. The product is produced in the NS0 murine cell line, and this cell line is known to introduce the carbohydrate sequence galactose-alpha 1, 3-galactose (alpha-gal) into the carbohydrate side-chains of the monoclonal antibody during glycosylation. Glycoproteins with the alpha-gal carbohydrate sequence are commonly produced by most mammals but not by Old World monkeys, apes, and humans due to lack of expression of the enzyme ∝-1, 3-galactosyl transferase (∝-1, 3 GT) that is responsible for the addition of alpha-gal to glycoproteins[1]. As a result, alpha-gal containing glycoproteins are highly immunogenic in humans, with as much as 1% of natural antibodies in sera, primarily IgG and IgM, being specific for this carbohydrate[2]. This is in part due to exposure to gut flora which have the ability to add alpha-gal to their glycoprotein and glycolipid molecules, and in part through dietary exposure. While the majority of the human population has anti-alpha-gal IgG antibodies in their sera, a proportion of the population develops IgE antibodies specific for alpha-gal, and these antibodies are associated with allergies to meat products, and tick bites. IgE to alpha-gal has also been implicated in anaphylactic responses in colorectal cancer patients treated with cetuximab, an anti-epidermal growth factor receptor monoclonal antibody[3]. Cetuximab is produced in Sp2/0 murine hybridoma cells, which also glycosylate proteins with alpha-gal-

[1] B.A. Macher, U. Galili. The Galalpha1,3-Gal-beta1,4GlcNAc-R (alpha-Gal) epitope: a carbohydrate of unique evolution and clinical relevance Biochim. Biophys. Acta (2008), 1780:75–88

[2] U. Galili, F. Anaraki, A. Thall. C. Hill-Black, M. Radic, One percent of human circulating B lymphocytes are capable of producing the natural anti-Gal antibody, Blood (1993), 82:2485–2493.

[3] Commins SP, TA Platts-Mill. Delayed anaphylaxis to red meat in patients with IgE specific for galactose alpha-1,3-galactose (alpha-gal). Curr Allergy Asthma Rep. (2013), 13:72-7.

containing carbohydrates. The prevalence of hypersensitivity to cetuximab had a regional distribution strongest in southeastern United States and was associated with pre-existing IgE antibodies to alpha-gal. The three cases of reslizumab-associated anaphylaxis occurred in geographical areas where tick allergies are known to arise. It is yet unclear however whether the three patients that suffered treatment-related anaphylaxis have IgE antibodies to alpha-gal because the sponsor did not evaluate these patients for anti-alpha gal IgE antibodies. Although the patients tested negative for ADA in the screening assay, the available immunogenicity assays have a reported sensitivity of 22 ng/mL, which is too high for reliably detecting antigen specific serum IgE. Levels of antigen-specific IgE in sera are typically present in the low nanogram to high picogram per mL range[4]. Currently, the sponsor has not provided sufficient information to eliminate the possibility that the anaphylactic responses were triggered by pre-existing sensitivities to alpha-gal. In addition, mepolizumab, a recently approved humanized IgG1 produced in CHO cells, also specific for IL-5 and used to treat similar patient population of asthmatics had only one potential reported case of anaphylaxis. CHO cells are of Chinese hamster origin and are the primary production system for licensed therapeutic monoclonals. This suggests that in addition to factors intrinsic to the study population, product specific factors are likely playing a role in the reslizumab-associated anaphylactic events.

Besides product glycosylation, the residual levels of NS0 derived host cell proteins and nucleic acids may also enhance product immunogenicity by potentially acting as adjuvants, or by stimulating pre-existing cross-reactive IgE responses to mouse proteins resulting in anaphylaxis. An impact of host cell derived impurities in the immunogenicity of a biologic was shown for Omnitrope where high concentrations of host cell proteins were associated with increased immunogenicity rates[5]. Omnitrope is a recombinant human growth hormone commercialized in Europe and in the United States. Once additional purification steps were added to the manufacturing process to reduce the level of residual host cell impurities, the immunogenicity rates in subsequent clinical studies were reduced for this product.

The contribution of host cell-derived impurities to reslizumab anaphylaxis is unclear at this time. The residual host cell proteins and nucleic acids and alpha-gal levels measured by the sponsor in reslizumab clinical lots, are consistent for the lots used across the phase 3 studies. Residual host cell proteins and nucleic acids levels are within the range expected for products produced in

[4] CLSI. Design and Validation of Immunoassays for the Assessment of Human Allergenicity of New Biotherapeutic Drugs; Approved Guideline. CLSI document I/LA34-A. Wayne, PA: Clinical and Laboratory Standards Institute; 2011.

[5] Thakrar K., Pr. Bodalia, A. Grosso. Assessing the safety of Omnitrope in Europe. Brit Med J Clin Pharm (2010), 2: 298-301.

murine cell lines. Currently there are eight licensed monoclonal antibodies manufactured in NS0 cells and five monoclonals produced in Sp2/0, and all but one, which is not glycosylated, have a reported incidence of anaphylaxis. However, there are seven other approved monoclonal antibodies produced in CHO cells, which also have reported cases of anaphylaxis, albeit at lower incidence rates, despite CHO cells typically not expressing the ∝-1, 3 GT enzyme responsible for the addition of alpha-gal during glycosylation[6]. Thus monoclonal antibody-triggered anaphylaxis is not restricted to products produced in murine cell lines.

In summary, there are product-specific and patient-specific factors that could be contributing to the anaphylaxis adverse events observed in the phase 3 clinical studies in eosinophilic asthma patients. The sponsor did not adequately investigate the root causes of the anaphylactic events. Therefore, the product safety profile is not well understood at this time.

[6] Guan M., YP. Zhou, JL Sun, SC. Chen. Adverse events of Monoclonal Antibodies used for Cancer Therapy. Biomed Res Int. (2015) , 2015:428169