CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	March 02, 2016
From	Badrul A. Chowdhury, MD, PhD, Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	BLA 761033 Original #1 (ages 18 years and older) (b) (4)
Applicant	Teva Pharmaceuticals
Date of Submission	March 29, 2015
PDUFA Goal Date	March 29, 2016
Proprietary Name / **Non-Proprietary Name**	Cinqair/Reslizumab
Dosage Form(s) / Strength(s)	Single-use 10 mL vial providing 100 mg reslizumab (10 mg/mL), for intravenous infusion
Applicant Proposed Indication(s)/Population(s)	"Cinqair in indicated 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."
Action/Recommended Action for NME:	Approval for patients 18 years of age and older (b) (4)
Approved/Recommended Indication/Population(s) (if applicable)	"Cinqair is an interleukin-5 antagonist monoclonal antibody indicated for add-on maintenance treatment of patients with severe asthma aged 18 years and older, and with an eosinophilic phenotype."

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	**Kathleen M. Donohue, MD**
Statistical Review	**Lan Zeng, MS; Freda Cooner, PhD**
Pharmacology Toxicology Review	**Carol M. Galvis, PhD; Marcie Wood, PhD**
OPQ Review	**Ramesh Potla, Tracy Denison, Jao Pedras-Vasconcelos**
Microbiology Review	**Bo Chi, Lakshmi Narasimhan**
Clinical Pharmacology Review	**Yunzhao Ren, MD, PhD**
OPDP	**Mathew Falter**
OSI	**Anthony Orencia**
CDTL Review	**Banu A. Karimi-Shah, MD**
OSE/DEPI	**Efe Wworuke**
OSE/DMEPA	**Hina Mehta**
OSE/DRISK	**Jasminder Kumar**
Other	

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Asthma with eosinophilic phenotype is a serious condition associated with chronic morbidity, including frequent exacerbations. These patients often require hospital or emergency department care, and may require treatment with high dose systemic corticosteroids. Due to the undesired effects of systemic corticosteroids, the aim of treating these severe asthma patients is to utilize the lowest effective dose or avoid use of systemic corticosteroids, when possible. Alternate therapeutic options for these patients are limited.

Reslizumab is an anit-IL5 monoclonal antibody studied in patients with severe asthma who continue to experience exacerbations despite standard of care treatment optimized to asthma severity (i.e., high-dose inhaled corticosteroids plus an additional controller with or without continuous oral corticosteroid use), and eosinophilic phenotype (defined by Teva for the studies as blood eosinophil threshold levels ≥400 cells/μL at baseline). In this target population consistent benefit in asthma exacerbation and improvement in FEV_1 was shown in patients 18 years of age and older. The submitted data did not show consistent efficacy in patients 12 to 17 years of age. While dose-ranging was not as robust as it could have been in this development program, efficacy of the dose studied and proposed for marketing (3 mg/kg IV every 4 weeks) was demonstrated in patients 18 years of age and older. The submitted safety data did not raise any substantial safety concerns. The major safety finding of note was anaphylaxis, which could be managed particularly given that the product will be administered in health care facility because of IV dosing, and with close health care provider supervision because of the risk of anaphylaxis.

The benefit risk assessment favors approval of reslizumab in patients 18 years of age and older, given the serious nature of the disease, and as reslizumab may provide an alternative to those patients who do not tolerate the other drug in the class approved by the FDA (i.e. mepolizumab). However, given the efficacy and safety information available, and that the pediatric population is considered to be a vulnerable patient population, the benefit risk assessment does not support approval in patients 12 to 17 years of age at this time.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Severe asthma with an eosinophilic phenotype affects 3-5% of asthma patients. They have exacerbations that are treated with, and prevented by, systemic corticosteroid use.	Severe asthma with an eosinophilic phenotype is a serious condition with chronic morbidity.
Current Treatment Options	• Mepolizumab (Nucala®), another anti-IL-5 monoclonal antibody, • administered subcutaneously • Corticosteroids	Current treatment options for this condition are effective. Additions to the treatment armamentarium would provide another choice in this subgroup of patients with asthma.
Benefit	• For patients 18 years of age and older: Improvement in lung function (FEV1) and asthma exacerbation as add-on therapy to standard of care treatment (i.e., high-dose inhaled corticosteroids plus an additional controller with or without continuous oral corticosteroid use), and eosinophilic phenotype. • For patients 18 years of age and older: Improvements in Asthma Control Questionnaire (ACQ) and The Asthma Quality of Life Questionnaire (AQLQ) improvements, which provide other dimensions of benefit and at earlier timepoints. • For patients 12 to 17 years of age: Exacerbation change point estimate favored placebo over reslizumab, suggesting an increased risk of exacerbation.	For patients 18 years of age and older: The clinical trials conducted in support of reslizumab were adequate, well-controlled, and demonstrated statistically significant improvements in clinically meaningful efficacy measures. For patients 12 to 17 years of age: Subgroup analyses with small number of patients are difficult to interpret. However, the findings of efficacy are generally acceptable when point estimates show a favorable treatment effect in subgroups with small numbers. Therefore, findings in a negative direction cannot be discarded when the point estimates are unfavorable.
Risk	• Anaphylaxis was the major finding. • Other finding of note were malignancy, and transient increase in CPK suggesting potential for muscle toxicity	Anaphylaxis event were not collected using prespecified criteria, nevertheless, events of anaphylaxis were seen in the clinical program.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	• Anaphylaxis: Health care providers should be prepared to manage anaphylaxis, and patients should be closely observed for an appropriate period in a health care facility after reslizumab administration.	Anaphylaxis risk can be communicated to health care providers and patients through appropriate labeling.

2. Background

There are several drug classes available for use in patients with persistent asthma. These include inhaled corticosteroids (ICSs), inhaled long-acting beta-adrenergic agents (LABAs), leukotriene modifying drugs, methylxanthines, and omalizumab. ICSs are the most effective long-term therapy for all severities of persistent asthma, and are commonly used as the first drug when a maintenance treatment is necessary. When an adequate dose of ICS has not provided asthma control, a second drug, such as a LABA is often added, preferably for a limited time period 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.[1, 2] However, some patients are not controlled despite step-wise treatments, e.g., high dose ICS plus additional controller medications, such as a LABA. These patients often have asthma exacerbations requiring hospital or emergency department (ED) care, and may require treatment with high dose oral corticosteroid (OCS). An American Thoracic Society (ATS) and European Respiratory Society (ERS) Task Force report from 2014 called these patients as "severe asthma" defined as "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." [3] An ATS Workshop report from 2000 called patients with similar characteristics as "refractory asthma." [4] Regular or periodic use of oral corticosteroids (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 effect dose or avoid use of OCS when possible. Therapeutic options for alternates for these patients are limited. For patients with allergic asthma, Xolair (anti-IgE antibody) is an option. Teva developed reslizumab as an add-on treatment for a subgroup of patients with uncontrolled asthma with an eosinophilic phenotype (so called "eosinophilic asthma"). There

[1] 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

[2] Global Initiative for Asthma (GIINA): Global strategy for asthma management and prevention, Updated 2015. At: http://www.ginasthma.org/

[3] 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.

[4] Proceedings of the ATS Workshop on Refractory Asthma. 2000. Am J Respir Crit Care Med 2000; 162:2341-2351.

are several cytokines that affect eosinophils, IL-5 is the main cytokine involved in the regulation of blood and tissue eosinophils. Reslizumab targets IL-5. There is another antibody targeting IL-5 called mepolizumab that was approved on November 4, 2015, as an add-on treatment of patients with severe asthma with an eosinophilic phenotype (BLA 125526).

One challenge in review of this application is the use of the qualifier "eosinophilic" to describe a phenotype of asthma. Eosinophilic asthma is not described as a phenotype in US and global asthma treatment guidelines. The asthma literature has often used the term "eosinophilic" to describe an asthma phenotype, which has been variably defined with different cut-off numbers for eosinophil counts in blood, sputum, BAL fluid, and other markers such as exhaled nitric oxide. A consensus has not been developed in the scientific academic community to uniformly identify and define this phenotype in a clinically useful way.

In this BLA submission, Teva cites publications of studies conducted with reslizumab (Study P00290, Study Res-5-0010),[5, 6] to indicate that eosinophilic asthma can be characterized by sputum eosinophil count of ≥3%, and reslizumab is expected to benefit patients with asthma with sputum eosinophil count of ≥3%. 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.[7, 8] 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 blood eosinophil threshold of ≥400 cells/μL has scientific merits; however, this is not definitive. Results of Teva's studies with reslizumab (discussed in section 7 below) did provide some support for the blood eosinophil threshold of ≥400 cells/μL.

Regulatory interaction between the Agency and Teva:

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

[5] Green RH, Brightling CE, McKenna S, et al. Asthma exacerbations and sputum eosinophil counts: a randomized controlled trial. Lancet 2002; 360:1715-1721.
[6] Castro M, Mathur S, Hargreave F, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. Am J Respir Crit Care Med 2011; 184:1125-1132.
[7] 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.
[8] 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 key interactions were as follows: End-of-Phase 2 (EOP 2) 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 EOP 2 meeting the key discussion items were as follows: 1. Division raised concerns on 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 to study more than one dose of reslizumab 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 needs to 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 spectrum of eosinophil counts. 2. The importance of study 3084 (includes patients irrespective of eosinophil counts) along with studies 3081, 3082 and 3083 (includes patients with eosinophil count of ≥400 cells/μL) to support eosinophil threshold values for labeling. 3. Inadequate support of labeling clause [redacted] (b) (4) for the proposed indication. 4. The Division accepted the definition of asthma exacerbation proposed for the pivotal studies.

3. Product Quality

Reslizumab is a humanized IgG4κ monoclonal antibody that binds to human IL-5. Reslizumab has a molecular weight of approximately 147 kDa. Reslizumab is produced by recombinant DNA technology in murine myeloma NSO 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.

There are product related factors in reslizumab that may impact immunogenicity and anaphylaxis. These factors include glycosylation, and potential to the formation of half-antibodies. Reslizumab is produced in the NSO murine cell line, and this cell line is known to introduce the carbohydrate sequence galactose-alpha1, 3-galactose (alpha-gal) into the carbohydrate side-chains of the monoclonal antibody during the glycosylation process. 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 α-1, 3-galactosyl transferase (α-1, 3GT) that is responsible for the addition of alpha-

gal to glycoproteins.[9] As a result, alpha-gal containing glycoproteins are immunogenic in humans. (b) (4)

Reslizumab drug substance will be manufactured at (b) (4) The drug product will be manufactured at (b) (4) All manufacturing and testing facilities associated with this application have acceptable inspection status. An expiry period of 36 months is proposed and supported by submitted data for reslizumab drug substance and drug product.

4. Nonclinical Pharmacology/Toxicology

Teva submitted results from a full nonclinical program to the Agency. The nonclinical program for reslizumab included studies conducted in mice, rabbits, and monkeys, which were all considered pharmacologically relevant species based on data from in vivo eosinophilia models in sensitized animals. Reslizumab binds with similar affinity to human, monkey, and mouse IL-5 (KD = 24, 20, and 31 pM; respectively). In a 6-month toxicology study, CD-1 mice were treated with 2, 10, or 25 mg/kg reslizumab IV once every 28 days. There were no drug-related findings observed in this study. Eosinophil counts were generally lower in treated animals compared to the vehicle control. In a 6-month toxicology study, cynomolgus monkeys were treated with 1, 5, or 25 mg/kg reslizumab IV once every 28 days. No drug-related toxicity findings were observed in this study. A few animals in this study developed ADA. However, reslizumab exposure was confirmed in an adequate number of animals to assess the toxicity parameters. Reproductive and developmental toxicology studies were conducted in CD-1 mice (fertility, embryo-fetal development, and pre-natal/post-natal development) and New Zealand rabbits (embryo-fetal development). There were no drug-related effects on female or male fertility, teratogenicity, or pre-natal and post-natal development. A carcinogenicity study was conducted in mouse because mouse was identified as a relevant species for reslizumab. Teva conducted a 26-week carcinogenicity study using HRAS transgenic mice (which was confirmed to be a pharmacologically relevant mouse strain). In the 26-week study, mice received 100, 250, or 500 mg/kg reslizumab IV once every two weeks. No statistically significant neoplastic findings were observed in males or females.

[9] 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, 1780 (2008), pp. 75–88

5. Clinical Pharmacology

Teva submitted results from a comprehensive clinical pharmacology program that included studies to assess pharmacokinetics and pharmacodynamics.

The pharmacokinetics of reslizumab is consistent with other IgG1 monoclonal antibodies targeting soluble ligands. The pharmacokinetics is linear, dose-proportional, and time-dependent after IV administration. The terminal half-life of reslizumab is about 24 days, which supports the proposed dosing interval of once every 4 weeks. Reslizumab is degraded by widely distributed proteolytic enzymes, which are not restricted to hepatic tissues. Hepatic function does not therefore influence the elimination of reslizumab. Reslizumab has a molecular weight of approximately 147 kDa, precluding elimination by glomerular filtration. For these reason no specific hepatic or renal impairment studies were necessary. Drug-drug interaction potential for reslizumab is low considering its proteolytic elimination pathway and also because IL-5 does not effect hepatocyte function. The PK of reslizumab was not significantly impacted by race, ethnicity, age, or gender.

Reslizumab exerts its activity by binding to human IL-5, preventing IL-5 from binding to the alpha chain of IL-5 receptor complex expressed on the eosinophil cell surface and thus inhibiting signaling. Neutralization of IL-5 leads to reduction in the production rate and survival of eosinophils. Reslizumab treatment produces a dose-dependent reduction in blood eosinophil count.

6. Clinical Microbiology

Teva proposed acceptable testing regimen involving the bulk drug product and the product packaged in the commercial presentation.

7. Clinical/Statistical-Efficacy

Overview of the clinical program:

Some characteristics of the relevant clinical studies that form the basis of review and regulatory decision for this application are shown in Table 1; with studies listed chronologically by the month and year of study conduct. The Phase 2 study 5-0010 was conducted by Ception. Teva conducted all other studies listed in Table 1. The database cut-off date for the submission was September 1, 2014. Study 3085 was ongoing at that time. Selected characteristics of the patients enrolled in these studies are shown in Table 2. Pediatric patients had disease severity based on exacerbation history and eosinophil counts similar to the

overall patients, but pediatric patients had higher FEV_1 values and less severe obstructive pattern based on FEV_1/FVC ratio, compared to the overall patients (Table 2).

Patients enrolled in the Studies 3081 (lung function study), 3082 and 3083 (exacerbation studies) were required to have blood eosinophil count of ≥400 cells/μL. Teva's rationale for selection of this blood eosinophil count threshold is discussed in Section 2 above. Teva subsequently conducted Study 3084 (lung function study), which did not require patients to have any blood eosinophil count threshold, to test FEV_1 efficacy benefit 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 at PPD Global Labs at sites in Kentucky, Belgium, and Singapore, 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. Relevant controlled clinical studies with reslizumab in moderate and severe asthma

ID Year* *Study*	**Study Characteristics †** **- Patient age** **- Patient characteristics** **- Study design, objective** **- Study duration**	**Treatment groups ‡**	**N §**	**Efficacy Variables ¶**	**Regions and Countries //**
"Eosinophilic" Asthma – Phase 2					
5-0010 [04/08 to 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	Resli 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 (63% US)
"Eosinophilic" Asthma – Dose Ranging Bronchodilator (lung function) study – Phase 3					
3081 [02/11 to 12/13] *Study III*	- 12 to 75 yr - ICS required, LABA allowed (≈77% used) and OCS allowed, blood eosinophil ≥400 cells/μL at screening, no prior asthma exacerbation required - Parallel arm, DB - 16 weeks	Resli 0.3 mg/kg IV Resli 3 mg/kg IV Placebo	104 106 105	1^o: ΔFEV_1 baseline to over 16 weeks 2^o: ΔACQ and ΔASUI baseline to over 16 weeks, ΔAQLQ baseline to week 16	US, North America, South America, Europe, Asia (37% US)
"Eosinophilic" Asthma – Exacerbation study –Phase 3					
3082 [04/11 to 03/14] *Study I*	- 12 to 75 yr (mean 47 yr) - ICS required, LABA allowed (≈85% used) , blood eosinophil ≥400 cells/μL at screening, ≥1 asthma exacerbation requiring	Resli 3 mg/kg IV Placebo	245 244	1^o: Frequency of exacerbation ** 2^o: ΔACQ and ΔASUI baseline to over 16 weeks,	US, North America, South America, Europe, Asia, Others (15% US)

ID Year* *Study*	**Study Characteristics †** **- Patient age** **- Patient characteristics** **- Study design, objective** **- Study duration**	**Treatment groups ‡**	**N §**	**Efficacy Variables ¶**	**Regions and Countries //**
	systemic corticosteroid in past year, - Parallel arm, DB - 52 weeks			ΔAQLQ baseline to week 16	
3083 [03/11 to 04/14] *Study II*	- 12 to 75 yr (mean ≈46 yr) - ICS required, LABA allowed (≈82% used), blood eosinophil ≥400 cells/μL at screening, ≥1 asthma exacerbation requiring systemic corticosteroid in past year, - Parallel arm, DB - 52 weeks	Resli 3 mg/kg IV Placebo	232 232	1^{O}: Frequency of exacerbation ** 2^{O}: ΔACQ and ΔASUI baseline to over 16 weeks, ΔAQLQ baseline to week 16	US, North America, South America, Europe (7% US)
"Eosinophilic" Asthma – Open Label Extension from Studies 3081, 3082, and 3083 – Phase 3					
3085 [06/11 to current	- Same as 3082 and 3083	Resli 3 mg/kg IV	1008	1^{O}: Safety 2^{O}: Asthma control	
Moderate to Severe Asthma – Bronchodilator (lung function) study – Phase 3					
3084 [02/12 to 08/13] *Study IV*	- 18 to 65 yr (mean 45) - ICS required, LABA allowed (≈80% used), any blood eosinophil count (≈80% had count less than 400 cells/μL), no prior asthma exacerbation required - Parallel arm, DB - 16 weeks	Resli 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], as identified in the product label
† DB = double blind, DD = double dummy
‡ Resli = Reslizumab dosed 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 was analyzed using negative-binomial regression model.
// North America countries include Canada, Mexico; South America countries include Argentina, Brazil, Chile, Columbia; Europe includes Belgium, Czech Republic, Denmark, France, Germany, Greece, Hungary, Netherlands, Poland, Russia, Slovak Republic, Sweden; Asia include Israel, Malaysia, Philippines, Republic of Korea, Taiwan, Thailand; Others include Australia, New Zealand, South Africa
** 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.

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

	3081	3084	3082	3083
Asthma duration, mean in years	20.4	26.1	19.2	18.4
Pulmonary function test				
Pre-bronchodilator FEV_1, % predicted	70%	67%	64%	69%
Post-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				
Baseline mean blood eosinophil count in μL, Arth mean	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				
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%
Patients : Pediatrics (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 test				
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				
Baseline mean blood eosinophil count in μL, Arth mean	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				

Design and conduct of the studies:

Study 5-0010:
Study 5-0010 was conducted in patients with poorly controlled active eosinophilic asthma (defined as sputum eosinophils ≥3%). This study is not relevant other than providing some information for the selection of eosinophil threshold (discussed in Section 2 above), and will not be discussed further in this review.

Lung function study, Study 3081:

Study 3081 was conducted in patients with asthma taking medium- to high-dose ICS (≥440 μg of fluticasone or equivalent) with or without another controller. Patients were required to have blood eosinophil count of ≥400 cells/μL, inadequate asthma control based on an ACQ score of ≥1.5, and airway reversibility of ≥12% to SABA during screening.

Exacerbation Studies 3082 and 3083:

Studies 3082 and 3083 were conducted in patients similar to those enrolled in Study 3081, and had additional inclusion criterion of a requirement for ≥1 asthma exacerbation during the year before enrollment, and use of OCS (prednisone up to 10 mg per day or equivalent) was permitted during the studies.

Lung function study, Study 3084:

Study 3084 design and conduct was similar to Study 3081, with the difference that patients were not required to have any blood eosinophil count threshold. The intent of the study was to test FEV_1 efficacy benefit and blood eosinophil count interaction.

Efficacy findings and conclusions:

The submitted data from the clinical program are adequate to support efficacy of reslizumab at a dose of 3 mg/kg IV every 4 weeks for patients with asthma in a specified target population. Teva states that based on reslizumab's mechanism of action and the demonstrated reduction of blood eosinophils, it is reasonable to consider that reslizumab will be a therapeutic intervention in asthma patients with eosinophilic inflammation. Based on efficacy data acquired throughout their development program, Teva identified the following target population for reslizumab: (a) patients who continue to remain not well controlled and experience exacerbations despite standard of care treatment optimized to asthma severity with ICS (additional controller and OCS used by some patients); and, (b) an eosinophilic phenotype with defined blood eosinophil levels ≥400 cells/μL within 4 weeks of start of treatment. Teva also implies that patients who do not meet the target population criteria described above are unlikely to benefit from treatment with reslizumab.

Teva's proposed target population for reslizumab based on lack of asthma control and exacerbation history and eosinophil threshold are reasonable. The data that support these conclusions are reviewed later in this section.

Dose and dosing schedule:

The proposed dose of reslizumab 3 mg/kg IV every 4 weeks is supported by the submitted data, primarily by exploratory analysis of studies published in literature and discussion in section 2 above, and Teva's pivotal clinical program showing efficacy with the 3 mg/kg IV dose. This dose provided meaningful FEV_1 benefit and meaningful reduction of exacerbations (discussed further below in this section), and no overwhelming safety risk (discussed in Section 8 below). Despite the Division's suggestion to study more than one dose in all phase 3 studies, Teva decided on the single dose of 3 mg/kg, which ultimately was supported by the submitted data. Teva's decision on the 3 mg/kg dose was supported by the safety profile of the 3 mg/kg dose, and the expectation of higher eosinophil suppression with that dose. Study 3081 was the only study that investigated more than one dose of reslizumab, 0.3 mg/kg and 3 mg/kg IV. 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 0.127, 0.238, 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=0.159 L, p=0.0018) than for patients in the reslizumab 0.3 mg/kg treatment group (treatment difference=0.111 L, p=0.0283), both doses demonstrated efficacy with respect to lung function (See Figure 1). In addition to FEV_1, both reslizumab treatment groups demonstrated improvements in both ACQ and AQLQ with a numerically higher AQLQ response with the 3 mg/kg dose compared to the 0.3 mg/kg dose. The 4-week dosing interval is supported by the approximately 24-day half-life of mepolizumab, providing approximately two-fold drug accumulation at steady-state along with maintaining consistent effect.

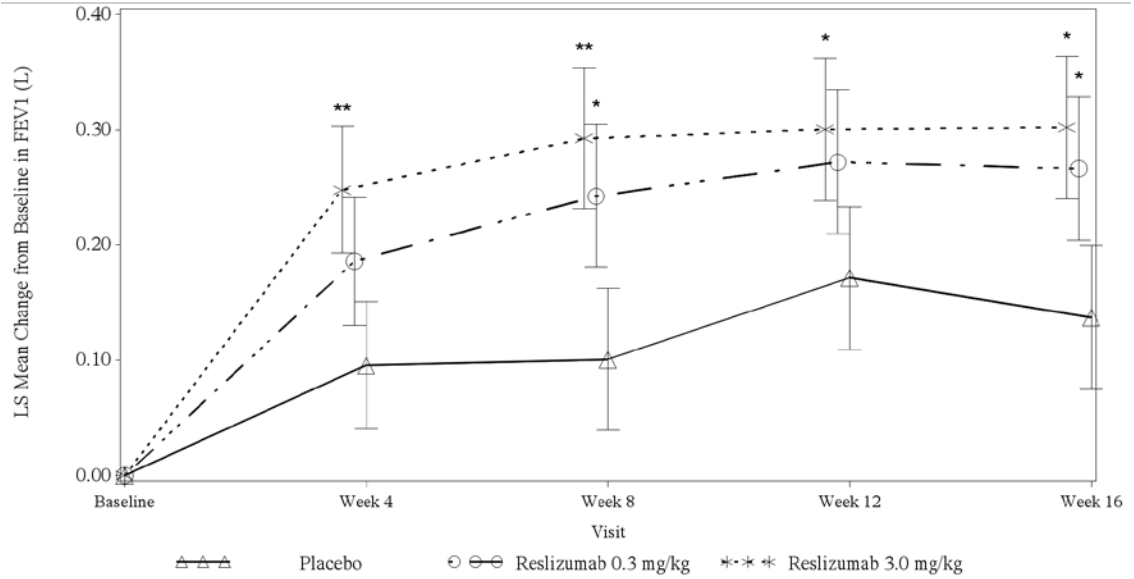

Figure 1. Mean change from baseline (standard error) in FEV_1 to each study visit and endpoint, Study 3081.

In study 3081, 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.

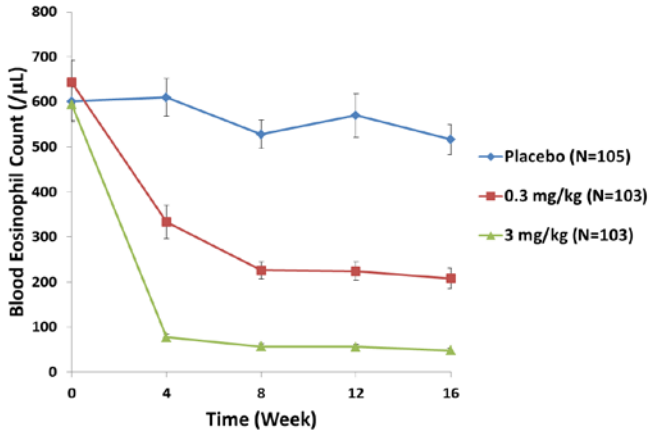

Figure 2. Arithmetic seam (standard error) of absolute blood eosinophil counts – time profile difference groups.

Bronchodilator (lung function) effects:

Spirometry was conducted in Studies 3081, 3082, 3083, and 3084 as an efficacy measure (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 3, and the time profile curves over study duration are shown from Study 3081 (Figure 1) and Study 3082 (Figure 3). Study 3081, which studied bronchodilation as the primary efficacy measure, showed statistically significant improvement with reslizumab over placebo (Table 3, Figure 1). Studies 3082 and 3083 (exacerbation studies) also showed statistically significant improvement with reslizumab over placebo (Table 3, Figure 3).

Table 3. Change in FEV_1 in 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	0.111 (0.012, 0.211)	0.125 (0.003, 0.253)	Not Available	Not Available
	Reslizumab 3 mg/kg IV	0.159 (0.060, 0.258)	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	0.075 (-0.008, 0.157)	0.066 (-0.032, 0.163)	Not Available	Not Available

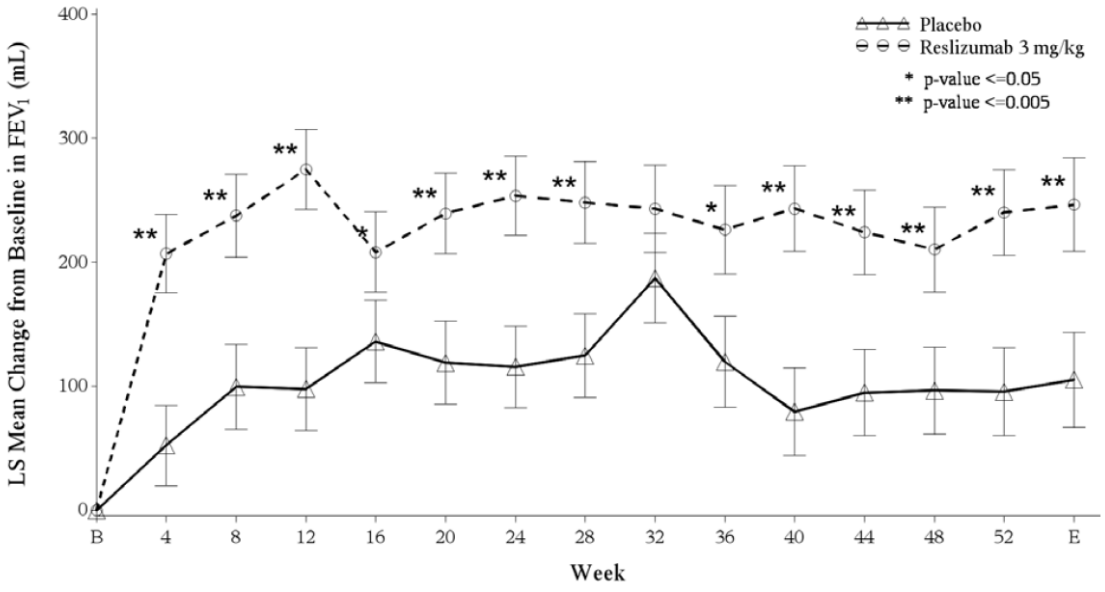

Figure 3. Mean change from baseline (± standard error) in FEV_1 to each visit and endpoint (Study 3082). Week 16 time point is controlled for multiplicity.

Study 3084, which studied bronchodilation as the primary efficacy measure, was designed to characterize the interaction between FEV_1 change from baseline and the baseline eosinophil counts. Patients were enrolled in this study unselected for blood eosinophil level. The primary efficacy analysis, a linear regression model, failed to show a significant overall interaction between baseline eosinophil counts and FEV_1 change at week 16 (Figure 4). 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 $\geq$ 400 cells/μL (Table 4, Figure 4). However, this relatively large treatment effect appeared to be 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).

Table 4. Comparison of FEV_1 in L as change from baseline between placebo group and reslizumab group at week 16 by various cutoffs of baseline eosinophil counts, Study 3084

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

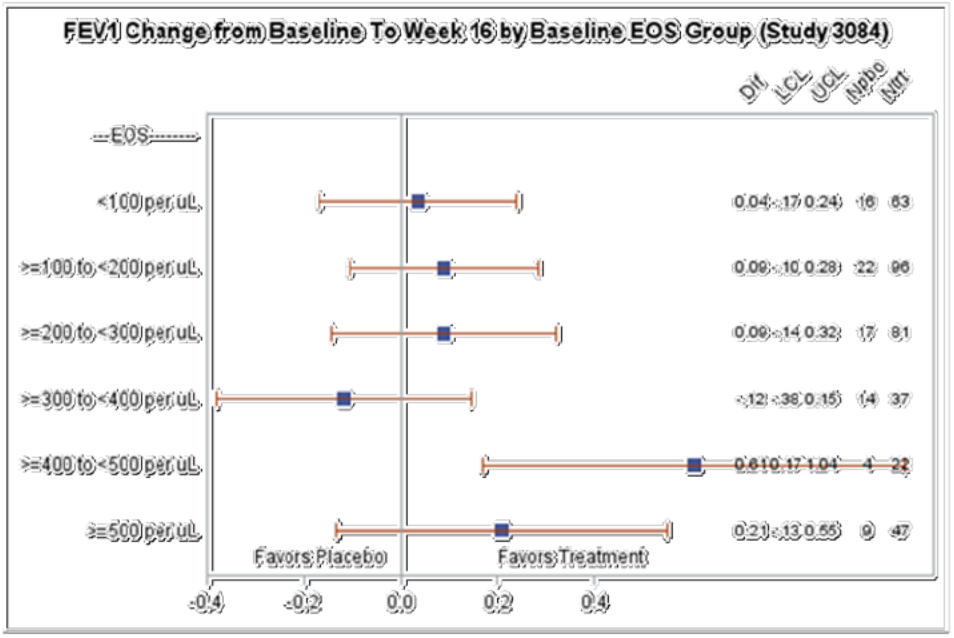

Figure 4. FEV1 change from baseline to week 16 by baseline blood eosinophil count, Study 3084. (Source: FDA biostatistical reviewer Lan Zeng)

Exacerbation effects:

The primary endpoint for Studies 3082 and 3083 was the frequency of 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 5). The majority of patients (>80%) who experienced at the least 1 exacerbation in the two studies were treated with systemic corticosteroids for 3 or more days and would generally be classified as moderate exacerbation. Reduction in moderate exacerbation rate was also seen in both exacerbation studies for reslizumab 3.0 mg/kg treatment groups compared to placebo (Table 5). Patients who had exacerbation defined by ER visit or hospitalization, generally classified as severe exacerbation, also had a numerical trend favoring reslizumab 3.0 mg/kg. While the rates of exacerbations leading to ER visit or hospitalization were low across treatment groups (approximate 1 in every 5 to 10 exacerbation required ER visit of hospitalization), the rate ration of reductions of these severe events were generally in the same range as for total and moderate exacerbation (Table 5). Kaplan-Meier analysis of time-to-first exacerbation also showed beneficial response for reslizumab-treated groups compared to placebo in both the studies (Figures 5 and 6).

Results of the exacerbation analyses were robust. Results of analyses using multiple imputations and from the tipping-point sensitivity analysis of the endpoint showed consistent beneficial effect for reslizumab.

Table 5. Asthma exacerbation frequency by treatment group over 52 weeks, Studies 3082 and 3083

Study	Treatment	n	Mean frequency of asthma exacerbation	Rate Ratio (95% CI), p-value [†]
Exacerbation, All *				
3082	Reslizumab 3 mg/kg IV	244	0.72	0.50 (0.37, 0.67), <0.0001
	Placebo	245	1.34	
3083	Reslizumab 3 mg/kg IV	232	0.46	0.41 (0.28, 0.59), <0.0001
	Placebo	232	1.01	
Exacerbation, Requiring oral corticosteroid for ≥ 3 days				
3082	Reslizumab 3 mg/kg IV	244	0.53	0.44 (0.32, 0.61), <0.0001
	Placebo	245	1.09	
3083	Reslizumab 3 mg/kg IV	232	0.34	0.40 (0.27, 0.61), <0.0001
	Placebo	232	0.75	
Exacerbation, Requiring systemic corticosteroid for ≥ 3 days				
3082	Reslizumab 3 mg/kg IV	244	0.55	0.45 (0.33, 0.62), <0.0001
	Placebo	245	1.12	
3083	Reslizumab 3 mg/kg IV	232	0.35	0.39 (0.26, 0.58), <0.0001
	Placebo	232	0.80	
Exacerbation, Requiring ER visit or hospitalization				
3082	Reslizumab 3 mg/kg IV	244	0.10	0.66 (0.32, 1.36), 0.2572
	Placebo	245	0.17	
3083	Reslizumab 3 mg/kg IV	232	0.04	0.69 (0.29, 1.64), 0.4020
	Placebo	232	0.06	

* 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

Study	Treatment	n	Mean frequency of asthma exacerbation	Rate Ratio (95% CI), p-value †
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. † Only p-value for the "Exacerbation, All" were appropriately adjusted for multiplicity. All the other p-values are nominal.				

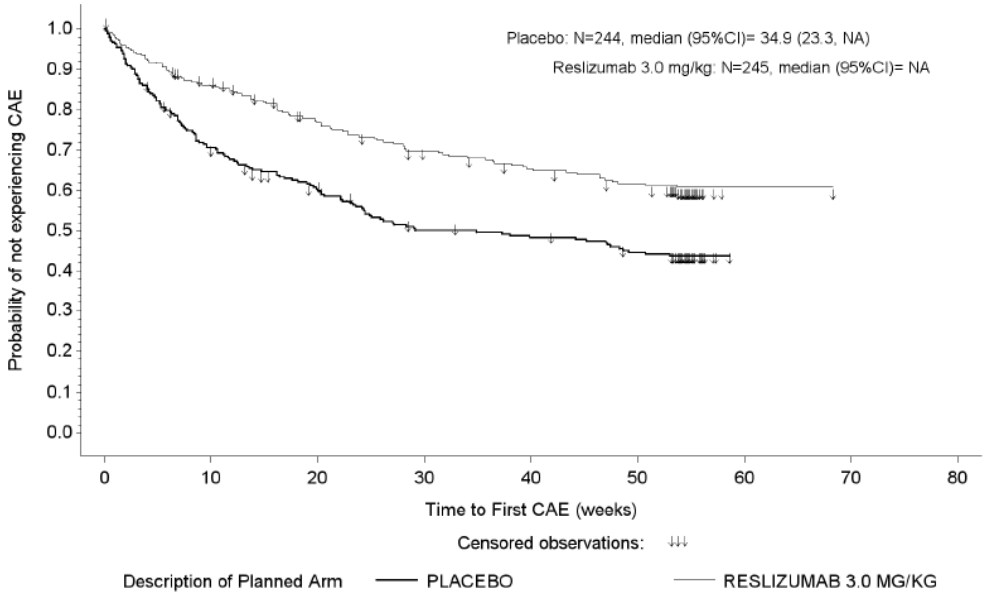

Figure 5. Kaplan-Meier cumulative incidence curve for time to first asthma exacerbation (all exacerbations), Study 3082.

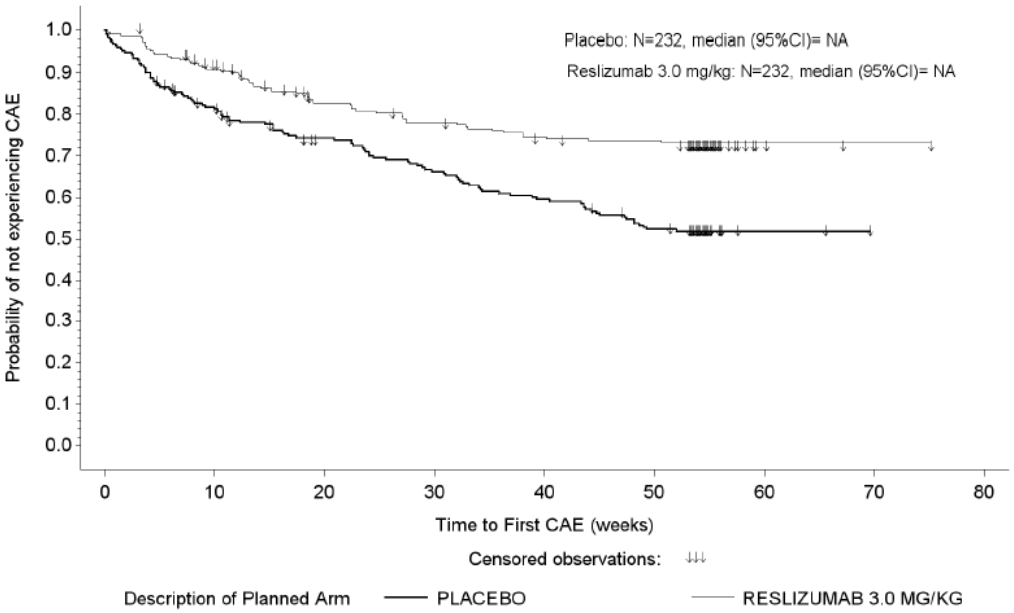

Figure 6. Kaplan-Meier cumulative incidence curve for time to first asthma exacerbation (all exacerbations), Study 3083.

The effect of blood eosinophil count at baseline was used for exploratory analyses by the FDA statistical team to further understand the relationship of exacerbation benefit and blood eosinophil count in the two exacerbation studies (Studies 3082 and 3083). Both studies were conducted in patients with blood eosinophil counts of 400 and higher, thus the number of patients at the lower spectrum of eosinophil counts was limited. On this exploratory analysis the exacerbation benefit of reslizumab did not appear to be related with increase in blood eosinophil count, with a nominal interaction p-value of 0.6761 (Figure 7).

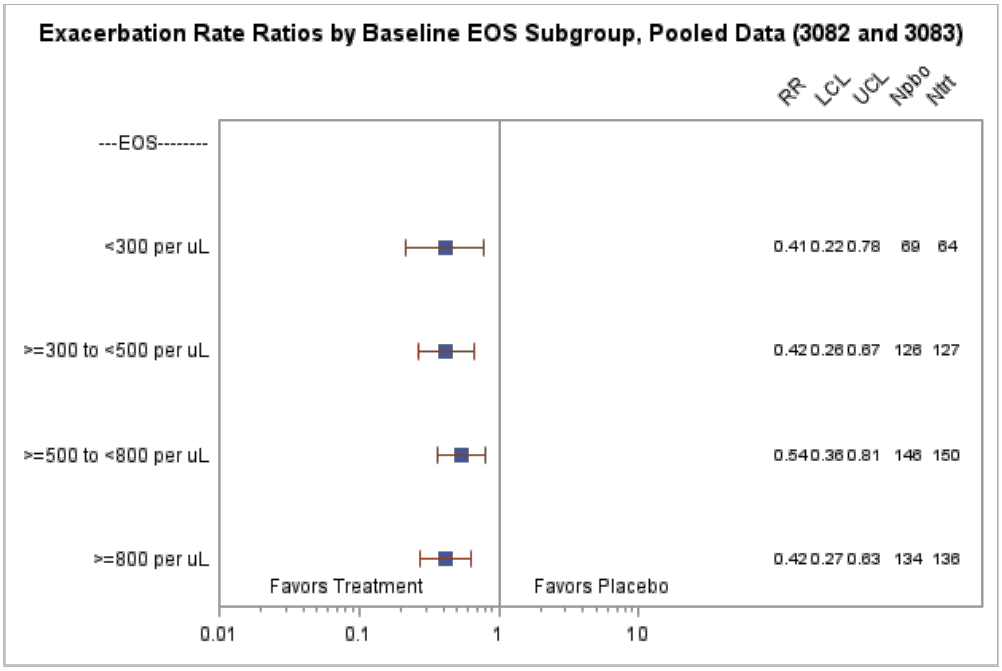

Figure 7. Exacerbation by baseline blood eosinophil count, Study 3082 and Study 3083. (Source: FDA biostatistical reviewer Dr. Lan Zeng)

Asthma Control Questionnaire (ACA), Asthma Quality of Life Questionnaire (AQLQ), and Asthma Symptom Utility Index (AUSI) effects:

ACQ and AQLQ are commonly used measurements tools for asthma with defined measurement properties,[10] and listed in common asthma treatment guidelines, [11, 12] and elsewhere.[13] ASUI is not as commonly used as ACQ and AQLQ.

[10] Measurement of Health-Related Quality of Life & Asthma Control. At: https://qoltech.co.uk/index htm
[11] 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
[12] Global Initiative for Asthma (GIINA): Global strategy for asthma management and prevention, Updated 2015. At: http://www.ginasthma.org/
[13] ATS website: http://www.thoracic.org/members/assemblies/assemblies/srn/questionaires/acq.php

ACQ is a questionnaire that measures the adequacy of asthma control and change in asthma control that occur 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. The shortened versions have good measurement qualities but not quite as good as those of the complete ACQ versions. A change in score of 0.5 on the 7-point scale is the smallest different that is considered clinically important, which is the minimal important difference for ACQ. An ACQ score ≥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 important difference for AQLQ.

ASUI measures the frequency and severity of four symptoms (cough, wheeze, dyspnea, and nighttime awakening) and medication side effects on two dimensions (frequency and severity). ASUI will not be further mentioned in this review because ASUI is not commonly used and has some overlapping measures with ACQ and AQLQ.

ACQ, AQLQ, and ASUI were assessed in Studies 3081, 3082, and 3083. Results of the exacerbation studies 3082 and 3083 are more relevant for these measures as these measures provide other dimensions of benefits and at earlier time points. Results are shown in Table 9 and Table 10.

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

	Resli 0.3	Resli 3	Placebo
Study 3081 (lung function study)			
At week 16 Resli 0.3 mg/kg vs Placebo, odds ratio (95% CI) Resli 3 mg/kg vs Placebo, odds ratio (95% CI)	61%	64%	58% 0.9 (0.5, 1.6) 0.8 (0.4, 1.5)
Study 3082 (exacerbation study)			
At week 16 Resli 3 mg/kg vs Placebo, odds ratio (95% CI)	-	69%	65% 0.9 (0.6, 1.3)
At week 52 Resli 3 mg/kg vs Placebo, odds ratio (95% CI)	-	77%	64% 0.5 (0.3, 0.8)
Study 3083 (exacerbation study)			
At week 16 Resli 3 mg/kg vs Placebo, odds ratio (95% CI)	-	70%	58% 0.6 (0.4, 0.9)
At week 52 Resli 3 mg/kg vs Placebo, odds ratio (95% CI)	-	81%	62% 0.4 (0.2, 0.6)
Resli = Reslizumab			

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

	Resli 0.3	Resli 3	Placebo
Study 3081 (lung function study)			
At week 16 Resli 0.3 mg/kg vs Placebo, odds ratio (95% CI) Resli 3 mg/kg vs Placebo, odds ratio (95% CI)	59%	64%	48% 0.6 (0.4, 1.1) 0.5 (0.3, 0.9)
Study 3082 (exacerbation study)			
At week 16 Resli 3 mg/kg vs Placebo, odds ratio (95% CI)	-	66%	58% 0.7 (0.5, 1.0)
At week 52 Resli 3 mg/kg vs Placebo, odds ratio (95% CI)	-	75%	65% 0.6 (0.4, 1.0)
Study 3083 (exacerbation study)			
At week 16 Resli 3 mg/kg vs Placebo, odds ratio (95% CI)		67%	55% 0.6 (0.4, 0.9)
At week 52 Resli 3 mg/kg vs Placebo, odds ratio (95% CI)		74%	64% 0.6 (0.4, 1.0)
Resli = Reslizumab			

Subgroup population analysis:

Efficacy data were analyzed based on various subgroups, such as gender, age, ethnicity, and geographical regions. In general, 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 8). It is likely that the paradoxical findings may be due to chance (driven by small sample size).

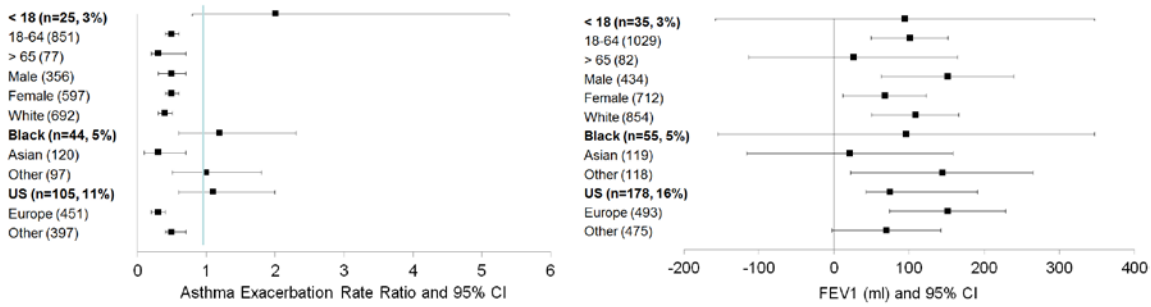

Figure 8. Efficacy analyses by subgroups, reslizumab vs placebo, exacerbation (left panel) and FEV_1 (right panel).

8. Safety

Safety database:

The safety assessment of reslizumab for asthma is based on the studies shown in Tables 1. The most robust safety data are from placebo-controlled studies 5-0010, 3081, 3082, 3083, and 3084. A total of 1870 patients were randomized in these studies of whom 1028 patients received reslizumab 3.0 mg/kg every 4 weeks for 612.54 patient-years. The safety database is reasonable.

Safety findings and conclusion:

The submitted data support the safety of reslizumab at a dose of 3 mg/kg IV for treatment of asthma.

Teva conducted a comprehensive safety analysis of the available data. Safety assessment in the clinical studies included evaluation of deaths, serious adverse events (SAEs[14]), common adverse events (AEs), vital signs, physical examination, clinical laboratory and hematology measures, and ECGs. Given the nature of the product, adverse events of interest were allergic reactions including anaphylaxis, local injection site reactions, musculoskeletal abnormalities, infections, malignancy, and immunogenicity.

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 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) occurred with comparable frequencies between mepolizumab 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 treatment related SAE was reported in 3 patients in the reslizumab 3 mg/kg treatment group. These were considered to be related to reslizumab by the investigators and by Teva.

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

[14] 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.

discontinuations. The most common event leading to discontinuation in all groups was asthma.

Common adverse events:

Common adverse events seen were typical of 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 was no adverse event for reslizumab that occurred with a frequency greater than 1% higher than that of corresponding placebo frequency.

Laboratory findings and ECGs:

No clinically meaningful effects on hematologic or chemistry parameters were noted in the clinical program, other than the expected decrease in blood eosinophil counts. Assessments of ECGs did not reveal a safety signal.

Adverse events of interest:

Allergic reactions including anaphylaxis are a risk with biologics. Unlike clinical programs for other biologic products, the reslizumab clinical program did not did not assess anaphylaxis events prospectively using accepted criteria, such as the commonly used and accepted criteria developed by NIAID and FAAN.[15] Post infusion timed recording of events of interest, including vital signs, were also not routinely recorded on the database. The anaphylaxis cases identified and reported were only those reported by investigators. On Agency request, Teva later convened a panel to identify cases of anaphylaxis by applying the NIAID and FAAN criteria, but the utility of this was limited because the patient level case report forms did not comprehensively record clinical events; at a minimum, even vital signs were not captured in the case reports. On investigator reporting, there were 5 cases of anaphylaxis in the asthma clinical pogrom. Of these, 3 cases had temporal link to infusion and were assessed as related to reslizumab. These cases occurred in ADA-negative patients. These reactions were treated at the study center and resolved with treatment. These 3 cases were considered to be related to reslizumab by the investigators and by Teva. The Teva convened panel identified 2 more cases of anaphylaxis, 1 in the reslizumab treatment arm and 1 in the placebo treatment arm. Given the limitations in assessment of anaphylaxis, it is possible that the reporting and identification of cases may be a best-case scenario with the possibility that some cases may have ben missed in the program. On the other hand, anaphylaxis are serious catastrophic event, thus it is possible that cases were not missed. Given that cases of anaphylaxis were seen in the program, and the reporting of anaphylaxis in labeling is more of a qualitative reporting, the assessment of anaphylaxis was deemed to be adequate.

[15] 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.

The presence of an anaphylaxis safety signal in the reslizumab program may be theoretically linked to a product attribute. Reslizumab is produced in a murine cell line NSO. Murine cell lines synthesize a blood group oligosaccharide, glactose-alpha-1,3-galactose, known as alpha-gal.[16] 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 serum samples from patients who later experienced anaphylaxis to cetuximab,[17] and alpha-gal was identified on cetuximab via mass spectrometry.[18] 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.[19] 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 for reslizumab is unclear.

CPK elevations occurred more often in the reslizumab arm for moderate, severe, and potentially life-threatening categories of severity. 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. One of the confounding factors in the CPK imbalance with treatment was the imbalance in the baseline values. In addition, the CPK elevations appeared to be transient and resolved with patients continuing to receive reslizumab. Nevertheless, the data is suggestive enough to warrant including this safety finding in the product label.

Infections, including serious infections and opportunistic infections, were reported with similar frequencies in reslizumab and placebo groups (41% in reslizumab treated group and 53% in

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

[17] 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.

[18] 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.

[19] 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.

placebo treatment group). The most commonly reported infection events were nasopharyngitis (14%), upper respiratory tract infection (12%), sinusitis (7%), and bronchitis (6%). There was no opportunistic infection reported. IL-5 blockage has a possible risk of impaired clearance of helminthic infection. Reslizumab clinical studies included regions where helminthic parasitic infections are prevalent, such as South and Central America, Africa, and Asia. There were no helminthic parasitic infections reported in the clinical program.

Malignancies were reported with a numerical imbalance with higher rate in reslizumab treatment group compared to placebo (6 cases in reslizumab 3 mg/kg treatment group with <1% event rate and 1.14 per 100 patient-years, 0 case in reslizumab 0.3 mg/kg treatment group, and 2 cases in placebo treatment group with <1% event rate and 0.77 per 100 patient-years). The observed malignancies were diverse and of common tissues types that would be expected in adult subjects. There were no malignancies in adolescents and children in the studies. Most of the malignancies were diagnosed within 6 months (range was 35 to 231 days) of starting treatment. Malignancy is a risk for reslizumab, but likely of a lower magnitude because IL-5 blocking is unlikely to induce general immunosuppression and alter host defense substantially. Preclinical studies, such as the bacterial mutagenicity study and chromosomal aberration in human peripheral blood lymphocytes, were negative for reslizumab.

Immunogenicity is a potential for all therapeutic proteins that can result in ADA response with risk of loss of efficacy and risk of allergic and immunologic events. Immunogenicity with reslizumab was not of major concern. Low titer, mostly transient ADA responses were seen in reslizumab treatment in the phase 3 studies. About 6% of reslizumab treated patients in the Phase 3 studies had ADA-positive events. There was no correlation between antibody titer (ADA-positive and ADA-negative) to change in blood eosinophil level, PK of reslizumab, efficacy, and no signals of allergic reactions or serum-sickness-like reactions associated with anti-reslizumab antibody status.

9. Advisory Committee Meeting

A meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) was held on December 9, 2015, to discuss this application. Issues for discussion on the efficacy side were the target patient population likely to benefit with reslizumab, adequacy of dose ranging data, adequacy of data in patients 12 to 17 years of age, and adequacy of data in various ethnic subgroups, particularly US population, and the role of blood eosinophil counts in determining target patient population. Issues for discussion on the safety side were the findings of anaphylaxis and the role of alpha gal in causing anaphylaxis, safety findings of muscle enzyme elevation, and potential impact of lack of dose-ranging data. The voting questions were broken down by age – adults 18 years of age and older, and pediatrics 12 to 17 years – because of the limited database in patients 12 to 17 years of age. In general the advisory committee members were of the opinion that the submitted data are adequate to support approval in adults, but not in patients 12 to 17 years of age (voting by committee members are shown in Table 10). The committee, although voting negatively for the adolescents, recognized that some adolescents will likely benefit from reslizumab and would prefer that they should have access to the product. The committee members were supportive of the narrow target

population identified by previous history of asthma exacerbation, and of the eosinophil phenotype. The committee members noted the lack of dose ranging data, but were not overly concerned because of demonstration of efficacy and lack of definite dose related safety findings. The major safety finding of note was anaphylaxis, which the committee members thought could be managed through labeling, particularly given that the product will be administered in health care facility because of IV dosing. The committee members were not particularly concerned with the presence of alpha-gal in the product, and an expert on alpha-gal anaphylaxis association (Dr. Platts-Mills) did not think that anaphylaxis was related to the presence of alpha-gal in this product. At the meeting, Teva presented data that showed that patients who had anaphylaxis did not have specific antibody to alpha-gal.

Table 8. AC voting on efficacy, safety, approvability, and large safety outcome trial

	Adults 18 years and older			**Pediatric 12 to 17 years**		
	Yes	No	Abstain	Yes	No	Abstain
Efficacy	13	1	0	0	14	0
Safety *	11	3	0	-	-	-
Approval	11	3	0	14	0	0
*Safety question was not broken down by age, the question applied to the whole age group						

10. Pediatrics

The agreed Pediatric Study Plan (PSP) for reslizumab is deferral for studies for asthma for patients <12 years of age. This PSP was agreed through iterative interactions between the Agency and Teva, and this agreed PSP was acceptable to the Pediatric Review Committee (PeRC) as discussed on a meeting on August 20, 2014.

The reslizumab development program included pediatric patients 12 to 17 years of age; however the number of patients was limited. When examined with respect to exacerbations (the primary endpoint to support approval), patients <18 years of age demonstrated a paradoxical increase in asthma exacerbation rates (point estimate favoring placebo). Interpretation of analyses in small subgroups is difficult. While the paradoxical and divergent findings could be due to chance and driven by small sample sizes, we don't usually question those point estimates that favor treatment, even when samples size is small; therefore it is difficult to discard the paradoxical result in pediatric patients. As discussed above, the Advisory Committee unanimously voted not to approve in patients 12 to 17 years of age (Section 9). Given the serious safety signals, the apparent lack of efficacy with this drug in patients 12 to 17 years of age, and the availability of other therapies, the benefit risk assessment does not support approval of reslizumab <18 years of age.

This finding of the BLA review was discussed with the PeRC on February 9, 2016. PeRC recommended granting a waiver for pediatric studies in children <12 years of age for the IV formulation, with the reasoning that reslizumab IV was not found to be effective in children 12 to 17 years of age. The pediatric assessment of 12 to 17 year olds is completed, and appropriate information for this age group will be included in the product label. (b) (4)

[redacted]

11. Other Relevant Regulatory Issues

Application Integrity Policy (AIP):

Review of the application did not raise concerns of any wrongful acts that raise significant questions regarding data reliability.

Exclusivity and patent issues of concern:

There are no exclusivity and patient issues of concerns with this application.

Office of Scientific Inspections (OSI) Audits:

OSI audited at the Sponsor level on request of the Division. Sponsor level inspection was done because recruitment in the clinical studies was widely distributed globally with each site enrolling a small number of patients. No irregularities were identified during the OSI audit that would impact data integrity.

Financial Disclosure:

The applicant submitted acceptable financial disclosure statements. Five investigators had significant financial interest in Teva. The number of subjects enrolled in the investigator sites was not large enough to alter the outcome of any study. Furthermore, the multi-center nature of the studies makes it unlikely that the financial interest could have influenced or biased the results of these studies.

Other Good Clinical Practice (GCP) issues:

There are no GCP issues with this application. All studies were conducted in accordance with accepted ethical standards.

Other regulatory issues – Regulatory Action:

The proposed regulatory action for this BLA is approval for patients 18 years of age and older, (b) (4)

(b) (4)

12. Labeling

Prescribing Information: The product label was reviewed by the Division, the Division of Medical Policy Programs (DMPP), DRISK, DMEPA, and by OPDP. Various changes to different sections of the label were done to reflect the data accurately and to better communicate the findings to healthcare providers. High-level summary of significant labeling elements are as follows:

- Indication and Usage: The product will be indication as add-on maintenance treatment of patients with severe asthma with an eosinophilic phenotype. This restricted patient groups is expected to cover approximately 3-5% of total asthma patients. The indicated age will be 18 years and olde (b) (4)
- Dosage and administration: Teva's proposed dose of 3 mg/kg IV every 4 weeks was deemed acceptable.
- Efficacy information: The main efficacy information that will be conveyed in the labeling will be the exacerbation data and the FEV_1 data. Also the measures of AQLQ and ACQ will be described. The blood eosinophil count threshold levels (≥400 cells/μL at baseline) will be mentioned in the Clinical Trials section of labeling.
- Safety information: There will be a boxed warning for the safety fining of anaphylaxis. Opportunistic information will be included as a warning because of the potential of

immunosuppression with reslizumab, and opportunistic infection was seen with another member of the class.

- Proprietary name: The proprietary name Cinqair was reviewed by DMEPA and found to be acceptable.

Patient labeling and Medication Guide: Reslizumab will have patient counseling information. There will be no Medication Guide for this product.

Carton and container labeling: These were reviewed by various disciplines of this Division and DMEPA, and found to be acceptable.

13. Postmarketing

Postmarketing Risk Evaluation and Mitigation Strategies:

REMS will not be required for this application. The information necessary to use reslizumab safely and effectively will be provided through prescribing information and patient labeling.

Other Postmarketing Requirements and Commitments:

Teva will conduct several post-marketing requirement and commitment studies to further assess immunogenicity (b) (4)

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/s/

BADRUL A CHOWDHURY
03/02/2016