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RESEARCH**

APPLICATION NUMBER:

761033Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	December 31, 2015
From	Banu A. Karimi-Shah, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	BLA 761033
Applicant	Teva Pharmaceutical Industries, Ltd. (Teva)
Date of Submission	April 15, 2015
PDUFA Goal Date	March 30, 2016
Proprietary Name / Non-Proprietary Name	Cinqair®/reslizumab
Dosage form(s)/Strength(s)	Single-use vials of solution for intravenous (IV) administration, 100 mg per 10 mL (10 mg/mL) Proposed dose/dosing regimen: 3 mg/kg IV every 4 weeks
Applicant Proposed Indication(s)/Population(s)	“reduce exacerbations, relieve symptoms, and improve lung function in adults and adolescents (12 years of age and above) with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids
Recommendation on Regulatory Action	Patients 18 years of age and older: Approval <div style="background-color: #cccccc; padding: 2px;">(b) (4)</div>
Recommended Indication(s)/Population(s) (if applicable)	“add-on maintenance treatment of patients with severe asthma aged 18 years and older, and with an eosinophilic phenotype”

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 have asthma exacerbations requiring hospital or emergency department (ED) care, and may require treatment with high dose systemic corticosteroids. Due to the undesired effects of OCS, the aim of treating these severe asthma patients is to utilize the lowest effective dose or avoid use of OCS when possible; however, the alternate therapeutic options for these patients are limited.

Reslizumab is an anti-IL5 monoclonal antibody studied in patients with severe asthma and an eosinophilic phenotype. The trials for reslizumab were adequate and well-controlled, and demonstrated statistically significant and clinically meaningful improvements in lung function and reductions in asthma exacerbations. Baseline maintenance oral corticosteroid use was higher among those randomized to placebo. Sensitivity analyses suggest that the efficacy findings are robust to this imbalance. A physician who treated 1,000 patients with asthma with eosinophilic phenotype with reslizumab for one year could prevent 182 asthma exacerbations and 5 asthma hospitalizations. 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. Evidence of efficacy was less robust in patients 12 to 17 years of age, with an apparent increased risk in exacerbations (with a point estimate favoring placebo). While the number of adolescent patients enrolled was small, it is notable that the treatment estimate was divergent from that of the overall patient population. The efficacy data do not support the benefit of reslizumab in patients 12 to 17 years of age.

There were several serious safety signals identified during review of this application. These included anaphylaxis, muscle toxicity (elevated CPK and musculoskeletal adverse events), and malignancy. Anaphylaxis was not prospectively evaluated in the development program, which may lead to an underestimation in the magnitude of this safety signal. Taking into account that patients will be under supervision during their intravenous infusion, and the subset of specialists that will be prescribing this medication, the appropriate safety measures can be described through labeling. Similarly, the CPK elevation and musculoskeletal safety signal can be handled through labeling. A physician who treated 1,000 patients with asthma with eosinophilic phenotype with reslizumab for one year could expect to manage 3 additional cases of anaphylaxis, 3 additional cases of malignancy, and 46 additional cases of CPK elevations.

This reviewer assesses that the risk:benefit 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 other drugs in the class (i.e. mepolizumab). However, given the efficacy and safety information available, and that the pediatric population is considered to be a vulnerable patient population afforded special protections under Subpart D, the risk:benefit assessment does not support approval in patients 12 to 17 years of age at this time.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	Severe asthma with an eosinophilic phenotype affects 3-5% of asthma patients. They have severe exacerbations which are treated with, and prevented by, systemic corticosteroid use.	Severe asthma with an eosinophilic phenotype is a serious condition with chronic morbidity.
<u>Current Treatment Options</u>	<ul style="list-style-type: none"> • Mepolizumab (Nucala®), another anti-IL-5 monoclonal antibody, administered subcutaneously • Corticosteroids 	Current treatment options for this condition are effective. However, other additions to the treatment armamentarium would provide patients and HCPs with another choice in this difficult-to-treat subgroup of patients with asthma.
<u>Benefit</u>	<p>Reslizumab 3 mg/kg IV was evaluated for both its effect on lung function (FEV1) and asthma exacerbations as add-on therapy to standard of care. FEV1 was statistically better in the reslizumab group vs. placebo (0.16L, 95% CI [0.06, 0.26]. Two exacerbation studies demonstrated a statistically significant reduction in exacerbations (rate ratio 0.50, 95% CI [0.37, 0.67] and rate ratio: 0.41, 95% CI [0.28, 0.59].</p> <p>The Asthma Control Questionnaire (ACQ) and The Asthma Quality of Life Questionnaire (AQLQ) were also assessed in the pivotal lung function and exacerbation studies. These endpoints are important, especially in the exacerbation studies, as they provide other dimensions of benefit and at earlier timepoints. Both the ACQ and the AQLQ provided evidence for benefit as well.</p> <p>Evidence for the adolescent subgroup (12 to 17 years of age) was less robust; subgroup analysis demonstrated a point estimate that favored placebo over reslizumab treatment for exacerbations, suggesting an increased risk of exacerbations in patients 12 to 17 years of age.</p>	<p>The clinical trials conducted in support of reslizumab were adequate, well-controlled, and demonstrated statistically significant and clinically meaningful reductions in asthma exacerbations and improvements in lung function.</p> <p>A physician who treated 1,000 patients with reslizumab for one year could prevent 182 asthma exacerbations and 5 asthma hospitalizations.</p> <p>Subgroup analyses are difficult to interpret because the number of patients in these analyses is often small. However, the findings of efficacy are often accepted when point estimates show a favorable treatment effect in subgroups with small numbers, so why they should be discarded when the point estimates</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		are unfavorable with respect to the treatment being studied is questionable. Efficacy in the 12 to 17 year old age group cannot be confirmed.
Risk	<p>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. It is important to note that there was an imbalance between the treatment and placebo groups in that more patients (9%) were taking corticosteroids in the reslizumab group than in the placebo group (5%).</p> <p>Three important safety signals emerged in the review:</p> <p><u>Anaphylaxis</u> Four cases of anaphylaxis were observed in the asthma clinical trials. Anaphylaxis is a known risk with biologic drug products, however it is unusual to observe 4 cases of anaphylaxis, which is typically rare in clinical development programs.</p> <p><u>Muscle Toxicity</u> Patients randomized to reslizumab were more likely to experience moderate, severe, or life-threatening elevations in CPK and more likely to report muscle pain; they are also more likely to report musculoskeletal adverse events in the 24 hours following reslizumab infusion.</p> <p><u>Malignancy</u> Eight cases of malignancy were observed in the controlled trials. There was a small numerical imbalance in malignancy events with 0.6% (n=6) of patients developing malignancy in the reslizumab group versus 0.3% (n=2) in the placebo group.</p> <p><u>Infection</u></p>	<p>The extent of exposure was adequate to evaluate the safety of reslizumab. It is important to note that there were several limitations in collection of the safety data:</p> <p><u>Anaphylaxis</u> 1) Anaphylaxis events were not collected prospectively according to NIAID/FAAN 2006 criteria; therefore, they had to be retrospectively collected and adjudicated 2) Post-infusion vital signs and time to onset of AEs were not uniformly captured to general narratives with respect to potential cases of anaphylaxis, retrospectively.</p> <p>Based on our analysis of the available safety data, a physician who treated 1,000 patients with reslizumab for one year could expect to manage 3 additional cases of anaphylaxis</p> <p><u>Muscle Toxicity</u> CPK measurements were taken pre-dose and not post-dose, so the true magnitude/nature of the toxicity is still unclear.</p> <p>Based on our analysis of the data, a physician</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>There were no cases of opportunistic infections (including herpes zoster) reported in the reslizumab treatment program. When stratified for corticosteroid use, those randomized to reslizumab had a higher incidence of sinusitis, upper respiratory tract infection, and pneumonia, compared to placebo.</p>	<p>who treated 1,000 patients with reslizumab for one year could expect to manage 46 additional cases of CPK elevations.</p> <p><u>Malignancy</u> Reslizumab is an immunomodulating drug, 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. For the most part, the tumor types were varied, and the imbalance was small.</p> <p>Based on our analysis of the data, a physician who treated 1,000 patients with reslizumab for one year could expect to manage 3 additional cases of malignancy.</p> <p><u>Infection</u> Eosinophils play a role in defense against helminthic infections and are immunomodulating; therefore infection is of concern with reslizumab and members of its class.</p>
<p><u>Risk Management</u></p>	<ul style="list-style-type: none"> • Anaphylaxis • Muscle Toxicity • Malignancy • Infections <p>Physicians should be prepared to manage potentially life-threatening</p>	<p>Given the seriousness of the condition being treated, these risks can be communicated to providers and patients through appropriate labeling. As anaphylaxis was observed in the clinical development program, and poses a life-threatening risk to the severe asthma population</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>cases of anaphylaxis, and patients should be closely observed for an appropriate period in a physician’s office after reslizumab administration. Clinicians will want to carefully weigh the risks and benefits of reslizumab therapy in patients with a history of or increased risk for malignancy, and may wish to adjust cancer screening accordingly. Clinicians will want to carefully weigh the risks and benefits of reslizumab therapy in patients with a history of or increased risk for infections, such as tuberculosis or parasitic infection, and may wish to adjust screening accordingly. Clinicians will want to monitor for muscle events and CPK elevations.</p>	<p>in whom it is to be used, this reviewer recommends that a boxed warning for anaphylaxis be placed in the current labeling.</p> <p>Information regarding muscle toxicity and appropriate monitoring should also be communicated via labeling in the Warnings and Precautions.</p> <p>Although there was no imbalance in opportunistic infections, this remains a concern with this class of immunomodulating drugs and should appear in the Warnings/Precautions as well.</p> <p>Finally, malignancy will be described in the product labeling so that clinicians may consider the appropriate risk:benefit for each patient and adjust cancer screening accordingly.</p>

2. Background

Teva Pharmaceuticals (Teva) submitted Biologics Licensing Application (BLA) 761033 on April 15, 2015 for reslizumab for intravenous use under section 351(a) of the Public Health Service Act for the treatment of patients with asthma. The proposed indication statement for reslizumab 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 (ICS).” The proposed dose is 3 mg/kg by intravenous administration once every 4 weeks. As a new BLA, this application is being reviewed under the PDUFA V “Program” and has a 12-month PDUFA clock. This review provides a summary of the overall application and my recommendation for the regulatory action.

Reslizumab is a humanized IgG4κ monoclonal antibody (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. The basis of approval for mepolizumab was a reduction in asthma exacerbations, oral corticosteroid (OCS) sparing, and a positive trend towards improvement in asthma symptoms. Therefore, 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 (US). 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 (anti-IgE mAb). With the appreciation that

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, editors. 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>

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>

asthma is a chronic inflammatory disorder, ICS have become the cornerstone of maintenance therapy for patients with persistent asthma. 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 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 US for patients with asthma. These are Advair Diskus and Advair HFA Inhalation Aerosol (fluticasone propionate and salmeterol xinafoate), Symbicort (budesonide and formoterol fumarate), Dulera (mometasone furoate and formoterol fumarate), and Breo Ellipta (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 are 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 systemic corticosteroids (e.g oral corticosteroid, 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 ICS plus a second controller, and/or systemic corticosteroids to prevent it from becoming “uncontrolled” or asthma 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 the undesired effects of OCS, the aim of treating these severe asthma patients is to utilize the lowest effective dose or avoid use of OCS when possible; however, the alternate therapeutic options for these patients are limited.

Within the eosinophilic phenotype of asthma, 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.

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 (GINA): 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.

Additionally, the levels of blood eosinophils that are considered “elevated” usually fall within the normal range. The mepolizumab clinical development program used an eosinophil count of ≥ 150 cells/ μL at screening together with criteria for severe persistent or refractory asthma to define their patient population. Teva’s patient selection criteria specified inclusion of a less severe population (those uncontrolled on ICS), however with an eosinophil count of ≥ 400 cells/ μL . 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.

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, who assumed responsibility for reslizumab development.

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 FEV₁ 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 Quality

The Office of Biotechnology Products (OBP) recommends approval of reslizumab with respect to the drug substance, drug product, quality microbiology, and facilities review with several post-marketing commitments as listed in Section 13. Their review of the submitted data supports the conclusion that the manufacture of reslizumab is well-controlled and leads to a product that is pure and potent. The claim of categorical exclusion from an environmental assessment is acceptable. Regarding quality microbiology, Teva has adequate control strategies in place with bioburden and endotoxin testing as part of (b) (4) release specifications. There are no outstanding issues for approval.

Reslizumab is a humanized IgG4κ mAb to human IL-5 produced by recombinant DNA technology in murine myeloma NS0 cells. It is composed of two light chains and two heavy chains linked by 12 intra-chain and 4 inter-chain disulfide bonds. The predicted molecular mass is 147 kDa. The drug substance contains reslizumab at (b) (4) mg/mL concentration. (b) (4)

The recommended storage conditions for both the DS and DP are 5±3°C. Based on the review of the provided stability data, the proposed expiry period of 36 months for the reslizumab drug substance when stored at 2-8°C is acceptable. The DS manufacturing process is well-controlled; however, (b) (4) DS control strategy can be implemented. (b) (4) The implementation (b) (4) may be conducted post-licensure and are listed as post-marketing commitments (to be discussed with the Sponsor) in Section 13.

The DP presentation is a colorless-to-slightly yellow aqueous solution supplied in 10 mL Type I clear, borosilicate glass vials with a (b) (4) rubber stopper which is sealed over with an aluminum flip-off seal. Each vial contains 100 mg of reslizumab for a concentration of 10 mg/mL. It is provided sterile and without preservatives, and is to be diluted with saline prior to infusion. Each vial is intended for single-use only and the remaining drug product is to be discarded after use. The DP manufacturing process is also well controlled; however, confirmatory information for worst case microbiology studies and method improvements will be needed post-marketing. Post-marketing commitments for the DP are also listed in Section 13.

(b) (4)

[REDACTED] (b) (4)

The product-related impurities include [REDACTED] (b) (4)

[REDACTED] (b) (4)
However, this is acceptable [REDACTED] (b) (4)
[REDACTED] for reslizumab. Overall, the evaluation and control strategy
for both product-related and process-related impurities is acceptable.

Facilities review/inspection

The DS is manufactured at [REDACTED] (b) (4). Inspection of this facility was conducted [REDACTED] (b) (4).
[REDACTED] A seven-item 483 was issued. The firm adequately address observations raised by the FDA 483, and
the final classification is VAI (Voluntary Action Indicated). The requirement for conducting a pre-licensing inspection for the DP
manufacturing facility at [REDACTED] (b) (4) was waived based on the facility's history of
compliance with [REDACTED] (b) (4) DP manufacturing and a recent satisfactory inspection [REDACTED] (b) (4) that resulted in no FDA Form 483 and was
classified as NAI (No Action Indicated). Adequate descriptions were provided for the [REDACTED] (b) (4)
[REDACTED] facilities proposed for reslizumab DS and DP manufacture. All proposed manufacturing and testing sites are recommended
for approval from a facilities standpoint.

4. Nonclinical Pharmacology/Toxicology

The nonclinical safety program for reslizumab is considered complete and adequate to support the safety of the proposed clinical dose of 3 mg/kg administered intravenously every 4 weeks. The nonclinical reviewer recommends approval of this application. There are no outstanding nonclinical issues at this time.

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. However, the change was not statistically significant. Reslizumab systemic exposure in mice decreased over time, suggesting the presence of neutralizing anti-reslizumab antibodies (ADA). However, the ADA test was affected by the presence of free drug in serum.

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.

Because the mouse was identified as a relevant species for reslizumab, the Sponsor conducted a 6-month 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.

5. Clinical Pharmacology

From a clinical pharmacology perspective, the information submitted in this BLA is acceptable to support approval. There are no outstanding issues.

Mechanism of Action

Reslizumab is a humanized monoclonal (IgG4 kappa) antibody that competitively binds to human IL-5. The reslizumab binding site on IL-5 is mapped to amino acids (b) (4). Reslizumab neutralizes soluble IL-5 and prevents this cytokine from interacting with its receptor, IL-5 receptor α , which can be found on eosinophils as well as other cell types. IL-5 is a soluble dimer and is not expressed on cell surfaces; therefore, Fc effector function does not contribute to the reslizumab mechanism of action.

Asthma is a chronic lung disease that involves inflammation of the airways. Microscopically, asthma is characterized by the presence of increased numbers of inflammatory cells including eosinophils, neutrophils, lymphocytes and plasma cells. Activated T-lymphocytes direct the release of inflammatory mediators from eosinophils, mast cells, and lymphocytes. In addition, the Th2-subset of activated T-lymphocytes produces IL-4, IL-5, and IL-13. IL-5 leads to the recruitment and activation of eosinophils; once activated, eosinophils and also mast cells also generate cytokines that help to perpetuate the inflammation.⁸ Therefore, IL-5 is proposed as a scientifically rational target for asthma therapies. However, the pathogenesis of asthma is complex, and although blocking IL-5 results in reduced eosinophils in the peripheral blood and (to some extent) in tissues, a direct correlation with the reduction of eosinophil levels to clinical efficacy has not been established.⁹

Pharmacokinetics (PK)

Reslizumab PK in healthy subjects was evaluated in Study 1102. Four parallel groups of healthy subjects received five doses of reslizumab IV (0.3, 1.0, 2.0, or 3.0 mg/kg) once every four weeks. The mean observed accumulation ratio following the 5th dose ranged from 1.5 to 1.9. The mean terminal half-life ranged from 25 to 32 days. The observed terminal half-life ($t_{1/2}$) supports the proposed dosing interval of once every 4 weeks. There was no consistent or notable trend toward a deviation from dose proportionality following either single or multiple doses. Reslizumab clearance is approximately 7 mL/hour. The PK of reslizumab was time-independent, with clearance being similar following both the first and fifth doses. The PK was generally similar between healthy subjects when compared with asthma patients. The PK of reslizumab was not significantly impacted by race, ethnicity, age, or gender. Body weight was the only covariate identified as having an impact on clearance, with clearance being higher in those of higher body weight. However, the effect of body weight on PK was determined not to be clinically important given the flatness of the exposure-response relationship for efficacy. Therefore, no dose adjustment is recommended with regard to body weight.

ADME

Reslizumab is administered by the intravenous route. The geometric mean of volume of distribution at steady state is 5.27 L (CV=26%). Reslizumab is believed to be degraded by enzymatic proteolysis into small peptides and amino acids. As reslizumab bind to a soluble target, linear non-target-mediated clearance is expected.

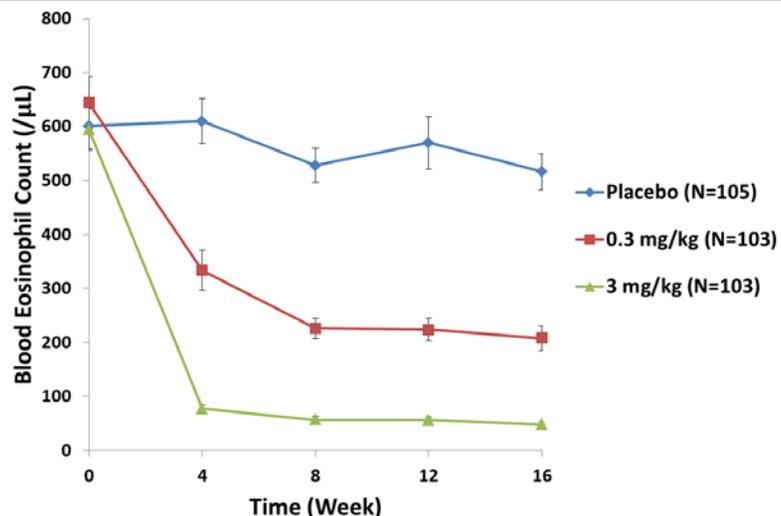
⁸ Fireman, Philip. Understanding asthma pathophysiology. *Allergy asthma Proc.* 2003 Mar-Apr; 24 (2): 79-83

⁹ Leckie MJ et.al Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyperresponsiveness, and the late asthmatic response. *Lancet* 2000; 356: 2144-8

Dose Selection

The dose selection of reslizumab was guided predominantly by the pharmacodynamic response of reslizumab in earlier studies (reduction in blood eosinophil count) with support from clinical efficacy measures (e.g. lung function). Study 3081 (described in more detail in Section 7) was the only asthma study in the intended patient population to investigate more than one dose of reslizumab (0.3 mg/kg and 3 mg/kg). A dose-dependent reduction in blood eosinophil count was demonstrated in Study 3081. The reduction plateau phase was reached at Week 4 and Week 8 for the 0.3 mg/kg and 3 mg/kg treatment groups, respectively. The absolute values of blood eosinophil counts reduced maximally to 517, 208, and 48 cells/ μ L (or reduced by 14%, 68%, and 92%) for placebo, 0.3 mg/kg, and 3 mg/kg treatment groups, respectively (See Figure 1).

Figure 1. Arithmetic mean (\pm 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)



The dose ranging study was conducted concurrently with the exacerbation and lung function studies; therefore, this study did not support the dose selected to carry forward in those studies. As discussed in Section 7, the lower dose also showed a statistically significant effect on lung function, but was not further studied for exacerbation. While dose ranging was not optimal, the data submitted do support the proposed dose of 3 mg/kg administered intravenously every 4 weeks.

Immunogenicity

The same homogeneous bridging ELISA assay for detecting anti-reslizumab antibody (with a confirmatory step to resolve IL-5 interference) was applied in all the pivotal studies. Following reslizumab 3 mg/kg, the rate of treatment emergent ADA incidence was 5.4%. Among ADA-positive patients, 43% were transient (only positive in one post-dose sample). The adverse event profile was similar in ADA-positive vs. negative patients.

There was no association of a positive anti-drug IgG antibody response with anaphylaxis or hypersensitivity reactions to reslizumab. The screening antibody assay has a sensitivity of 22 ng/ml, which is adequate to detect IgG, but insufficient to detect clinically relevant IgE. Typically, sensitivity below 5 ng/ml is required in order to detect clinically relevant IgE. Discussions between the Applicant and the Agency are ongoing at the time of this review regarding development of an anti-drug antibody assay with sufficient sensitivity to detect IgE. Similarly, the assay to evaluate neutralizing potential of ADA is also under development; however there no apparent impact of ADA on reslizumab PK, safety, or efficacy.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

a. Overview of the clinical program

Teva submitted four principal efficacy and safety studies in support of the proposed asthma indication. These included 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 $\geq 400/\mu\text{l}$. A fourth study, 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 for the presence of treatment interaction between FEV₁ response and blood eosinophil count.

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/ μ L. Teva’s threshold eosinophil count of ≥ 400 cells/ μ L 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 8 when relevant.

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 $\geq 3\%$ at screening, no prior asthma exacerbation required - Parallel arm, DB - 15 weeks	Res 3 mg/kg IV Placebo	53 53	1 ^o : Δ ACQ 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/ μ L at screening - Parallel arm, DB - 16 weeks	Res 0.3 mg/kg IV Res 3 mg/kg IV Placebo	104 106 105	1 ^o : Δ FEV ₁ baseline to over 16 weeks 2 ^o : Δ ACQ baseline to over 16 weeks, Δ AQLQ baseline to week 16	US, North America, South America, Europe, Asia (37% US)
Exacerbation Studies					
3082	- 12 to 75 yr - ICS required, LABA allowed	Res 3 mg/kg IV Placebo	245 244	1 ^o : Frequency of exacerbation ** 2 ^o : Δ FEV ₁ baseline	US, North America, South America,

ID Year*	Study Characteristics † - Patient age - Patient characteristics - Study design, objective - Study duration	Treatment groups ‡	N §	Efficacy Variables ¶	Regions and Countries //
[04/11- 03/14]	- blood eosinophil \geq 400 cells/ μ L at screening - \geq 1 asthma exacerbation requiring systemic corticosteroid in past year, - Parallel arm, DB - 52 weeks			to over 16 weeks Δ ACQ baseline to over 16 weeks, Δ AQLQ baseline to week 16	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 : Δ FEV ₁ baseline to over 16 weeks Δ ACQ baseline to over 16 weeks, Δ AQLQ 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 (\approx 80% used) - any blood eosinophil count - Parallel arm, DB - 16 weeks	Res 3 mg/kg IV Placebo	398 98	1 ^o : Δ FEV ₁ baseline to week 16 2 ^o : Δ ACQ baseline to over 16 weeks	US, (100% US)
<p>* 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) ¶ FEV₁ 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) \downarrow in FEV1 by 20% or more from baseline, 2) a \downarrow 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.</p>					

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 IV once every 4 weeks) 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 $\geq 12\%$ to SABA during screening. The primary efficacy endpoint was overall change from baseline in trough FEV₁.

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 PEF_R 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 for the presence of FEV₁ efficacy benefit and blood eosinophil count interaction. The primary endpoint was change from baseline to Week 16 in trough FEV₁.

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/ μ L, when inclusion specified only that patients be ≥ 400 cells/ μ L. 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. Based on the patients enrolled in the development program, the indication statement will include those patients who were actually enrolled and studies (i.e. severe asthma), (b) (4)

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 % Δ FEV ₁ post SABA	25%	26%	26%	28%
Eosinophil counts				
Baseline mean blood eosinophil count/ μ L	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%

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	3081	3084	3082	3083
All Patients: Adults + Pediatrics				
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				

Choice of eosinophil threshold

In this BLA submission, Teva cites published studies conducted with reslizumab (Study P00290 and Study Res-5-0010),^{10, 11} to indicate that asthma with elevated blood eosinophils can be characterized by a sputum eosinophil count of $\geq 3\%$, 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.^{12, 13} 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 $\geq 3\%$, and a count of < 400 cells/ μL identified the majority of patients without sputum eosinophilia.

Dose Ranging:

Study 3081 was the only study to investigate more than one dose of reslizumab (0.3 and 3 mg/kg IV) in the intended asthma patient population. 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 was the change from baseline in FEV₁ over 16 weeks. Significant improvement in FEV₁ was seen for patients in both reslizumab treatment groups compared with patients in the placebo group; the overall change from baseline in FEV₁ 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 2). 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.

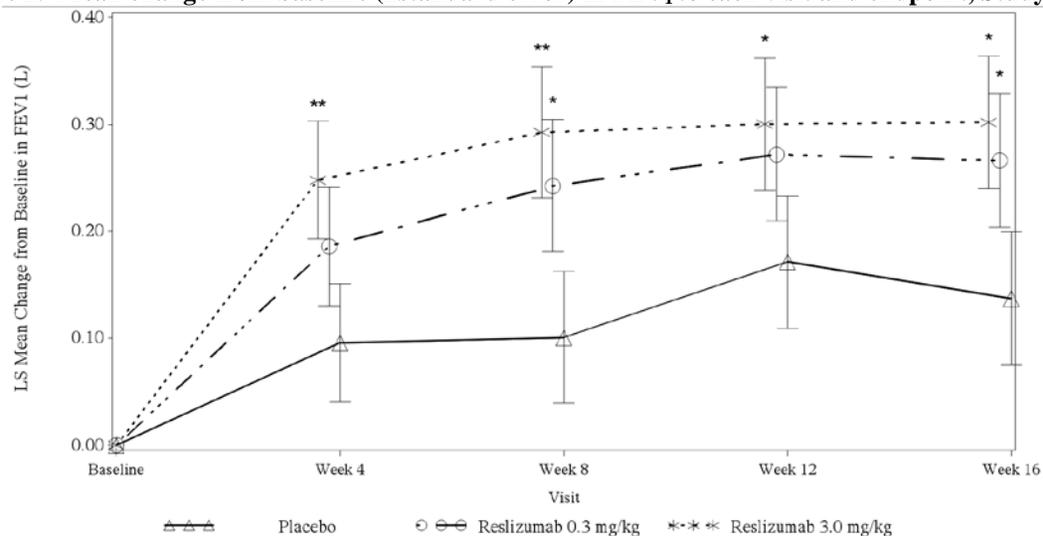
¹⁰ Green RH, Brightling CE, McKenna S, et al. Asthma exacerbations and sputum eosinophil counts: a randomized controlled trial. *Lancet* 2002; 360:1715-1721.

¹¹ 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.

¹² 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.

¹³ 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 Immunol* 2009; 124: 615-617.

Figure 2. Mean change from baseline (\pm standard error) in FEV₁ to each visit and endpoint, Study 3081



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

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 and described in Section 5). While the reduction in blood eosinophils is greater with the higher reslizumab dose (Figure 1), 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. However, the 3 mg/kg IV dose of reslizumab did demonstrate efficacy with respect to lung function, as will be discussed below.

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

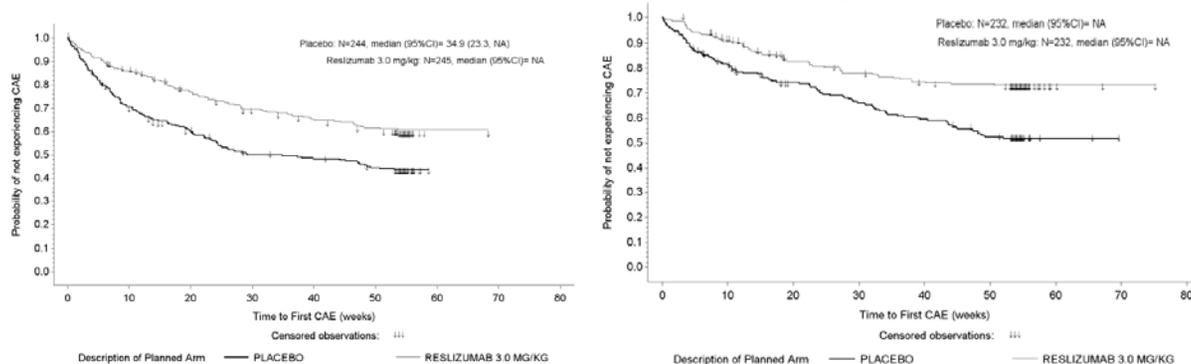
treatment needed for exacerbations (e.g. oral steroids, systemic steroids, and ED visit/hospitalization). The exacerbation rates and rate ratios compared to placebo for this secondary analysis are also shown in Table 3.

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				

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 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 trends favoring reslizumab 3.0 mg/kg. While the rates of exacerbations leading to ED visit or hospitalization were low across treatment groups (approximately 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).

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)



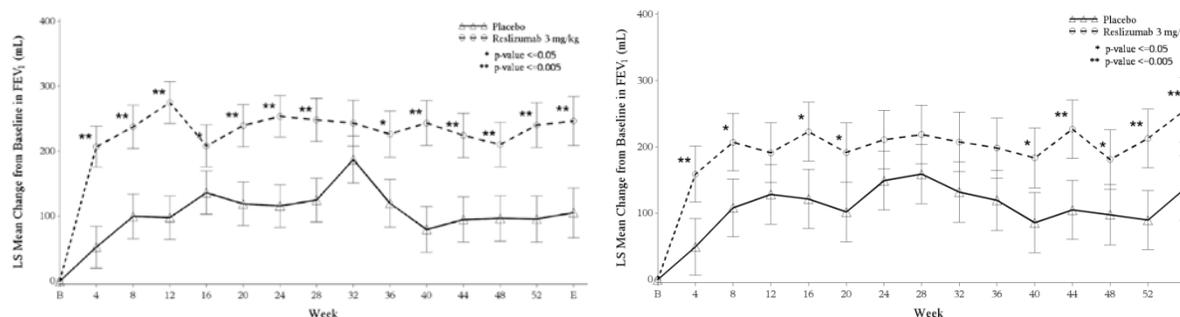
Bronchodilator (lung function) effects:

Spirometry was conducted in Studies 3081 and 3084 (as the primary endpoint), and in Studies 3082 and 3083 as a secondary endpoint (Table 1). Trough FEV₁ was the measure of interest, which assesses sustained effect over time on lung function. Trough FEV₁ 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 Studies 3082 and 2083 (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 FEV₁ (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 (FEV₁) and included patients unselected for baseline blood eosinophil counts. This study was designed to test the interaction between FEV₁ change from baseline and the baseline eosinophil counts. The primary analysis utilized a linear regression model with model effects including treatment, blood eosinophil count at baseline, and the interaction of treatment by eosinophil count. Interaction was tested at the significance level 0.10. A total of 496 patients were enrolled, with 492 receiving at least one dose of study drug. Seventy-four (15%) patients stopped medication early and 87 (18%) discontinued from the study prematurely.

The primary efficacy analysis, a linear regression model, failed to show a significant overall interaction between baseline eosinophil counts and FEV₁ change at Week 16. The slope difference (active – placebo) was 0.3007 if measurements taken within 7 days of use of confounding medication were excluded or 0.3082 otherwise. The treatment difference between reslizumab and placebo did not appear to be related to the baseline eosinophil count.

The key secondary variable, change from baseline in FEV₁ at Week 16, was analyzed in the overall population and in subsets of patients grouped by baseline eosinophil category using different cutoff points: 100 cells/μL, 200 cells/μL, 300 cells/μL, or 400 cells/μL. Table 5 shows the results in the overall population and according to baseline eosinophil count ‘less than’ or ‘no less than’ 400 cells/μL, the threshold for patient inclusion into the other 3 studies (3081, 3082, and 3083). Reslizumab produced a modest treatment effect on FEV₁ in the overall population unselected for baseline eosinophils. No meaningful treatment effect was observed for the subset patients with a baseline eosinophil count < 400 cells/μL while a 272 mL improvement above placebo was noted for patients with a baseline eosinophil level ≥400 cells/μL. However, there were only 96 (20%) patients with baseline eosinophil count ≥400 cells/μL. In addition, this relatively large treatment effect was driven primarily by a differential response in the placebo patients in this subgroup/ The p-value of 0.0436 should be interpreted cautiously since the primary analysis for the interaction test failed and multiplicity was not controlled for in these analyses.

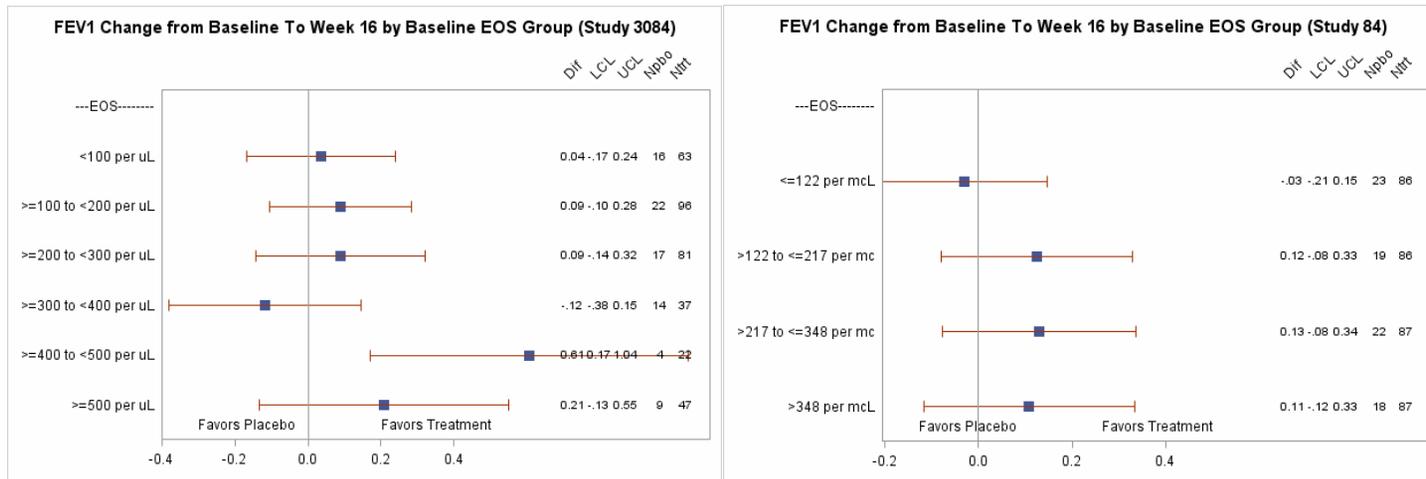
Table 5. Change from baseline in FEV₁ at Week 16 by baseline blood eosinophil count (Study 3084, FAS with All Measurements Included)

Variable (unit) Statistic	Overall		EOS <400 cells/μL		EOS ≥400 cells/μL	
	Placebo (N=97)	Reslizumab (N=395)	Placebo (N=76)	Reslizuma b (N=317)	Placebo (N=19)	Reslizumab (N=77)
FEV1 (L)	n=84	n=345	n=69	n=276	n=13	n=69
Baseline mean	2.172	2.098	2.182	2.068	2.153	2.224
LS mean change	0.186	0.252	0.213	0.244	0.002	0.272
Treatment diff.	0.066		0.031		0.270	
(95% CI)	(-0.032, 0.163)		(-0.076, 0.137)		(0.008, 0.532)	
p-value	0.1859		0.5678		0.0436	

Source: Biostatistical Reviewer, Lan Zeng

To further evaluate the FEV1 efficacy benefit and blood eosinophil count interaction, the FEV1 change from baseline to Week 16 by baseline eosinophil subgroups was examined by 100 cell/ μ L increments or by quartiles. There was no apparent relationship between reslizumab treatment effect and blood eosinophil count at baseline (Figure 5).

Figure 5. FEV1 change from baseline to week 16 by baseline eosinophil group 100 cells/ μ L increments (left panel) and by quartiles (right panel), Study 3084



Source: Biostatistical Reviewer, Lan Zeng

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,¹⁴ and listed in common asthma treatment guidelines,^{15, 16} and elsewhere.¹⁷

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 FEV₁ 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 FEV₁. 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 ≥ 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.

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.

¹⁴ Measurement of Health-Related Quality of Life & Asthma Control. At: <https://qoltech.co.uk/index.htm>

¹⁵ 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>

¹⁶ Global Initiative for Asthma (GINA): Global strategy for asthma management and prevention, Updated 2015. At: <http://www.ginasthma.org/>

¹⁷ ATS website: <http://www.thoracic.org/members/assemblies/assemblies/srn/questionnaires/acq.php>

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			

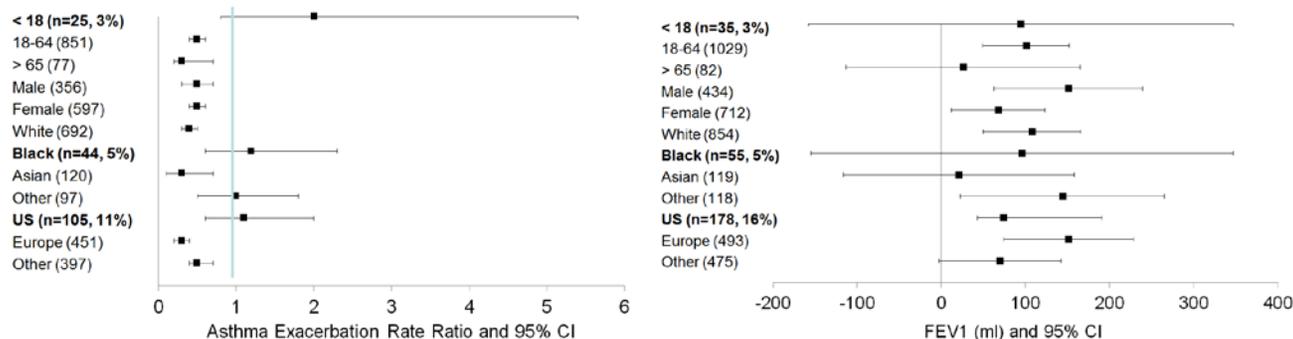
Table 7. AQLQ responder analysis at ≥ 0.5 threshold at week 16 (primary time point) and week 52

	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 US patients, though evidence for improvement in lung function generally was supportive (Figure 6). While the paradoxical findings may be due to chance (driven by small sample size), findings of efficacy are often accepted when point estimates show a favorable treatment effect in subgroups with small numbers, so it is difficult to a priori discard negative results.

Figure 6. Efficacy analyses by subgroup, reslizumab vs. placebo, exacerbation rate ratios (left panel) and FEV1 (right panel)



Source: Figure generated by clinical reviewer from subgroup analyses of pooled data reported in the Integrated Summary of Efficacy

d. Efficacy conclusions

Teva submitted four principal efficacy and safety studies in support of the proposed asthma indication. They were a 16-week lung function study (Study 3081) and two 52-week exacerbation studies (Studies 3082 and 3083). These studies were performed in patients 12 years of age and older with moderate to severe asthma and baseline blood eosinophil counts $\geq 400/\mu\text{l}$. 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 $\geq 400/\mu\text{l}$ in the other studies. Study 3081 observed a mean 0.286 L increase in FEV1 for reslizumab 3.0 mg/kg compared to a mean 0.126 L 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 asthma exacerbation rate of 0.9 per year for reslizumab compared to 1.8 per year for placebo, a 50% reduction over 52 weeks (Rate Ratio 0.50 (95% CI 0.37, 0.67), $p<0.0001$). Study 3083 observed an exacerbation rate of 0.9 per year for reslizumab compared to 2.1 per year for placebo, a 59% reduction over 52 weeks (Rate Ratio 0.41 (95% CI 0.28, 0.59), $p<0.0001$).

Study 3084 did not provide statistically significant evidence of interaction by eosinophil level. Evidence of efficacy was less robust for subgroups with low enrollment. A paradoxical increase in asthma exacerbation rates was observed for adolescent, African American, and U.S. patients, though evidence for improvement in lung function generally was supportive.

The submitted data show a consistent effect for reduction in exacerbations in those with severe asthma and an eosinophilic phenotype. Reslizumab-treated patients also experienced an improvement in lung function as compared with placebo. In addition, patient-reported outcomes of ACQ and AQLQ supported the treatment effect of reslizumab. However, the point estimate in the small subgroup of adolescents aged 12 to 17 years of age demonstrated an apparent increase in exacerbations. Based on a demonstration in the reduction in the rate of asthma exacerbations, the Applicant has provided substantial evidence of effectiveness to support the approval of reslizumab in patients with asthma 18 years of age and older.

8. 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. It is important to note that the proportion of patients on baseline oral corticosteroids was nearly double for the placebo (9%) vs. the reslizumab treatment group (5%).

b. Safety findings

Deaths, SAEs, dropouts, and discontinuations

Four deaths were reported during the asthma clinical studies. Three of the four deaths occurred in a reslizumab treatment arm in Study 3085, and one in the placebo arm of Study 3082. 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)¹⁸ occurred with comparable frequencies between reslizumab and placebo groups. The majority of the events were related to asthma (2% in reslizumab 3 mg/kg treatment group and 3% in placebo 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. Anaphylaxis as a safety signal will be discussed in further detail below.

Dropouts and discontinuations were low (approximately 5% in both reslizumab and placebo groups) in the controlled clinical studies and generally were well-balanced across groups, with the exception of anaphylaxis which led to discontinuation of 3 patients in the reslizumab group as compared with no patients in the placebo group. The most common event leading to discontinuation in all groups was asthma.

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 reslizumab 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).¹⁹ 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. Due to lack of a prospective evaluation, the Agency asked the Sponsor to perform a retrospective investigation and adjudication for anaphylaxis events. As the time of onset of the adverse event was not available in the safety database, the Sponsor was asked to perform a broad standard MedDRA query for anaphylactic reaction on either the day of or the day after the infusion. The Sponsor was asked to query all of the asthma studies, including both reslizumab and placebo patients. The resulting cases were adjudicated by two blinded independent adjudicators according to NIAID/FAAN criterion 1. Per our usual practice, the Agency also included all cases identified by investigators at the bedside to be anaphylaxis.

¹⁸ 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.

¹⁹ 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.

Three cases were identified by investigators at the bedside, and two additional cases, one in a reslizumab-treated patient and one in a placebo patient, were identified during the adjudication process. A brief description of the anaphylaxis cases is provided below:

- 45 year-old white female with history of drug hypersensitivity (novalminulfon allergy and aspirin sensitivity). On Day 22, the patient experienced a reaction 14 minutes after initiation of the second reslizumab 3.0 mg/kg infusion characterized by dyspnea, shivering, vomiting, flushing, and oxygen saturation of 89%. The patient was treated with systemic corticosteroids, antihistamines, IV fluids, and discontinued from the study. The episode resolved with no residual effect.
- 47 year-old white female with a history of allergies (mold and dog hair) and drug hypersensitivities (penicillin and aspirin). 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.
- 52 year-old black female with a history of allergic rhinitis. On day 36, shortly after the completion of the 2nd reslizumab 3.0 mg/kg infusion, the patient experienced an anaphylactic reaction to the study drug (shortness of breath, wheezing, could not speak, swollen eyes, and flushing). The reaction was considered a serious adverse event of moderate intensity by the investigator and 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.
- 52 year-old female in the setting of an ongoing asthma exacerbation. After her 12th infusion, her respiratory status deteriorated precipitously, requiring intubation. The next day she developed a rash on her arms and face. Teva does not consider this a case of anaphylaxis as the patient continued on reslizumab, but this is the case that was identified retrospectively and adjudicated as (+) for anaphylaxis by the committee.
- A 45 year-old man developed hypotension (BP 137/81->77/68) and a rash on his left arm that were self-limited and resolved within fifteen minutes after placebo infusion.

During review of this application, there was some concern that the observed anaphylaxis signal was due to the presence of xenogeneic side chain on reslizumab. Murine cell lines synthesize a blood group oligosaccharide, galactose-alpha-1,3-galactose, known as alpha-gal.²⁰ 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

²⁰ Li F, Vijayasankaran N, Shen AY, Kiss R, Amanullah A. Cell culture processes for monoclonal antibody production. *MAbs* 2010; 2: 466-479.

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,²¹ and alpha-gal was identified on cetuximab via mass spectrometry.²² 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.²³ 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. However, recently the Sponsor had the sera of the four anaphylaxis patients evaluated for anti-alpha gal IgE antibodies and reported negative findings. While this information is still under review by the Agency and will be addressed in an addendum to the immunogenicity review by Dr. João Pedras-Vasconcelos, if confirmed, this makes anaphylaxis as a result of alpha-gal appears unlikely.

While anaphylaxis events were suboptimally captured, this safety issue can be communicated adequately through labeling. Given that the intended patient population may be more at risk for anaphylaxis and hypersensitivity events, and the relatively large number of events seen in the clinical development program, this reviewer recommends a boxed warning in the product label.

2) Creatine Phosphokinase (CPK) Elevation/Muscle Safety Signal

Reslizumab treatment is associated with an ill-defined muscle toxicity. Patients randomized to reslizumab had a higher incidence of elevation in CPK. CPK elevations occurred more often in the reslizumab arm for moderate, severe, and potentially life-threatening categories of severity. Overall, 18% of patients randomized to reslizumab experienced one of these classes of elevation, compared to 14% of those randomized to placebo. 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%). Most patients with CPK elevations continued on reslizumab treatment

²¹ 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.

²² 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.

²³ 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

with return of their CPK to baseline (with the exception of 3 patients who discontinued reslizumab, two for muscle pain and one for CPK elevation to ~1200 U/L). Not all patients with CPK elevations had musculoskeletal complaints; of 24 reslizumab-treated patients who experienced a musculoskeletal adverse event within 24 hours of infusion, 7 patients had CPK elevations. While some cases were identified by investigators as “rhabdomyolysis”, it is notable that no patients experienced renal failure.

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 (as reported by the investigator) 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; however, in the opinion of this reviewer, this safety signal can be adequately communicated through labeling and be monitored for in clinical practice.

3) Malignancy

Reslizumab is an immunomodulator, and therefore malignancy is a safety issue of special concern. Twenty-three (23) cases of malignancy were observed in the reslizumab development program, 8 in controlled trials, and 15 in the open-label extension trial. The 8 cases of malignancy observed in controlled trials included 6 in the reslizumab arms (prostate, 2 lung cancers, squamous cell, keratocanthoma and plasmacytoma) and 2 in the placebo arms (bladder and colon). The 15 cases in the open-label extension trial included 5 cases of basal cell carcinoma, 3 breast cancers, 2 malignant melanomas, and 1 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%), but the cancers were of varied type. Preclinical studies did not raise concern for mutagenicity or carcinogenicity. This safety signal will be communicated in the product label.

4) Infections (including opportunistic infections)

Infection is also a concern with any immunomodulating drug, like reslizumab. Overall, no imbalance was observed in the Infections and Infestations SOC, and no opportunistic infections were reported. However, given the imbalance in baseline oral corticosteroid use (with a higher percentage of patients using OCS in the placebo group), it is important to investigate this in a stratified fashion. Among patients taking oral corticosteroids at baseline, those randomized to reslizumab had a higher incidence of pneumonia (7%) compared to placebo (1%). The risk of infection will be communicated as a class warning in the product label.

Common Adverse Events

Common adverse events seen were typical of an asthma program. Common adverse events that occurred in $\geq 2\%$ of the safety population included asthma, nasopharyngitis, upper respiratory tract infection, headache, sinusitis, bronchitis, urinary tract infection, back pain, influenza, allergic rhinitis, oropharyngeal pain, pharyngitis, cough, and dyspnea. Only oropharyngeal pain occurred at a greater frequency in the reslizumab vs. placebo groups (2.6% vs. 2.2%).

c. Safety conclusions

Anaphylaxis, muscle toxicity, and malignancy have been identified as safety signals of interest during the review of this application. While it is unclear if these have been optimally characterized in terms of their magnitude and nature, given the risk-benefit evaluation in this patient population, and with recommendations from the Advisory Committee, these safety issues can be communicated through the product label, including a boxed warning for anaphylaxis.

9. Advisory Committee Meeting

This application was discussed at a Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting on December 9, 2015. The committee was advised that the exact wording of the indication was undergoing review and would be worked out by Teva and the Agency. The major points for discussion raised by the Division were adequacy of dose-ranging and adequacy of the collected safety information. Specifically, with respect to safety, the Division raised the possibility that the full nature and magnitude of anaphylaxis and muscle toxicity had not been established, as these were not prospectively/completely evaluated by the Sponsor. In addition, the Division raised the paradoxical efficacy results in patients 12 to 17 years of age as an issue for discussion. Several panel members raised concern with respect to the safety data regarding malignancy, and the potential imbalance in malignancy events that was observed in the development program.

While there was some discussion that the dose-ranging and safety evaluation could have been more robust, and there were some underlying concerns regarding the efficacy/safety in the US population (especially African Americans), the committee voted almost unanimously in favor of approval of reslizumab in adults > 18 years of age (11 yes, 3 No) and voted unanimously against approval in adolescents 12 to 17 years of age (0 yes, 14 no). The committee recommended that the labeling reflect the patient population who actually participated in the trials, and not just the patient selection criteria.

10. Pediatrics

The Sponsor submitted their initial Pediatric Study Plan (iPSP) on January 29, 2014. In this iPSP, the proposed (b) (4) (b) (4) The iPSP was discussed with the Pediatric Review Committee (PeRC) on April 9, 2014. The PeRC agreed with the Division's recommendation to defer studies in patients from 0 to 12 years (b) (4) (b) (4) A letter was sent to the Sponsor on April 29, 2014, requesting amendment of the iPSP. The PSP was resubmitted on August 7, 2014 in which the Sponsor included the changes as per our earlier advice letter. The amended PSP was discussed with the PeRC on August 20, 2014, and was deemed as an agreed PSP. The agreed PSP included a deferral of studies for patients 0 through 5 years of age, as well as those 6 through 11 years of age. Agreement was communicated to the Sponsor on August 26, 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 *a priori*. Given the serious safety signals with this drug and the availability of other therapies, it is the recommendation of this reviewer that the risk:benefit assessment does not support approval in patients < 18 years of age. Review of the BLA submission with the Pediatric Review Committee is scheduled for February 10, 2016. The Division will propose that the PREA requirement to study children 12 to 17 years of age should be considered fulfilled and will work with the Sponsor to include the appropriate information in the product label. (b) (4)

11. Other Relevant Regulatory Issues

Inspections

A Sponsor-level inspection was requested by the Division because recruitment was widely distributed globally. Thus, each site enrolled only a small number of patients, such that inspection of any one site would not be especially informative. The investigation

focused on Studies 3082, 3083, and 3084. The inspection was conducted from September 28 through October 2, 2015. The inspection evaluated documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, and training of staff and site monitors.

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

Compliance with Good Clinical Practices

The clinical studies were conducted in accordance with Good Clinical Practices and a statement of compliance with Good Clinical Practices is located in each complete study report.

Financial Disclosures

Teva provided a list of clinical investigators in the BLA. Of the 433 investigator, there were 5 investigators with disclosable financial interests/arrangements as defined in 21 CFR 54.2(a). None of the investigators had proprietary interest in mepolizumab. The 5 investigators with disclosable financial interests recruited a (b) (6) sample ((b) (6) %) of the total study population and it is unlikely that any misconduct would impact the study results.

12. Labeling

Proprietary Name

The proposed proprietary name of CINQAIR has been reviewed by DMEPA and deemed acceptable.

Physician Labeling

Labeling discussions are ongoing with the Sponsor at the time of finalization of this review. After the Advisory Committee meeting, a teleconference was held with the Sponsor to discuss modifications to the proposed reslizumab label. Areas of discussion included:

- Addition of a boxed warning for anaphylaxis
- Modification of the indication statement to be aligned with other drugs in the class
- Modification of the indication statement to include adults only
- Inclusion of opportunistic infections as a class warning
- Inclusion of muscle toxicity, malignancy, and immunogenicity in the adverse reactions section
- Inclusion of specific demographics (in table format) in the clinical studies section

At the time of this review, submission of revised labeling from the Sponsor is pending. Patient labeling teams will be consulted once the Division has a substantially complete package insert (SCPI).

Carton and container labeling

Carton and container labeling reviews are also ongoing at this time.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

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

Postmarketing Requirements (PMRs) and Commitments (PMCs)

The DS and DP manufacturing processes are well-controlled, (b) (4) can be implemented, as included in the following recommended PMCs from OBP:

1. To improve the overall control strategy of the drug substance manufacturing process (b) (4)
2. To implement (b) (4) in the drug substance manufacturing process.

3. To re-evaluate and tighten the (b) (4) endotoxin acceptance criteria for the (b) (4) samples after manufacturing 30 batches of reslizumab.
4. To establish a hold time limit for the intermediate (b) (4). These hold times should be validated at scale to demonstrate that these (b) (4) can be held under proposed worst-case conditions without compromising the microbial quality of the product.
5. To develop, validate and establish an identity test for incoming bulk drug substance to the drug product manufacturing site that uniquely confirms identity of reslizumab.
6. To requalify the microbial retention study at routine manufacturing/room temperature and submit the results in accordance with 21 CFR 601.12 by June 2016.
7. To requalify the dye ingress CCI test method with reslizumab 10 mL/20 mm vial under worst case challenge conditions using comprised positive controls with a breach size of (b) (4) μm and submit the data in accordance with 21 CFR 601.12 by April 2016.
8. To reduce the vial overfill to comply with compendial recommendations.
9. To evaluate and revise, as needed, the acceptance criteria for all the drug substance and drug product release and stability specifications based on data from at least thirty released lots of reslizumab drug substance and drug product.

14. Recommended Comments to the Applicant

None.

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/s/

BANU A KARIMI SHAH
12/30/2015