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APPLICATION NUMBER:

761033Orig1s000

OFFICE DIRECTOR MEMO

Summary Basis for Regulatory Action

Date	March 23, 2016
From	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA #	BLA 761033
Supp #	
Applicant Name	Teva Pharmaceutical Industries, Ltd. (Teva)
Proprietary / Established (USAN) Names	Cinqair Reslizumab
Dosage Forms / Strength	Single-use vials of solution for intravenous (IV) administration 100 mg per 10 mL Proposed dose: 3 mg/kg IV every 4 weeks
Proposed Indication(s)	“Reduce exacerbations, relieve symptoms, and improve lung function in adults and adolescents (12 years of age and above) with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids”
Action:	<i>Approval for patients with severe asthma 18 years of age and older</i> (b) (4)

1. Introduction

This review will be a brief summary of the basis for the regulatory action regarding reslizumab and I refer the reader to the other reviews in the action package for a more detailed discussion. Reslizumab is a humanized IgG4κ monoclonal antibody produced in murine cells that binds to human interleukin 5 (IL-5), a cytokine that is involved in the regulation (activation) of blood and tissue eosinophils. IL-5 activity has been associated with asthma where it is thought that predominantly eosinophils (or increased eosinophils) are involved. There has been speculation that IL-5 and eosinophils may be responsible, or at least heavily involved, in some patients with ‘severe’ or ‘refractory’ asthma, defined as those requiring high-dose inhaled corticosteroids plus a second controller, or those that are ‘uncontrolled’ despite this therapy. This small group of patients often contains individuals referred to as having an ‘eosinophilic phenotype’ although identification by current laboratory methods cannot be done confidently.¹ In any regard, this concept has made modulation of eosinophil action in severe asthma, and in the case of this application modification by IL-5 manipulation, an attractive target.

Recently another monoclonal antibody targeting IL-5 (mepolizumab²) has been approved for use in those with severe asthma. The approval of mepolizumab is instructive and supports the concept that direct modulation of IL-5 with indirect effects on eosinophils has merit.

¹ Please read the excellent clinical reviews for discussion of the efforts that have been made to use various measures of eosinophils to try to help identify those that may be included in an eosinophilic phenotype group.

² This approval was on the basis of reduction in asthma exacerbations and oral corticosteroid sparing.

During the review of this application, clear efficacy was demonstrated as will be discussed below. Safety demonstrated what might be expected with use of a monoclonal antibody with the exception of a high number of cases of anaphylaxis (for the size of the program) and increases in muscle symptoms and CPK. These will also be discussed below.

The review team is recommending approval in patients ≥ 18 years of age, and I agree.

Efficacy

This has been thoroughly covered in reviews authored by Drs. Karimi-Shah, Chowdhury and Ms. Zeng. Four principal trials supported efficacy and safety and are in the table below (as well as one Phase 2 trial and a lung function trial) from Dr. Shah's review (pages 16-17).

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 [04/11- 03/14]	- 12 to 75 yr - ICS required, LABA allowed - blood eosinophil ≥ 400 cells/ μ L at screening - ≥ 1 asthma exacerbation requiring systemic corticosteroid in past year, - Parallel arm, DB - 52 weeks	Res 3 mg/kg IV Placebo	245 244	1 ^o : Frequency of exacerbation ** 2 ^o : 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, 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)

ID Year*	Study Characteristics † - Patient age - Patient characteristics - Study design, objective - Study duration	Treatment groups ‡	N §	Efficacy Variables ¶	Regions and Countries //
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°: Safety 2°: Asthma control	
Moderate to Severe Asthma – Bronchodilator (lung function) study					
3084 [02/12-08/13]	- 18 to 65 yr - ICS required, LABA allowed (~80% used) - any blood eosinophil count - Parallel arm, DB - 16 weeks	Res 3 mg/kg IV Placebo	398 98	1°: ΔFEV ₁ baseline to week 16 2°: ΔACQ 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) ↓ in FEV₁ by 20% or more from baseline, 2) a ↓ in peak expiratory flow rate (PEFR) by 30% or more from baseline on 2 consecutive days, or 3) worsening of symptoms or other clinical signs per physician evaluation or the event.</p>					

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 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.

Results based on exacerbation frequency are demonstrated in the table below from Dr. Shah's review (page 23).

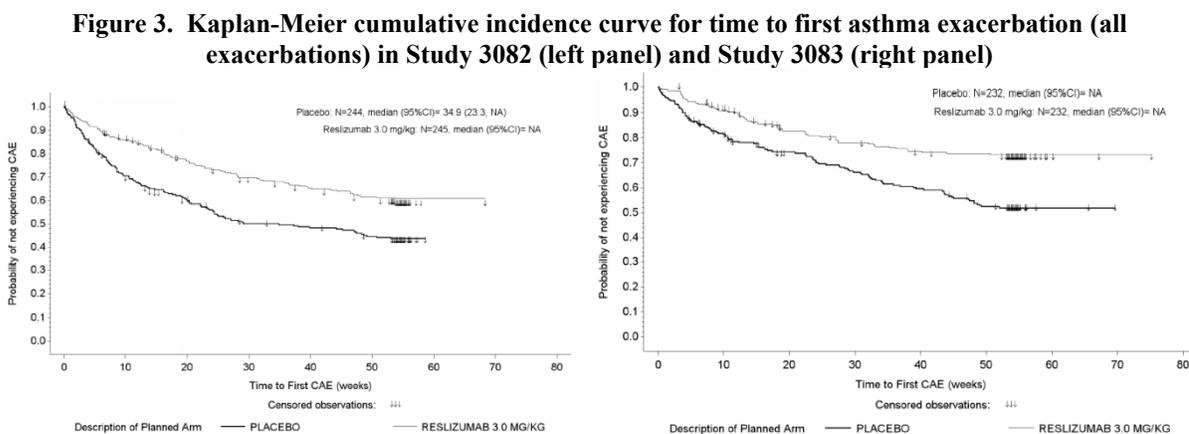
Table 3. Asthma exacerbation frequency by treatment group over 52 weeks, Studies 3082 and 3083

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	
<p>* 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.</p> <p>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.</p>				

The majority of patients (>80%) experiencing 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 having a moderate exacerbation. Rates of exacerbations leading to ED visit or hospitalization, generally classified as severe exacerbations, were low trending favorably for reslizumab.

Kaplan-Meier analysis of time-to-first exacerbation also showed a beneficial response for reslizumab-treated groups compared to placebo in both the studies as demonstrated in Figure 3 from Dr. Shah's review (page 24).



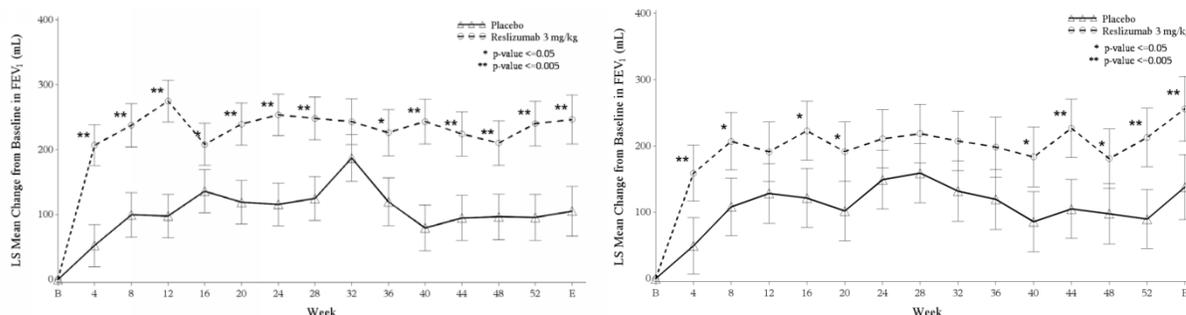
Spirometry was also conducted and is demonstrated in the table and figure below from Dr. Shah's review (page 25).

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	0.101	0.090	0.123

		(0.030, 0.155)	(0.023, 0.179)	(0.026, 0.153)	(0.047, 0.199)
Study 3084	Reslizumab 3 mg/kg IV	0.076	0.050	Not Available	Not Available
		(-0.006, 0.158)	(-0.030, 0.165)		

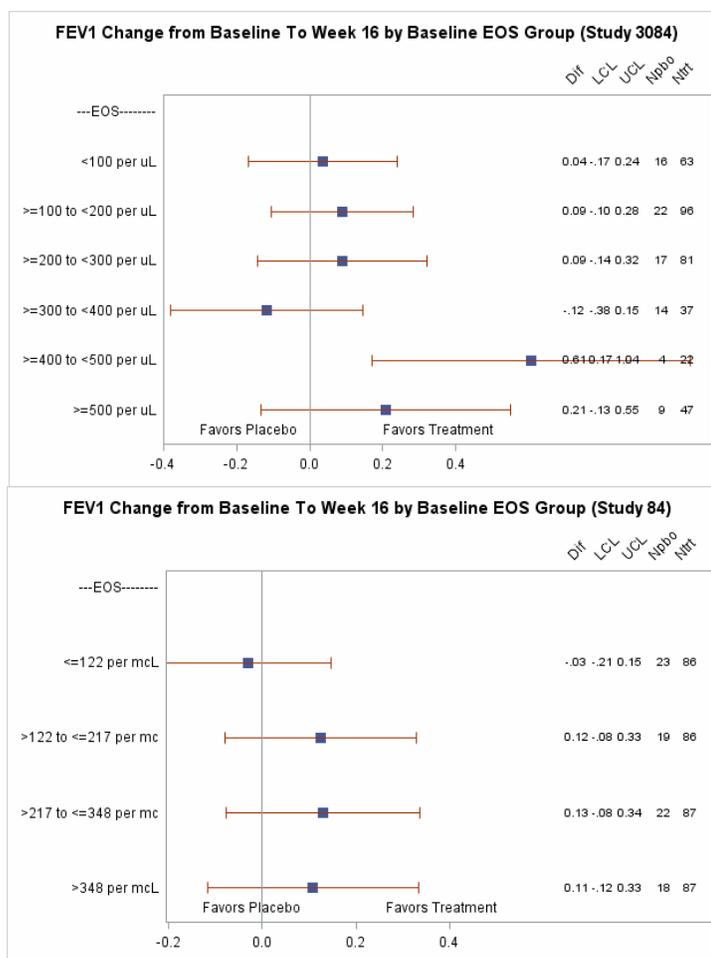
Figure 4. Mean change from baseline (\pm standard error) in FEV₁ to each visit in Study 3082 (left panel) and Study 3083 (right panel).



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

Study 3084 was designed to test the interaction between FEV₁ change and baseline eosinophil counts and included patients without regard for baseline blood eosinophil counts. The linear regression model failed to show a significant overall interaction. Further evaluation based on subgroups also did not demonstrate an apparent relationship (Dr. Shah's review, page 27).

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



Source: Biostatistical Reviewer, Lan Zeng

Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ) were used in the program and as outlined in the clinical reviews demonstrated supportive evidence of patient-perceived benefit.

Efficacy analyses of subgroups did not demonstrate efficacy in those less than 18 years old. The numbers for this group were very small, so it is difficult to know if this is a chance finding or if this group would react differently for some yet to be discovered reason.

The reviewers note that there was not adequate or ideal dose-ranging for this application. This could be an issue when considering the overall benefit to safety consideration if the drug demonstrated a severe adverse event that may be related to the dose; however, the submitted trials demonstrate a consistent overall effect for reduction in exacerbations in those with severe asthma for the dose used.³ The point estimate in the small subgroup of adolescents aged 12 to 17 years old demonstrated an apparent increase in exacerbations (with wide confidence margins) even though there did not appear to be any notable differences between the overall

³ The 0.3 mg/kg dose also demonstrated improvement in FEV1 indicating it would not be unreasonable to speculate that this dose would probably also be effective.

patient population and pediatric patients. Therefore, reslizumab has demonstrated substantial evidence of effectiveness for those with severe asthma 18 years of age and older.

Safety

Overall 2187 patients were exposed to at least one dose of reslizumab, with 1189 exposed for more than six months and 922 exposed for more than twelve months. Most of the common adverse events were what would be expected from a biologic product and were similar to those expressed in the mepolizumab package. There were however more cases of anaphylaxis than one might expect for the size of the program and there also were elevations in CPK.⁴

Allergic reactions including anaphylaxis are an expected risk with biological agents. There were four cases identified in the reslizumab treatment group compared to one in a placebo patient. This is particularly of interest in this case because reslizumab is produced in a murine cell line NSO which is known to cause inclusion of a blood group oligosaccharide, galactose-alpha-1,3-galactose, known as alpha-gal⁵ and reslizumab does contain alpha-gal. Alpha-gal, depending upon where it is located on the antibody, is hypothesized to lead to sensitization which may result in IgE antibody reactions. This theory has been put forth to explain the anaphylaxis that is demonstrated with cetuximab and also with regional variability that is seen for anaphylaxis with cetuximab use.⁶ While it is still an open question regarding the role of alpha-gal and anaphylaxis in general, and for reslizumab, the sponsor has analyzed sera from the four patients experiencing anaphylaxis and report negative findings for anti-alpha-gal IgE antibodies. If confirmed, it is unlikely that alpha-gal plays a role in this finding, however it remains that there are more cases than one would expect for this size of program compared to other biologic products on the market.

Reslizumab use was associated with an ill-defined muscle toxicity and there was a higher incidence of elevation in CPK in the group receiving the agent (18% compared to 14%). Elevations of CPK >10x ULN were also elevated (0.8% vs 0.4%). No patients experienced renal failure or other permanent sequelae.

Advisory Committee Meeting

An Advisory Committee meeting was held on December 9, 2015. The committee voted 11 yes, 3 no for approval of reslizumab in adults > 18 years of age and 0 yes, 14 no for approval in adolescents 12 to 17 years of age.

2. Conclusions and Recommendations

⁴ Post infusion timed recording of events of interest, including vital signs, were also not routinely recorded on the database and the anaphylaxis cases identified and reported were only those reported by investigators. Therefore accurate rate estimates are not possible.

⁵ Li F, Vijayasankaran N, Shen AY, Kiss R, Amanullah A. Cell culture processes for monoclonal antibody production. *MAbs* 2010; 2: 466-479.

⁶ Please read Drs. Shah and Chowdhury's reviews for a thorough discussion of this topic.

Reslizumab has clearly demonstrated efficacy at the dose chosen for those 18 years of age and above. This is important as the population in question periodically (or continually in some cases) requires oral corticosteroid use which carries with it a host of adverse sequelae. Therefore other options are greatly needed in this population. The dose selected for testing also demonstrated two adverse events (anaphylaxis and CPK elevations) that perhaps would have had decreased rates at lower doses. It would have been prudent on the part of the sponsor to include other doses, to see if there was a 'sweet spot' where the balance of efficacy and safety were optimal. But this was not done, so we must make a determination on the data before us, not the data we wish were generated.

Although there is an anaphylaxis risk, this drug is given by IV infusion under observation by health care provider that will be experienced in dealing with these types of reactions. I believe that the efficacy to safety considerations allow for marketing of this product for this very sick population and therefore this application should receive an approval action with appropriate labeling.

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/s/

CURTIS J ROSEBRAUGH
03/23/2016