CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761033
PDUFA Goal Date	March 30, 2016
OSE RCM #	2015-1252
Reviewer Name(s)	Jasminder Kumar, PharmD
DRISK Team Leader	Jamie Wilkins Parker, PharmD
Acting Deputy Director	Kellie Taylor, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	February 24, 2016
Subject	To determine if a REMS is necessary for reslizumab
Established Name	reslizumab
(Proposed) Trade Name	Cinqair
Applicant	Teva Branded Pharmaceutical Products, R&D, Inc.
Therapeutic Class	Anti-interleukin 5 (IL-5) antibody, Single-use vials (10 mL/100 mg) for intravenous infusion
Formulation(s)	
Dosing Regimen	3 mg/kg every 4 weeks administered as a 20-50 minute intravenous infusion
Proposed Indication(s)	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

***** This document contains proprietary information that cannot be released to the public*****

Reference ID: 3891793

Table of Contents

1 Introduction 3

2 Background 3

2.1 Product Information 3

2.2 Regulatory History 3

3 Therapeutic Context and Treatment Options 4

3.2 Description of Current Treatment Options 5

4 Benefit Assessment 5

5 Risk Assessment & Safe Use Conditions 7

Anaphylaxis 7

Malignancy 8

Muscle Toxicity 9

6 Expected Postmarket Use 9

7 Discussion of Need for a REMS 9

8 Risk Management Activities Proposed by the Applicant 10

9 Conclusion & Recommendations 11

Reference ID: 3891793

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Cinqair (reslizumab) is necessary to ensure the benefits of this product outweigh its risks. Teva Branded Pharmaceutical Products, R&D, Inc. (Teva) submitted a Biologic Licensing Application (BLA 761033) to the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) for reslizumab with the proposed indication to reduce exacerbations, relieve symptoms and improve lung function in adults and adolescents (12 years of age and above) with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids. The Applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 Product Information

Reslizumab is an humanized IgG4κ monoclonal antibody that targets interleukin 5 (IL-5). Teva's original proposed indication is to reduce exacerbations, relieve symptoms and improve lung function in adults and adolescents (12 years of age and above) with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids. Reslizumab binds specifically to IL-5 and interferes with IL-5 binding to its cell-surface receptor. IL-5 is a key cytokine responsible for the differentiation, maturation, recruitment, and activation of human eosinophils. IL-5, therefore, plays a key role in the pathophysiology of eosinophilic inflammation in the lung in patients with asthma. Eosinophilic inflammation that persists despite treatment with inhaled corticosteroids defines the eosinophilic asthma phenotype.

The proposed dosing for reslizumab is 3 mg/kg every 4 weeks. Reslizumab is for intravenous (IV) infusion only, administered over 20-50 minutes. Reslizumab is supplied as a liquid solution in a single-use vial (100mg/10mL) and should be prepared by a healthcare professional (HCP) using aseptic technique. The time between preparation of reslizumab and administration should not exceed 16 hours. Patients should be monitored during and for an appropriate time after administration of reslizumab due to the risk of anaphylaxis. Use with caution in patients at high risk of helminth infection, particularly when traveling to areas where helminth infections are prevalent. Reslizumab is contraindicated in patients with known hypersensitivity to reslizumab or any of its excipients.

Reslizumab is not currently licensed in any jurisdiction, at the time of this review.

2.2 Regulatory History

The following is a summary of the regulatory history for BLA 761033 relevant to this review:

- 03/30/2015: The Agency received a BLA submission for reslizumab. The submission did not include a proposed REMS or risk management plan.

Reference ID: 3891793

- 09/08/2015: A Mid-Cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, a REMS was not needed for reslizumab, at this time.
- 11/23/2015: A Late-Cycle Meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that no issues related to risk management have been identified to date.
- 12/09/2015: A Pulmonary-Allergy Drugs Advisory Committee Meeting was held to discuss the safety and efficacy of reslizumab. The committee voted 13 to 1 in favor that the efficacy data provided substantial evidence of a clinically meaningful benefit of reslizumab 3 mg/kg IV once every 4 weeks for the treatment of asthma in adults, 18 years and older but voted 14-0 against efficacy in children 12-17 years of age. The committee voted 11 to 3 that reslizumab's safety profile supported approval. Overall, the Committee voted 11-3 that the efficacy and safety data support approval of reslizumab 3 mg/kg intravenous every four weeks for treatment of asthma patients age 18 years and older.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Asthma is a chronic inflammatory disease of the airways that affects approximately 25.7 million people in the United States, including 7 million children under the age of 18.[1] Airway inflammation contributes to airway hyperresponsiveness, airflow limitation, respiratory symptoms, and disease chronicity. The National Institutes of Health, National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3 (EPR3), describe asthma as a disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T-lymphocytes, macrophages, neutrophils, and epithelial cells. This inflammation can also cause recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, especially at night or in the early morning. Episodes may be associated with variable airflow obstruction that is reversible either spontaneously or with treatment. However, airway obstruction in asthma may become irreversible.[2] Asthma prevalence has increased from 3.1% in 1980 to 5.5% in 1996 and 7.3% in 2001 to 8.4% in 2010 and is more likely to occur in Blacks when compared to both Whites and Hispanics, females, and in those with a lower annual household

[1] Centers for Disease Control and Prevention: National Center for Health Statistics, National Health Interview Survey Raw Data, 2009. Analysis by the American Lung Association Research and Program Services Division using SPSS and SUDAAN software.

[2] National Institutes of Health, National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program. Full Report of the Expert Panel: Guidelines for the Diagnosis and Management of Asthma (EPR-3). July 2007, http://www.nhlbi.nih.gov/guidelines/asthma.

Reference ID: 3891793

income.[3] Asthma related costs include both direct health care costs, as well as indirect costs (e.g. lost productivity).

3.2 Description of Current Treatment Options

The severity of asthma is classified by using domains of current impairment and future risk, which includes symptoms, use of a short-acting-beta2-agonist (SABA) for quick relief, exacerbations, and pulmonary functions. Severe asthma affects less than 10% of patients with asthma. The goals of asthma treatment include improving quality of life for people who have asthma in addition to controlling symptoms, reducing the risk of exacerbations, and preventing asthma-related death. The majority of patients with asthma can be adequately controlled by following a step-wise treatment approach.

However, a minority of patients experience uncontrolled asthma despite attempts to control their disease using the step-wise treatment recommendations. Treatment options for patients with severe asthma as limited to oral corticosteroids or anti-IgE. Newer therapies have focused on interrupting the inflammatory processes that play a central role in the pathophysiology of asthma. Xolair (omalizumab) is a recombinant humanized monoclonal antibody (IgG1) that inhibits the binding of IgE to the high-affinity IgE receptor (FcεR1) on the surface of mast cells and basophils, resulting in receptor down regulation and inhibition of inflammatory mediator release.

One subset of asthma patients that is most likely to benefit from specific anti-inflammatory therapies is characterized by increased numbers of eosinophils in their airways. Interleukin-5 (IL-5) plays a large role in promoting eosinophil growth and activation in the tissues. IL-5 targets may contribute to reducing eosinophil maturation, migration, and survival. FDA recently approved Nucala (mepolizumab) on November 4, 2015 indicated for add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. Severe eosinophilic asthma is a chronic condition with few therapeutic options, and reslizumab, if approved, may provide another treatment for these patients.

4 Benefit Assessment

The safety and efficacy of reslizumab were evaluated in four randomized, double-blind, placebo-controlled, parallel-group, Phase 3 clinical studies in patients aged 12-75 years old, or 18-65 years old (in Study 3084) and one Phase 2 supportive study in patients with poorly controlled, active eosinophilic asthma (Res-5-0010, N=106). The Phase 3 studies included: a 16-week (Study 3081, N=315) dose-ranging lung function study that evaluated the efficacy of reslizumab 0.3 mg/kg or 3 mg/kg in patients with eosinophilic asthma, two 52-week replicate exacerbation studies (Study 3082, (N=489) and Study 3083, (N=464)) that evaluated reslizumab 3 mg/kg in the reduction of clinical asthma exacerbation, and a 16-week lung function study (Study 3084, (N=496)) that evaluated reslizumab

[3] CDC National Center for Health Statistics, National Health Interview Survey (NHIS) National Surveillance of Asthma: United States, 2001-2010.

Reference ID: 3891793

3 mg/kg in patients with moderate to severe asthma. Patients in Study 3081, Study 3082, and Study 2083 had a baseline blood eosinophil count ≥400 cells/µL, but patients in Study 3084 were unselected for baseline eosinophil levels. In addition, there is an ongoing open-label extension (OLE) study (Study 3085) aimed to evaluate the long term safety and efficacy of reslizumab 3mg/kg in patients with eosinophilic asthma.

The primary endpoint in Studies 3081 and 3084 was overall change from baseline in trough forced expiratory volume in one second (FEV_1) to week 16. In Studies 3082 and 3083 the primary endpoint was frequency of asthma exacerbation per patient during the 52-week treatment period. The primary objective of Study Res-5-0010 was to demonstrate the ability of reslizumab treatment to improve asthma control in patients with active asthma and eosinophilic airway inflammation, by change from baseline to end of treatment in Asthma Control Questionnaire (ACQ) score.

In Study 3081, there was a significant improvement in FEV_1 for patients in the reslizumab treatment group compared to the placebo group, with the change in FEV_1 0.126 L, 0.242 L, and 0.286 L for patients in the placebo group, reslizumab 0.3 mg/kg, and reslizumab 3 mg/kg groups, respectively. The treatment effect was larger for patients in the reslizumab 3 mg/kg treatment group (treatment difference=0.160L, p=0.0018) than for patients in the reslizumab 0.3 mg/kg treatment group (treatment difference=0.115L, p=0.0237). Study 3081 was the only study to include dose ranging, but only included two doses, and all other phase 3 trials were initiated prior to the results of Study 3081. The clinical reviewer notes that the lack of dose-ranging data is a limitation of the reslizumab program, especially because the reslizumab 0.3 mg/kg dose showed statistical significance of efficacy.[4]

Patients in Studies 3082 and Study 3083 demonstrated a statistically significant reduction in exacerbation rate compared with those in the placebo treatment group (50%, p<0.0001 and 59% reduction, p<0.0001, respectively). Of note, randomization of patients was stratified by maintenance oral corticosteroid use and region, but was misclassified and resulted in a greater number of patients taking maintenance oral corticosteroids in the placebo arm of Study 3082, and in the overall placebo arm of the safety population, described in Section 5. The clinical reviewer notes that sensitivity analyses were robust to the imbalance, making this misclassification less relevant to the efficacy discussion.[4]

In Study 3084 there were clinically meaningful improvements in FEV_1 in patients with baseline blood eosinophil counts ≥400 cells/µL (least squares (LS) mean difference at week 16=0.270 L, p=0.0436), but only small improvements in patients with a blood eosinophil count <400 cell/µL as a group (LS mean difference at week 16=0.033 L). However, the clinical reviewer notes that interpretation of the results in the >400 cells/µL group is limited due to the small sample size and the study was not designed to test this group of patients. [4]

In the supportive study, R-5-0010, the reduction in ACQ score at the end of treatment was numerically greater in reslizumab-treated patients with higher blood eosinophil levels (>500 cells/µL) at baseline (p=-.0720) compared with patients with lower blood eosinophils levels at baseline (p=0.8039). A

[4] Donohue KM. DPARP. Clinical Review for reslizumab, BLA 761033, dated December 17, 2015.

Reference ID: 3891793

treatment effect on the frequency of asthma exacerbations was not observed in the following subgroups: patients aged 12-17 years, patients who were black, and patients from the United States (U.S.). Inconsistent results may have been related to the small size of the subgroups.

5 Risk Assessment & Safe Use Conditions

The Safety Analysis Set for reslizumab included patients who received at least one dose of study drug in controlled studies (Studies 3081, 3082, 3083, 3084, and Res-5-0010), through 52 weeks (N=1861). Information from the eosinophilic esophagitis (EoE) program also helped inform the safety profile of reslizumab. Data from the open-label extension, Study 3085, was not included in this safety population and was reviewed separately. In the Safety Analysis Set, the adverse events occurring in ≥1% of patients in the reslizumab 3mg/kg treatment group that occurred more frequently than in the placebo group included: urinary tract infection, oropharyngeal pain, blood creatinine phosphokinase increased, and nasal congestion.

There were three deaths during the Study 3085 and one additional death in the placebo arm of Study 3082. No deaths were considered related to the study drug by the Investigator and clinical reviewer.[5] Serious adverse events (SAEs) were generally uncommon and occurred more frequently in the placebo arm compared to the reslizumab arm (9% vs. 6%, respectively). SAEs that were reported by more than one patient in the reslizumab group and not in the placebo group included chest pain, anaphylaxis reactions, and falls. Asthma, anaphylaxis, and muscle pain/creatine phosphokinase (CPK) elevations were the only adverse events that led to treatment discontinuation in >2 patients in the reslizumab 3mg/kg arm. In addition, during the reslizumab clinical trials, cases of malignancy were reported, with a numerical imbalance between those arising in the reslizumab-treated groups compared with control groups.

In comparison to mepolizumab, another IL-5 antagonist monoclonal antibody indicated for add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype, reslizumab has unique safety signals associated with its use including anaphylaxis, muscle toxicity, and malignancy.

Although anaphylaxis is a known risk associated with monoclonal antibodies, anaphylaxis was considered an adverse event of special interest (AESI) with reslizumab due to the frequency with which is occurred in reslizumab controlled trials. In addition, muscle toxicity/CPK elevations and malignancy were considered AESIs. These AESIs will be described in further detail in the sections below.

ANAPHYLAXIS

Compared to placebo, reslizumab was associated with higher rates of anaphylaxis (3 cases versus 0 in reslizumab and placebo arms, respectively). In the EoE program, 7 patients experienced anaphylaxis in the reslizumab arm and 1 in the placebo arm, with 1 additional potential case identified by the clinical

[5] Donohue KM. DPARP. Clinical Review for reslizumab, BLA 761033, dated December 17, 2015.

Reference ID: 3891793

reviewer. The imbalance in the EoE program may be due to the randomization scheme, and all were considered related to previously known food allergies by the investigator. However, the clinical reviewer notes one case from the EoE studies may be drug related given the timing and discontinuation of study drug. Overall, a higher rate of anaphylaxis was observed in patients treated with reslizumab, compared to those treated with placebo.

Of note, the Applicant did not prospectively look for anaphylaxis. Based on the occurrence of anaphylaxis in the reslizumab clinical program, the Agency requested that the Applicant have an independent committee adjudicate the subset of anaphylaxis cases with onset of reaction within 24 hours of study drug administration using the NIAID/FAAN criteria. The adjudication committee identified 4 events in 4 patients, one of which occurred in the placebo arm. Among the 3 cases that occurred in in the reslizumab-treated patients and were adjudicated as anaphylaxis by the committee, 2 were previously reported by the investigators as anaphylactic reactions and 1 case was a new, previously unreported case. However, the Agency noted during the Late-Cycle meeting, that the anaphylaxis adjudication the Applicant performed utilizing a blinded adjudication committee would not change the assessment performed by the investigators.

Of the total four cases of anaphylaxis, 2 cases occurred after the 2nd and 2 cases occurred after the 12th infusion of reslizumab. The Applicant stated that 3 cases of anaphylaxis occurred in the clinic and resolved, after a few hours.[6] Although anaphylaxis is a known risk for monoclonal anitbodies, it is rare to observe four cases of anaphylaxis in a clinical trials database as was seen in the reslizumab program.[7] Based on the data seen related to the risk of anaphylaxis, the Division recommends a Boxed Warning for inclusion of the risk in the reslizumab label.

MALIGNANCY

Reslizumab is an immunomodulator, and therefore malignancy is an AESI. There were 23 cases of malignancy observed, in 19 patients, in the reslizumab development program, 8 in controlled trials, and 15 in the open-label extension trial. Of the 8 patients in the controlled trials, there were 6 patients that experienced malignancy in the reslizumab 3 mg/kg group and 2 patients in the placebo group. Overall, the incidence of malignancy was higher for the reslizumab group (0.6%) compared to placebo (0.3%) in the controlled studies, and higher than the National Cancer Institute's Surveillance, Epidemiology, and End Results database. Of note, patients with a history of malignancy were not excluded from clinical trials, and 4 of the 19 reslizumab treated patients with malignancy had a history of prior malignancy. In addition, the clinical reviewer notes, preclinical studies did not raise concern for mutagenicity or carcinogenicity. DPARP recommends that the risk of malignancy be included in the Warnings and Precautions section of the product labeling.

[6] Teva. Sponsor Late Cycle Meeting Minutes, BLA 761033, submitted December 2, 2015 (eCTD Sequence No. 0031).

[7] Donohue KM. DPARP. Clinical Review for reslizumab, BLA 761033, dated December 17, 2015.

MUSCLE TOXICITY

Reslizumab was associated with a higher frequency of mild to moderate myalgia events compared to placebo (1% vs. 0.5%). CPK elevations >5x upper limit of normal (ULN) occurred more frequently during reslizumab 3 mg/kg treatment compared with placebo (2% vs. 1%, respectively). Grade 4 CPK elevations (>10x ULN), were observed more frequently with reslizumab versus placebo (0.8% vs. 0.4%, respectively) during routine laboratory assessments. These elevations were generally transient and did not result in treatment discontinuation. In addition, the incidence of muscle complaints within 24 hours of infusion was higher in the reslizumab-treated patients (2.2% vs. 1.5%, respectively). Overall, the clinical reviewer notes that although there was a numerical imbalance in CPK elevations, none progressed to rhabdomyolysis with acute renal failure, and many experienced a return of their CPK to baseline with continued reslizumab therapy.[8] Of note, about half of these patients presented with elevated baseline CPK levels, and median CPK levels did not increase over time.

6 Expected Postmarket Use

Reslizumab is provided as a liquid solution in a single-use vial for IV infusion only. It should be prepared by a HCP and administered as a 20-50 minute IV infusion. If approved, reslizumab is likely to be used by pulmonologists, reserved for patients who are inadequately controlled on inhaled corticosteroids.

Because of the risk of anaphylaxis, reslizumab should only be administered in a healthcare setting by HCPs who are prepared to manage anaphylaxis, which can be life-threatening. HCPs should observe patients closely for an appropriate period of time after administration of reslizumab. The appropriate monitoring period should take into account the time to onset of anaphylaxis seen in the reslizumab pre-marketing clinical trials and consider other drugs in the class, such as omalizumab, given that data from the reslizumab clinical trials is limited. At the time of this review, labeling negations are currently in progress and details of monitoring have not been finalized. However, DPARP recommends that Dosage and Administration be consistent with omalizumab regarding monitoring and preparation to treat anaphylaxis.[8]

7 Discussion of Need for a REMS

Based on results of the Phase 3 trials, reslizumab was found to be efficacious versus placebo as add-on maintenance treatment of patients with severe asthma aged 18 years and older, and with an eosinophilic phenotype. During the December 9, 2015 Pulmonary-Allergy Drugs Advisory Committee Meeting panelists voted against approval for use in adolescents 12-17 years of age.

The AESIs with reslizumab were anaphylaxis, malignancy, and muscle toxicity. Although anaphylaxis is a known risk with biologics, the frequency with which it occurred with reslizumab may be high relative to other biologics, and will be communicated in a Boxed Warning to inform HCPs of this risk. The Boxed

[8] Donohue KM. DPARP. Clinical Review for reslizumab, BLA 761033, dated December 17, 2015.

Warning communicates the importance of observing patients for an appropriate period of time after administration and informs patients of the signs and symptoms of anaphylaxis.

Because reslizumab is an immunomodulator, malignancy was also AESI. Malignancy was also noted with a higher incidence with reslizumab relative to placebo and national cancer registries. Although preclinical studies did not raise a concern for mutagenicity or carcinogenicity, given the observed cases in controlled study and in the OLE, this risk is proposed to be included in the Warnings and Precautions section of labeling. The observations are consistent with omalizumab, another monoclonal antibody, and the proposed labeling approach is consistent with this other product.

Although CPK elevations and a higher frequency of myalgia were observed with reslizumab, the cases were generally transient in nature and the majority did not result in discontinuation of medication. Patients with CPK elevations were also generally asymptomatic. Although there is an imbalance with CPK elevations in patients on reslizumab, none progressed to rhabdomyolysis with acute renal failure, many had their CPK return to baseline, and the majority of patients continued on study drug. Therefore, labeling does not include any Warnings and Precautions regarding the risk of muscle toxicity at this time, but has been proposed to be included as part of the clinical trial experience section.

Overall, the most likely prescribers of reslizumab are specialists who are familiar with the management of severe asthma, frequently monitor patients, and understand the risks of treatment. Specifically the risks of anaphylaxis and malignancy are well-established and known to occur with immunomodulators . Reslizumab is also proposed for IV infusion administration by a HCP. Therefore, a Boxed Warning and as well as a Warnings and Precautions section will be used to communicate the risks described above. After considering DPARP's review of efficacy and safety DRISK does not recommend a REMS as necessary to ensure the benefits of reslizumab outweigh the risks. Severe eosinophilic asthma is a chronic condition with few therapeutic options, and reslizumab, if approved, may provide another treatment option.

8 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for reslizumab beyond labeling and routine pharmacovigilance.

Teva states that based on evaluation of the safety profile of reslizumab 3 mg/kg administration in patients with asthma and elevated blood eosinophils, they believe that the full prescribing information and routine pharmacovigilance would be sufficient to maintain a positive benefit/risk balance of reslizumab treatment in this patient population. Consistent with other recently approved biologics, Teva includes a Medication Guide, as a component of the labeling, to communicate the identified risks and appropriate use of reslizumab. Although labeling negotiations are ongoing, at the time of this review, the Division recommends a Boxed Warning for inclusion of the risk of anaphylaxis in the reslizumab label.

9 Conclusion & Recommendations

Based on the available data, the risk mitigation measures beyond professional labeling are not warranted for reslizumab and a REMS is not necessary to ensure the benefits outweigh the risks. In general, HCPs who treat moderate to severe asthma with monoclonal antibodies are familiar with the risk of anaphylaxis and the importance of patient monitoring.

Should DPARP have any concerns or questions, or feel that a REMS is warranted for this product, or if new safety information becomes available, please send a consult to DRISK.

10 Appendices

MATERIALS REVIEWED

- Teva Pharmaceutical Industries, Ltd. Clinical Overview for reslizumab, dated March 30, 2015.
- Teva Pharmaceutical Industries, Ltd. Summary of Clinical Safety for reslizumab, dated March 30, 2015.
- Teva Pharmaceutical Industries, Ltd. Summary of Clinical Efficacy for reslizumab, dated March 30, 2015.
- Teva Pharmaceutical Industries, Ltd. Proposed Prescribing Information for reslizumab, dated March 30, 2015, updated January 4, 2016, and February 17, 2016.
- Donohue KM. DPARP. Clinical Review for reslizumab, BLA 761033, dated December 17, 2015.
- Karimi-Shah, BA. DPARP. Cross-Discipline Team Leader Review for reslizumab, BLA 761033, dated December 30, 2015.

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/s/

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02/24/2016

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