Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Pulmonary-Allergy Drugs Advisory Committee Meeting

December 9, 2015

Location: FDA White Oak Campus, Building 31 Conference Center, The Great Room (Rm. 1503), Silver Spring, Maryland

Topic: The committee discussed biologics license application 761033, reslizumab for injection, submitted by Teva Pharmaceutical Industries, Ltd., for the proposed indication to reduce exacerbations, relieve symptoms, and improve lung function in adults and adolescents 12 years of age and above, with asthma and elevated blood eosinophils, who are inadequately controlled on inhaled corticosteroids.

These summary minutes for the December 9, 2015 meeting of the Pulmonary-Allergy Drugs Advisory Committee of the Food and Drug Administration were approved on __January 11, 2016_____.

I certify that I attended the December 9, 2015 meeting of the Pulmonary-Allergy Drugs Advisory Committee and that these minutes accurately reflect what transpired.

_____/s/_____
Cindy Hong, PharmD
Designated Federal Officer
Pulmonary-Allergy Drugs
Advisory Committee (PADAC)

_____/s/_____
Dennis Ownby, MD
Chairperson, PADAC

Summary Minutes of the Pulmonary-Allergy Drugs Advisory Committee Meeting
December 9, 2015

The following is a final report of the meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) held on December 9, 2015. A verbatim transcript will be available in approximately six weeks, sent to the Division of Pulmonary, Allergy, and Rheumatology Products and posted on the FDA website at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/ucm433815.htm

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Pulmonary-Allergy Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on December 9, 2015 at the FDA White Oak Campus, Building 31 Conference Center, The Great Room (Rm. 1503), Silver Spring, Maryland. Prior to the meeting, members and temporary voting members were provided copies of the background material from the FDA and Teva Pharmaceuticals Industries, Ltd. The meeting was called to order by Dennis Ownby, MD (Chairperson). The conflict of interest statement was read into the record by Cindy Hong, PharmD (Designated Federal Officer). There were approximately 180 people in attendance. There were no Open Public Hearing speakers.

Issue: The committee discussed biologics license application 761033, reslizumab for injection, submitted by Teva Pharmaceutical Industries, Ltd., for the proposed indication to reduce exacerbations, relieve symptoms, and improve lung function in adults and adolescents 12 years of age and above, with asthma and elevated blood eosinophils, who are inadequately controlled on inhaled corticosteroids.

Attendance:
PADAC Members Present (Voting): John E. Connett, PhD; Steve N. Georas, MD; Elaine H. Morrato, DrPH, MPH; Dennis R. Ownby, MD (Chairperson); James M. Tracy, DO; Richard Weber, MD; Yanling Yu, MS, PhD (Consumer Representative)

PADAC Members Not Present (Voting): Mitchell H. Grayson, MD; Michelle S. Harkins, MD, FCCP; Nizar N. Jarjour, MD; Francis X. McCormack, MD

Temporary Members (Voting): Erica Brittain, PhD; Mark Dykewicz, MD; Paul A. Greenberger, MD; Andrea Holka (Patient Representative); Thomas Platt-Mills, MD, PhD, FRS; James K. Stoller, MD, MS; Judith A. Voynow, MD

Acting Industry Representative to the Committee (Non-voting): Jack Cook, PhD

FDA Participants (Non-Voting): Badrul Chowdhury, MD, PhD; Kathleen Donohue, MD; Banu Karimi-Shah, MD; João Pedras-Vasconcelos, PhD; Curtis Rosebraugh, MD; Lan Zeng, MS

Designated Federal Officer (Non-Voting): Cindy Hong, PharmD

Open Public Hearing Speakers: None

***The agenda proceeded as follows*:**

Call to Order and Introduction of Committee	**Dennis Ownby, MD** Chairperson, PADAC
Conflict of Interest Statement	**Cindy Hong, PharmD** Designated Federal Officer, PADAC
FDA Opening Remarks	**Banu A. Karimi-Shah, MD** Clinical Team Leader Division of Pulmonary, Allergy, Rheumatology Products (DPARP) Office of Drug Evaluation II (ODE II) Office of New Drugs (OND), CDER, FDA
SPONSOR PRESENTATIONS	**Teva Pharmaceuticals**
Introduction	**Tushar Shah, MD** Sr. Vice President Global Respiratory R&D Teva Branded Pharmaceutical Products R&D, Inc.
Clinician's Perspective on Unmet Need	**Mario Castro, MD, MPH, FCCP** Alan A. and Edith L. Wolff Professor of Pulmonology and Critical Care Medicine Professor of Medicine and Pediatrics Washington University School of Medicine in St. Louis
Clinical Efficacy	**James Zangrilli, MD, FACP, FCCP** Senior Director, Clinical Project Lead Teva Branded Pharmaceutical Products R&D, Inc.
Clinical Safety	**Yael Shalit, MD** Director, Global Patient Safety & Pharmacovigilance Teva Branded Pharmaceutical Products R&D, Inc.
Clinician's Perspective	**Mario Castro, MD, MPH, FCCP**
Conclusion	**Tushar Shah, MD**
Clarifying Questions to the Presenters	
BREAK	
FDA PRESENTATIONS	
Overview of the Clinical Program	**Kathleen M. Donohue, MD**

	Clinical Reviewer DPARP, ODE II, OND, CDER, FDA
Statistical Review of Efficacy	**Lan Zeng, MS** Statistical Reviewer Division of Biometrics II (DB II) Office of Translational Sciences (OTS), CDER, FDA
Summary of Safety	**Kathleen Donohue, MD**
Product and Immunogenicity Issues	**João Pedras-Vasconcelos, PhD** Immunogenicity Reviewer Division of Biotechnology Review and Research III Office of Biotechnology Products (OBP) Office of Pharmaceutical Quality (OPQ), CDER, FDA
Risk-Benefit Considerations	**Kathleen Donohue, MD**
Clarifying Questions to the Presenters	
LUNCH	
Open Public Hearing	
Charge to the Committee	**Banu A. Karimi-Shah, MD**
Questions to the Committee/Committee Discussion	
BREAK	
Questions to the Committee/Committee Discussion (cont.)	
ADJOURNMENT	

Questions to the Committee:

1. **DISCUSSION**: Discuss the efficacy data for reslizumab 3 mg/kg IV administered once every 4 weeks to support its use in the treatment of asthma. Consider the following issues in the discussion:
    a) adequacy of the dose ranging data
    b) adequacy of the efficacy data in children 12 to 17 years of age
    c) adequacy of the data in the US population
    d) the role of blood eosinophil counts in determining the target patient population

    Committee Discussion: *The members of the committee commented that they would like to see an analysis of what the blood eosinophil count signifies. The members further commented that there is a lack of data about exacerbation at different doses and that pediatric data is inconsistent and often favors the placebo which is less than compelling. Some members noted that reslizumab does address an unmet need for some patients with severe asthma, but there needs to be better dose ranging data. Members also commented*

on the inadequate number of U.S.patients in the reslizumab studies. In addition, the concern over lack of data in African American patient population was also expressed. Please see the transcript for details of the committee discussion.

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

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

      YES=13 **NO=1** **ABSTAIN=0**

   Committee Discussion: *The majority of the committee voted that the efficacy data do provide 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 of age and older. The committee members voting "Yes" commented on the benefit of FEV1 and stated that primary efficacy endpoints were met. The committee member voting "No" commented on the inadequate U.S. efficacy data. Please see the transcript for details of the committee discussion.*

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

      YES=0 **NO=14** **ABSTAIN=0**

   Committee Discussion: *The committee members unanimously agreed that the efficacy data does not provide substantial evidence of a clinically meaningful benefit of reslizumab 3 mg/kg IV once every 4 weeks for the treatment of asthma in children 12 – 17 years of age. Members commented that the study in this age group did not meet the primary outcome. It was noted that the study results favored the placebo and was not compelling. Please see the transcript for details of the committee discussion.*

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

   Committee Discussion: *Committee members commented that the sponsor adequately demonstrated that the anaphylaxis events were not due to alpha gal, but noted that the dose response cannot be excluded as the unknown mechanism of the anaphylaxis. A committee member also noted the difficulty in adequately assessing the safety of the drug due to the small sample size of the study. Another committee member noted the importance of vigilance of muscle toxicity which was higher in the treatment group. Please see the transcript for details of the committee discussion.*

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

   YES=11 **NO=3** **ABSTAIN=0**

   Committee Discussion: *The majority of the committee voted that the safety profile of reslizumab 3 mg/kg IV administered once every 4 weeks is adequate to support approval for patients with asthma. The committee members voting "Yes" commented that the presence of safety issues is obvious, but it would not preclude from approval of the drug. It was also noted that CPK elevation did not persist with repeated dosing of reslizumab and the malignancy signals were comparable with other biologics, but there should be post marketing surveillance. The committee member voting "No" commented that the safety data is insufficient in children and the unexplained CPK elevation led to the "No" vote. Please see the transcript for details of the committee discussion.*

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

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

      YES=11 **NO=3** **ABSTAIN=0**

      Committee Discussion: *The majority of the committee agreed that the efficacy and safety data support approval of reslizumab 3 mg/kg IV every 4 weeks for the treatment of patients with asthma in adults 18 years of age and older. The committee members voting, "Yes," commented that unmet need would be addressed for patients with the approval of the drug. The committee members voting "No" emphasized the need for post-marketing surveillance. Please see the transcript for details of the committee discussion.*

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

      YES=0 **NO=14** **ABSTAIN=0**

      Committee Discussion: *The committee members unanimously agreed that the efficacy and safety data do not support approval of reslizumab 3 mg/kg IV every 4 weeks for the treatment of patients with asthma in children 12 – 17 years of age. Members commented on the lack of efficacy in this age group and the safety issues. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 3:45 p.m.