Summary Minutes of the
Pulmonary-Allergy Drugs Advisory Committee (PADAC)
FDA White Oak Campus, the Great Room, White Oak Conference Center
Silver Spring, Maryland

March 8, 2011

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

These summary minutes for the Pulmonary-Allergy Drugs Advisory Committee meeting of the Food and Drug Administration were approved on 3/28/11.

I certify that I attended the March 8, 2011 meeting of Pulmonary-Allergy Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

_____/s/_____
Kristine Khuc, Pharm.D.
Designated Federal Officer,
PADAC

_____/s/_____
Peter Terry, M.D.
Acting Committee Chair,
PADAC

FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)
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The Pulmonary-Allergy Drugs Advisory Committee (PADAC) met on March 8, 2011 at the FDA White Oak Campus, the Great Room, White Oak Conference Center, Silver Spring, Maryland. Prior to the meeting, the members and the invited consultants had been provided the background materials from the FDA and Sponsor. The meeting was called to order by Peter Terry, M.D., (Acting Chair); the conflict of interest statement was read into the record by Kristine Khuc, Pharm.D. (Designated Federal Officer). There were approximately 175 persons in attendance. There were three speakers for the Open Public Hearing session.

Attendance:
Pulmonary-Allergy Drugs Advisory Committee Members Present (Voting):
Paul Greenberger, M.D., David Jacoby, M.D., Daren Knoell, Pharm.D., Rodney Mullins (Consumer Representative), Thomas Alexander Platts-Mills, M.D., Ph.D., Carrie Redlich, M.D., Kelly Stone, M.D., Ph.D., Peter Terry, M.D.(Acting Chair), Judith Voynow, M.D.

Pulmonary-Allergy Drugs Advisory Committee Member Present (Non-Voting):
Richard Hubbard, M.D. (Industry Representative)

Special Government Employee Consultants Present (Temporary Voting Members):
Edna Fiore (Patient Representative), Jacqueline Gardner, Ph.D., Charles Mouton, M.D., Ganesh Raghu, M.D., Susan Roberts, Ph.D., Deborah Shatin, Ph.D., Julie Zito, Ph.D.

Regular Government Employee Present (Temporary Voting Member):
Erica Brittain, Ph.D.

FDA Participants Present (Non-Voting):
Badrul Chowdhury, M.D., Ph.D., Anya Harry, M.D., Ph.D., Dongmei Liu, Ph.D., Theresa Michele, M.D., Curtis Rosebraugh, M.D.

Designated Federal Officer:
Kristine Khuc, Pharm.D.

Open Public Hearing Speakers:
Michael Carome, M.D., Public Citizen Health Research Group; Nuala Moore, American Thoracic Society; John Walsh, COPD Foundation

Issue: The Committee discussed new drug application (NDA) 022-383, indacaterol maleate (Arcapta™ Neohaler™) by Novartis Pharmaceuticals Corporation, for the long-term once daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

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The agenda was as follows:

Call to Order at 8:00 a.m. Introduction of Committee	Peter Terry, M.D. Chair (Acting), PADAC
Conflict of Interest Statement	Kristine Khuc, Pharm.D., Designated Federal Officer, PADAC
Opening Remarks	Badrul Chowdhury, M.D., Ph.D. Director, Division of Pulmonary, Allergy, and Rheumatology Products Center for Drug Evaluation and Research (CDER), FDA
Sponsor Presentation	Novartis Pharmaceuticals Corporation
Introduction and Background	Trevor Mundel, M.D., Ph.D. Head of Development Novartis Pharma AG
Perspectives on COPD	James Donohue, M.D. Professor and Chief, Division of Pulmonary and Critical Care Medicine University of North Carolina at Chapel Hill
Dose Selection, Efficacy	David Morris, M.D. Franchise Head, Respiratory Novartis Pharma AG
Safety, Risk Mitigation	Linda Armstrong, M.D. Drug Safety and Epidemiology Novartis Pharmaceuticals Corporation
Benefit-Risk, Clinical Perspective	James Donohue, M.D.
Questions for clarification for Sponsor	
Break	
FDA Presentation	
Overview of Clinical Program and Statistical Perspective – Efficacy	Dongmei Liu, Ph.D. Mathematical Statistician, Division of Biometrics II CDER, FDA

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Clinical Perspective – Safety	Anya Harry, M.D., Ph.D. Medical Officer, Division of Pulmonary, Allergy, and Rheumatology Products CDER, FDA
	Banu Karimi-Shah, M.D. Medical Officer, Division of Pulmonary, Allergy, and Rheumatology Products CDER, FDA
Risk Benefit Discussion	Theresa Michele, M.D. Clinical Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
Questions for Clarification for FDA	
Lunch	
Open Public Hearing	
Continue Questions for Clarification	
Charge to the Committee	Theresa Michele, M.D.
Discussion and Questions	
Break	
Continue Discussion and Questions	
Adjourn	

Questions to Committee:

1. Discuss the efficacy data of indacaterol considering the following
    a) Dosing regimen or dosing frequency
    b) Total daily dose lower than 75 mcg
    c) Are there advantages of 150 mcg once-daily dose over 75 mcg once-daily dose
    d) Claim that 150 mcg once-daily dose improves St. George's Respiratory Questionnaire (SGRQ) considering the totality of the SGRQ data

The committee members discussed that there was data to support a once-daily dosing, which would increase compliance. The pharmacoeconomics of the drug also needs to be explored as pharmacokinetic (PK) data suggests that once-daily and every other day dosing is equivocal. A majority of the committee agreed that the 37.5mcg dose was just as sufficient as the 75mcg dose. The great majority opined that modeling data only gives estimates and the most useful way of looking at data is through head to head comparisons (75mcg versus 150 mcg). Some members noted that there was only a slight indication that the 150mcg was advantageous, but there was no hard evidence. Other committee members did not see any advantages of 150mcg over the 75mcg. A committee member indicated that there was a small indication of better results in the 150mcg versus 75mcg considering the totality of the SGRQ data.

(Please see official transcript for details)

2. Discuss the overall safety profile of indacaterol considering the following
   a) Safety data from asthma studies
   b) Proposed indication specific to chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema
   c) Comparative safety assessment of 75 mcg and 150 mcg dose for balancing safety risk relative to efficacy

The committee members discussed whether the criteria for defining emphysema and chronic bronchitis were clear and appropriate in the context of this study and proposed that a more specific definition would have been helpful. Several committee members remarked that they are concerned about lack of safety data on the 75mcg and felt uneasy about data extrapolation from higher doses. One member felt that there was a concern of adverse events for patients treated for greater than 12 weeks. In addition, a committee member expressed that there was not a safety signal at 150 mcg versus 75 mcg.

(Please see official transcript for details)

3. Considering the totality of the data, has indacaterol demonstrated substantial evidence of efficacy for the long term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema
   a) For the 75 mcg dose? **(Vote)**

YES: 15 **NO: 2** **Abstain: 0**

The overall committee agreed that for the 75mcg dose, the endpoints were met and there are data to support efficacy. The minority of the committee felt that the data was not convincing.

b) For the 150 mcg dose over the 75mcg dose? **(Vote)**

YES: 6 **NO: 11** **Abstain: 0**

The overall committee members who voted "NO" agreed that there was not sufficient or convincing data to support efficacy of 150mcg over 75mcg. Those members also commented that there were no long term head to head comparisons.

The committee members who voted "YES" felt that there was evidence of efficacy from FEV1 and secondary data. One member expressed that additional post-marketing data should be collected.

c) If not, what further data should be obtained? **(Discuss)**

Some members expressed the need to:

- *examine doses with different stages of COPD severity;*
- *perform a head to head comparison trial of 150mcg, 75mcg, and 37.5mcg doses;*
- *conduct a trial with different doses in a homogenous population and heterogenous population;*
- *perform a cross-over study from 75mcg to 150mcg and then perform dose titration;*
- *conduct longer term study (i.e. 3 months);*
- *address inhaled corticosteroid (ICS) use.*

(Please see official transcript for details)

4. Is the safety profile of indacaterol adequate for approval for the long term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema

a) For the 75 mcg dose? **(Vote)**

YES: 12 **NO: 5** **Abstain: 0**

The overall committee members who voted "YES" agreed that there was a nominal safety profile. For the committee members who voted "NO", they expressed concern that there was sparse data with inadequate power and not sufficient long term data.

b) For the 150 mcg dose? **(Vote)**

YES: 11 **NO: 6** **Abstain: 0**

The majority of the committee who voted "YES" felt that the safety profile was adequate. The minority of the members who voted "NO" had concerns that there were no long term data and concerns of a class safety effect among Long-Acting Beta Agonists (LABA).

c) If not, what further data should be obtained? **(Discuss)**

The committee members recommended performing direct comparisons of the 75mcg to 150mcg dose, and conducting studies on appropriate subgroup populations.

(Please see official transcript for details)

5. Does the totality of the data provide substantial evidence to support a claim that indacaterol improves health-related quality of life as measured using St. George's Respiratory Questionnaire (SGRQ)

a) For the 75 mcg dose? **(Vote)**

YES: 10 **NO: 7** **Abstain: 0**

The committee members who voted "YES" felt that the MCID of 4 was met, contributed to the totality of the data, and the responder analysis was successful. Those who voted "NO" expressed that there was no substantial evidence and that there were high data variability.

b) For the 150 mcg dose? **(Vote)**

YES: 13 **NO: 4** **Abstain: 0**

The vast majority of the committee members who voted "YES" agreed that there is a need for more precise data at the higher dose.

The minority of the members who voted "NO" felt that there were insufficient data and did not see improvements in quality of life.

(Please see official transcript for details)

6. Do the efficacy and safety data provide substantial evidence to support approval of indacaterol inhalation powder for the long term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema? **(Vote)**

After a discussion period about this question, the committee was asked to directly vote on this question based on a 75mcg once-daily and a 150mcg once-daily dose.

If yes, should the dose be

a) 75 mcg once-daily? **(Vote)**

YES: 13 **NO: 4** **Abstain: 0**

The overall committee members who voted "YES" felt that there were strong efficacy data and adequate safety data. Some members questioned whether this is the lowest possible safe dose. Others commented that for moderate to severe COPD patients, this would be beneficial and there is a need to conduct long term studies.

The committee members who voted "NO" commented that both efficacy and safety data were not substantial and there were concerns in the FEV1 and sub-group population data.

b) 150 mcg once-daily? **(Vote)**

YES: 5 **NO: 12** **Abstain: 0**

The minority of the committee members who voted "YES" agreed that there was some benefit of efficacy and that the safety profile was adequate.

The majority of the committee members who voted "NO" expressed that there was only a small indication or no indication that there was improved efficacy with a higher dose.

c) If not, what further data should be obtained? **(Discuss)**

The committee members recommended the following:

- *Head to head dose comparisons, including in the severe COPD subgroup;*
- *Conduct cross-over studies and examine seasonal variations;*
- *Broaden study groups (more heterogenous populations);*
- *Conduct post-marketing studies and long term studies;*
- *Examine other functional measures as endpoints (i.e. serial complete pulmonary function tests- lung volumes and DLCO at times 0, 4, 8 and 12 weeks with 75mcg and 150mcg dosages;*
- *Conduct studies on COPD severity stages.*

(Please see official transcript for details)

Meeting adjourned at approximately 4:30 p.m.