Summary Minutes of the
Pulmonary-Allergy Drugs Advisory Committee (PADAC)
February 04, 2009
Hilton Washington, DC/Gaithersburg
The Ballrooms, 620 Perry Parkway, Gaithersburg, Maryland

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 March 04, 2009.

I certify that I attended the February 04, 2009 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 Official,
PADAC

_____/s/_____
William Calhoun, M.D.
Acting Committee Chair,
PADAC

The Pulmonary-Allergy Drugs Advisory Committee (PADAC) met on February 4, 2009 at the Hilton Washington DC/Gaithersburg, The Ballrooms, 620 Perry Parkway, Gaithersburg, Maryland. Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA. The meeting was called to order by William Calhoun, M.D., (Acting Chair); the conflict of interest statement was read into the record by Kristine Khuc, Pharm.D. (Designated Federal Official). There were approximately 150 persons in attendance. There were six speakers for the Open Public Hearing session.

Attendance:
Pulmonary-Allergy Drugs Advisory Committee Members Present (Voting):
Michael Foggs, M.D., Richard Honsinger, M.D., Paula Carvalho, M.D.

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

Endocrinologic and Metabolic Drugs Advisory Committee Member Present (Voting):
Michael Proschan, Ph.D.

Blood Products Advisory Committee Member Present (Voting):
Mark Ballow, M.D.

Special Government Employee Consultants Present (Temporary Voting Members):
William Calhoun, M.D (Acting Chair), Larry Borish, M.D., Rebecca Gruchalla, M.D, Ph.D., Leslie Hendeles, Pharm.D., Peter Terry, M.D., N. Franklin Adkinson, M.D., John Hoidal, M.D., Michael Schatz, M.D.

FDA Participants Present (Non-Voting):
Curtis Rosebraugh, M.D., Badrul Chowdhury, M.D., Ph.D., Thomas Permutt Ph.D., Sally Seymour, M.D., Susan Limb, M.D., Dongmei Liu, Ph.D.

Open Public Hearing Speakers: Sally Urbaniak, Jenny Barnes, H. Henry Li, M.D., Ph.D., (Institute for Asthma and Allergy), Janet Long, Michelle Williamson, Jenna Long

Designated Federal Official:
Kristine Khuc, Pharm.D.

Issue: To discuss biologic license application (BLA) #125277, KALBITOR, ecallantide injection by Dyax Corp., for the proposed indication of treatment of acute attacks of hereditary angioedema.

The Agenda was as follows:

Call to Order at 8:30 a.m.	William Calhoun, M.D.
Introduction of Committee	Acting Chair, PADAC

Conflict of Interest Statement	Kristine Khuc, Pharm.D. Designated Federal Official, PADAC
Opening Remarks	Badrul Chowdhury, M.D., Ph.D., Director, Division of Pulmonary Allergy Products, Center for Drug Evaluation and Research (CDER), FDA

Sponsor Presentation

Introduction and Overview	William Pullman, M.D., Ph.D. Executive Vice President of Clinical Development and Medical Affairs, Dyax Corp.
Clinical Efficacy and Safety	Patrick Horn, M.D., Ph.D. Vice President of Clinical Development and Medical Affairs, Dyax Corp.
Safe-Use Conditions	William Pullman, M.D., Ph.D. Executive Vice President of Clinical Development and Medical Affairs, Dyax Corp.
Clinical Perspective	Marc Riedl, M.D., M.S. Clinical Immunology and Allergy, UCLA David Geffen School of Medicine
Concluding Remarks	William Pullman, M.D., Ph.D. Executive Vice President of Clinical Development and Medical Affairs, Dyax Corp.

Questions for clarification

Break

FDA Presentation

Clinical Overview of the Efficacy of Ecallantide for the Treatment of Acute Attacks of Hereditary Angioedema	Susan Limb, M.D. Medical Officer, Division of Pulmonary and Allergy Products, CDER, FDA
Statistical Considerations	Dongmei Liu, Ph.D. Statistical Reviewer Office of Biostatistics, CDER, FDA
Clinical Overview of the Safety of Ecallantide for the Treatment of Acute Attacks of Hereditary Angioedema	Susan Limb, M.D. Medical Officer, Division of Pulmonary and Allergy Products, CDER, FDA

Questions for clarification

Lunch

Open Public Hearing

Charge and Questions to the Committee

Committee Discussion/Vote

Adjournment at 3:20 p.m.

Questions to the Committee:

1. Discuss the hypersensitivity and anaphylaxis data and provide recommendations for further evaluation, if necessary.

Committee members commented:

- *about the need to learn more about the nature of IgE and IgG antibodies*
- *estimates of hypersensitivity risks may be underestimated*
- *there is concern about drug rechallenge assessment once hypersensitivity reactions occur*
- *basic immunoassays are insufficient and better sensitivity is needed*

Committee members recommended:

- *risk assessment programs to identify patients who are at risk for life-threatening or fatal anaphylaxis reactions*
- *studies of IgE and IgG immunoassays upon the first exposure to the drug and on subsequent exposures*
- *improvement of sensitivity of IgE and IgG immunoassays*
- *conducting skin tests on patients as a predictive tool for anaphylaxis risk*
- *studies of other mediators and pathways leading to anaphylaxis reactions*
- *conducting hematologic and thrombotic studies*

(Please see official transcript for details)

2. Does the data provide substantial and convincing evidence that ecallantide provides a clinically meaningful beneficial effect on acute attacks of hereditary angioedema? **(Voting Question)**
    a) In patients 18 years of age and older
        If not, what further efficacy data should be obtained?

        Yes: 8 No: 4 Abstain: 1

        The Committee wanted to see studies looking at C1 esterase inhibitors functionality and its correlation with response.

    b) In patients 10 to 17 years of age.
        If not, what further efficacy data should be obtained?

        Yes: 3 No: 10 Abstain: 0

        A majority of the committee felt that the limitations of the current data are too great, making the data inadequate for this subgroup.

    (Please see official transcript for details)

3. Has the safety of ecallantide been adequately assessed for the treatment of acute attacks of hereditary angioedema? **(Voting Question)**
    a) In patients 18 years of age and older
        If not, what further safety data should be obtained?

        Yes: 5 No: 8 Abstain: 0

The Committee members who voted "yes" commented:

- *the safety data was adequate, but not complete in this patient population*
- *better risk assessment methods of anaphylaxis reactions are needed*

The Committee members who voted "no" commented:

- *that more studies are needed on IgE and IgG immunoassays*
- *additional studies are needed to find a better method of predicting patients at risk for anaphylaxis*
- *additional need for postmarketing coagulation studies*

b) In patients 10 to 17 years of age.
If not, what further safety data should be obtained?

Yes: 2 No: 11 Abstain: 0

The Committee's consensus is that safety data is lacking in this subgroup.

(Please see official transcript for details)

4. Do the safety and efficacy data provide substantial and convincing evidence to support the approval of ecallantide for the treatment of acute attacks of hereditary angioedema? **(Voting Question)**
   a) If not, what additional information is necessary to support approval?

Yes: 6 No: 5 Abstain: 2

The Committee members who voted "yes" commented:

- *efficacy data was adequate but there is still a strong safety signal*
- *the therapy option is needed because there are no other treatments*

The Committee members who voted "no" commented:

- *efficacy data is adequate to modest and safety is still a strong concern*
- *orphan status drugs should meet the same safety and efficacy standards as other drugs*

(Please see official transcript for details)

5. Does the committee have recommendations regarding the following:
   a) Labeling

Committee members recommended:

- *stronger precautions to warn about anaphylaxis reactions*
- *comprehensive education regarding monitoring of drug after injection*

- *recommending injections to be given at emergency rooms, allergist's office, urgent care centers for appropriate hypersensitivity monitoring*

b) Risk mitigation strategies for hypersensitivity and anaphylaxis reactions

Committee members recommended:

- *prevention protocol to predict and eliminate risks of anaphylaxis by performing immunoassays or skin tests*
- *concerted effort to educate institutions and patients of anaphylaxis risk with drug*
- *conduct more studies to find more sensitive immunoassays to better predict anaphylaxis reactions*

c) Potential for self-administration

Committee members recommended:

- *properly educating patients for self-administration of epinephrine*

d) Other

Committee members recommended:

- *Thorough analysis of C1 esterase levels and its correlation to drug response*

(Please see official transcript for details)