Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the
**Pulmonary-Allergy Drugs Advisory Committee**

June 6, 2005

5630 Fishers Lane, Rockville, MD 20857

**Pulmonary-Allergy Drugs Advisory Committee Members Present (voting):**
Erik R. Swenson, M.D. (Chair)
Mark L. Brantly, M.D.
Steven Gay, M.D.
I. Marc Moss, M.D.
Calman P. Prussin, M.D.
David A. Schoenfeld, Ph.D.

**Pulmonary-Allergy Drugs Advisory Committee Consultants (voting):**
Lawrence Hunsicker, M.D.
Jurgen Venitz, M.D.
Jeffrey S. Barrett, Ph.D.
Allan R. Sampson, Ph.D.
Karen Schell, RRT
Mary Lou Drittler
Jim Burdick, M.D.
John Tisdale, M.D.
Michael A. Proschan, Ph.D.
Roslyn B. Mannon, M.D.

**Industry Representative (non-voting):**
Theodore Reiss, M.D.

**Pulmonary-Allergy Drugs Advisory Committee Members Absent:**
William J. Calhoun, M.D.
Carolyn M. Kercsmar, M.D.
Fernando D. Martinez, M.D.
Peter E. Morris, M.D.
Lee S. Newman, M.D.
Michael Schatz, M.D.

**FDA Participants:**
Mark J. Goldberger, M.D., M.P.H.
Renata Albrecht, M.D.
Marc Cavaillé-Coll, M.D., Ph.D.
Arturo Hernandez, M.D.
Jyoti Zalkikar, Ph.D.

**Open Public Hearing Speakers:**
Esther Suss
John C. Sullivan
Renee Moeller
Bill Stein

**Executive Secretary**
Teresa A. Watkins

I certify that I attended the June 6, 2005 meeting of the Nonprescription Drugs Advisory Committee with the Dermatologic and Ophthalmic Drugs Advisory Committee and that these minutes accurately reflect what transpired.

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| Teresa A. Watkins | Erik R. Swenson, M.D. |
| Acting Executive Secretary, NDAC | Chair, PADAC |

**Final Minutes**
**Pulmonary-Allergy Drugs Advisory Committee Meeting**
**June 6, 2005**

A verbatim transcript will be available in approximately two weeks, sent to the Division and posted on the FDA website at:

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

Prior to the meeting, the members and the invited consultants were provided the background material from the FDA and Sponsor. The members and invited consultants were also provided written submissions from the public prior to the meeting. The meeting was called to order by Erik R. Swenson (Chair, PADAC); the conflict of interest statement was read into the record by Teresa Watkins (Executive Secretary). There were approximately 100 persons in attendance. There were 4 speakers for the Open Public Hearing Session (see below for a listing of the speakers).

**Attendance:**
**Pulmonary-Allergy Drugs Advisory Committee Members Present (voting)**
Erik R. Swenson, M.D., Mark L. Brantly, M.D., Steven Gay, M.D., M.S., I. Marc Moss, M.D., Calman P. Prussin, M.D., David A. Schoenfeld Ph.D..

**Pulmonary-Allergy Drugs Advisory Committee Consultants (voting):**
Jeffrey S. Barrett, Ph.D., Lawrence Hunsicker, M.D., Allan R. Sampson, Ph.D., Jurgen Venitz, Ph.D., Mary Lou Drittler (Patient Representative), Karen Schell, RRT (Consumer Representative).

**Federal Employee Consultants (voting):**
James F. Burdick, M.D., Roslyn B. Mannon, M.D., Michael A. Proschan, Ph.D., John Tisdale, M.D.

**Industry Representative (non-voting):**
Theodore Reiss, M.D.

**Pulmonary-Allergy Drugs Advisory Committee Members Absent:**
William J. Calhoun, M.D., Carolyn M. Kercsmar, M.D., Fernando D. Martinez, M.D., Peter E. Morris, M.D., Lee S. Newman, M.D., Michael Schatz, M.D.

**FDA Participants:**
Mark J. Goldberger, M.D., M.P.H, Renata Albrecht, M.D., Robert T. O'Neill, Ph.D., Marc Cavaillé-Coll, M.D., Ph.D., Arturo Hernandez, M.D., and Jyoti Zalkikar, Ph.D.

**Open Public Hearing Speakers:**
Esther Suss, John C. Sullivan, Bill Stein, and Renee Moeller

**Issue:**
The committee discussed NDA 50-799, Pulminiq™ (cyclosporine), inhalation solution, Chiron, proposed for the increase in survival and for the prevention of chronic rejection in patients receiving allogenic lung transplants, in combination with standard immunosuppressive therapy.

The agenda proceeded as follows:

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| Call to Order and Opening Remarks | Erik R. Swenson, M.D.<br>Chair, Pulmonary-Allergy Drugs Advisory Committee |
| Introduction of Committee | |
| Conflict of Interest Statement | Teresa A. Watkins, R.Ph.<br>Executive Secretary, PADAC |
| FDA Introductory Remarks | Renata Albrecht, M.D.<br>Director, Division of Special Pathogen and Immunologic Drug Products, FDA |
| **Sponsor Presentation** | Chiron Corporation |
| Introduction | Michael Scaife, Ph.D.<br>Chiron Corporation<br>Senior VP Regulatory Affairs, Compliance and Quality |
| Clinical Pharmacology | Jeffrey A. Golden, M.D.<br>UCSF Medical Center<br>Pulmonary and Critical Care Medicine |
| Efficacy | Sarah Noonberg, M.D., Ph.D.<br>Chiron Corporation<br>Associate Director, General Medicines Therapeutic Unit |

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| Safety and Benefit Risk | Robert W. Helms, Ph.D.<br>Rho, Inc.<br>Professor Emeritus, Biostatistics<br>University of North Carolina<br>Fellow, American Statistical Association<br><br>Stephen Dilly, M.D., Ph.D.<br>Chiron Corporation<br>Chief Medical Officer |
| Conclusion | Michael Scaife, Ph.D.<br>Chiron Corporation<br>Senior VP Regulatory Affairs, Compliance and Quality |

**FDA Presentation**

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| Overview of Clinical Trial<br>Efficacy and Safety Evaluation<br>Discussion of Analysis | Arturo Hernandez, M.D.<br>Medical Officer,<br>Division of Special Pathogen and Immunologic Drug Products, FDA<br><br>Marc Cavaillé-Coll, M.D., Ph.D.<br>Medical Team Leader,<br>Division of Special Pathogens and Immunologic Drug Products, FDA<br><br>Jyoti Zalkikar, Ph.D.<br>Lead Statistical Reviewer,<br>Division of Special Pathogen and Immunologic Drug Products, FDA |

## Open Public Hearing

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| Charge to the Committee | Renata Albrecht, M.D.<br>Director, Division of Special Pathogen and Immunologic Drug Products, FDA |

**QUESTIONS to the Committee**

1.) Is there sufficient information to make the determination whether the observed survival difference in study ACS001 is due to study treatment or some other factor?

YES - 8
NO - 8

In your deliberations, please consider the statistical issues raised by this application, as well as the differences in baseline donor/recipient characteristics, and whether the product has demonstrated an effect on another endpoint that is pathophysiologically related to the mortality endpoint, including acute rejection, bronchiolitis obliterans syndrome, and histological bronchiolitis obliterans. Also consider whether the product has demonstrated a benefit on some other clinical endpoint?

If YES:

1. a.) Please discuss the generalizability of these results obtained from a single study at one institution to the treatment of lung transplantation recipients in the US.
A larger multicenter trial is needed before the results can be extrapolated to the general population. Further validation is necessary in a subsequent pre or post approval unrandomized trial evaluating efficacy, survival, 5- year safety and optimal dosing.
There are questions about maintenance of survivability outcomes for patients who received a limited number of doses. There are also questions about local tissue exposure behavior of the drug.
The current trial is not ethnically diverse. There should be Standard Operating procedures for nebulization and for the lidocaine dosing.
There are balance issues between the characteristics of double-lung transplants and single lung transplants in this trial. Recommended studies include a study of double vs. single lung transplants, using both high and low doses of inhaled cyclosporine.

If NO:

1. b.) What additional information would be needed to make this determination? In your discussion please consider what additional clinical studies you would recommend be conducted. Do you have any specific recommendations regarding: patient population, drug dosing regimen and administration, efficacy endpoint(s)?

The Members who voted "no" listed the following reasons:

- more information about the donor's lung status pre-donation
- post-op factors (i.e. FEV1)
- Baseline systemic immunosuppression needs to be standardized.
- There needs to be a prospective, randomized, blinded, sequentially designed (low dose vs. high dose) trial.
- There needs to be a randomized trial with mortality as the primary end point, larger than the original trial, and perhaps multicenter.
- There should be another trial 2 to 3 times larger, multicentered with an agreed upon stopping point.
- Trials should include long term outcomes that address carcinogenicity issues of inhaled cyclosporine.
- There needs to be a randomized trial, balanced as to treatment assignments within each single/double lung transplant stratum. Baseline immunosuppressant therapies should be standardized. A standard therapy for acute rejection should be developed. Assays of cellular and humoral immunity should be included and long term safety data should all be included.
- Pre-clinical studies could be considered to determine mechanism. Mortality should be a major end point as well as fibrosis and function. It should be powered sufficiently. There should be randomization schemes (i.e., Randomization should be stratified by a few important baseline characteristics such as single/double lung transplantation).
- BOS free interval should be evaluated on therapy and off therapy
- If the treatment is not approved, a follow up study would need to be designed to confirm the benefit shown in the original study. Such a study would randomize patients between the two treatments and would follow them until chronic rejection or death whichever came first. The primary endpoint would be rejection-free survival, which showed a highly significant difference in the first study. Deaths before chronic rejection would be considered as events as would biopsy demonstrated OB or clinical BOS. Such a trial could cross patients to active treatment after chronic rejection because the primary endpoint would have been reached for those patients. The trial should have sequential efficacy early stopping rule (using Pocock boundaries) to minimize the number of patients treated on placebo if treatment is effective.

2.) Has the safety of the product been adequately characterized for its intended use?

YES - 11
NO - 5

In your deliberations, please consider the amount of pre-clinical and clinical information available on the administration of cyclosporine and the vehicle through this route, as well as the number of human subjects in this application exposed to the proposed recommended dosage.

If YES:

2. a.) For what population should the product be labeled?

- It should be labeled for single and double lung transplant patients.
- It should be labeled to improve survival.

2. b.) What information should be included on dosing regimen, dose preparation/administration, dosing intervals and duration?

- The dose studied in the trial should be the regimen used.
- The label should state that use of the drug beyond two years has not been evaluated.
- The label should state that inhaled lidocaine is not approved for use with inhaled cyclosporine
- The labeling should address the tolerability of dosing, premedication regimens and dose escalation guidelines
- The labeling should also address long term safety issues
- The labeling should address the particular nebulizer used in the trial and indicate the drug is to be used with this fixed delivery system only.
- The label should state that inhaled cyclosporine should be used **WITH** standard immunosuppression and not as a replacement for standard immunosuppression in an attempt to decrease systemic toxicity.

2. c.) What information should be included in the labeling regarding expected benefit on acute rejection, bronchiolitis obliterans syndrome or obliterative bronchiolitis?

- The label should state that the drug shows a survival benefit presumably due to a decrease in chronic rejection. It should explicitly state there is no evidence to support its use in acute rejection.
- The label should state there is incomplete data on carcinogenesis potential of inhaled cyclosporine.
- The label should address drug interactions with inhaled cyclosporine as they compare to systemically administered cyclosporine.

If NO:

2. d.) What additional preclinical or clinical information would be needed?

- Animal data on lung toxicity.
- Post-marketing surveillance for carcinogenesis
- Open label prospective exposure studies
- OPTN post-marketing
- Long term follow-up for irritability of the drug on the lungs
- Follow-up polyethylene glycol and cyclosporine toxicity studies

4:30 p.m. Adjourn