

**Summary Minutes of the
Anti-Infective Drugs Advisory Committee
November 18-20, 2008**

Location: Holiday Inn, The Ballrooms, 10000 Baltimore Avenue, College Park, MD

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

These summary minutes for the November 18-20, 2008, Meeting of the Anti-Infective Drugs Advisory Committee of the Food and Drug Administration were approved on December 9, 2008.

I certify that I attended the November 18-20, 2008, meeting of the Anti-Infective Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

_____/s/_____
Janie Kim, Pharm.D.
Designated Federal Official, AIDAC

_____/s/_____
L. Barth Reller, M.D.
Acting Committee Chair

Meeting of the Anti-Infective Drugs Advisory Committee November 18, 2008

The Anti-Infective Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on November 18, 2008 at the Holiday Inn Ballroom, 10000 Baltimore Ave, College Park, Maryland. Prior to the meeting, members and invited consultants were provided copies of the background material from the FDA and the sponsor. The meeting was called to order by L. Barth Reller, M.D. (Acting Committee Chair); the conflict of interest statement was read into the record by Janie Kim, Pharm.D. (Designated Federal Official). There were approximately 250 persons in attendance. There was one (1) speaker for the Open Public Hearing session.

Issue: The committees will discuss the justifications of the non-inferiority margin for complicated skin and skin structure infections (cSSSIs).

Attendance:

Dean Follmann, Ph.D., Kathleen Gutierrez, M.D., Carol Kauffman, M.D., Bernhard Wiedermann, M.D

Anti-Infective Drug Advisory Committee Member Present (Non-Voting):

John Rex, M.D. (Industry Representative)

Special Government Employee Consultants Present (Voting):

W. Kemper Alston, M.D., Alan Cross, M.D., Thomas Fleming, Ph.D., Matthew Goetz, M.D., Joan Hilton, Sc.D., Peter Katona, M.D., James Leggett, M.D., Timothy S. Lesar, Pharm.D., Arthur Levin, M.P.H. (Consumer Representative), Lewis Nelson, M.D., Edward Septimus, M.D., James Steckelberg, M.D., Jeanine Thomas (Patient Representative), Melvin Weinstein, M.D.

Special Government Employee Consultants Present (Non-voting):

Henry Black, M.D., Philip Mirkes, Ph.D., Emil Paganini, M.D., Mary Alice Smith, Ph.D.

Regular Government Employee Consultants Present (Voting):

John Bennett, M.D.

Regular Government Employee Consultants Present (Non-voting)

Janet Cragan, M.D., Jeffrey Kopp, M.D., Michael Shelby, Ph.D.

Guest Speaker Present (Non-Voting):

Brad Spellberg, M.D. (Infectious Diseases Society of America)

Anti-Infective Drugs Advisory Committee Members Not Present:

Susan Rehm, M.D., Margo Smith, M.D., Gregory Townsend, M.D., Allan Tunkel, M.D., Ph.D., Annie Wong-Beringer, Pharm.D. (Consumer Representative)

FDA Participants (Non-Voting): Edward Cox, M.D., M.P.H., Katherine Laessig, M.D., Sumati Nambiar, M.D., M.P.H., Janice Pohlman, M.D., M.P.H., Thamban Valappil, Ph.D.

Designated Federal Official:

Janie Kim, Pharm.D.

Open Public Hearing Speaker:

Susan C. Nicholson, M.D., Therapeutic Area Lead, Anti-Infective Franchise, Ortho-McNeil Janssen Scientific Affairs

The agenda was as follows:

Call to Order and Introductions **L. Barth Reller, M.D.**
Acting Chair

Conflict of Interest Statement **Janie Kim, Pharm.D.**
Designated Federal Official

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FDA Presentation

Regulatory Approach to Non-inferiority Margin Justification for cSSSI

Sumati Nambiar, MD, MPH
Thamban Valappil, Ph.D.

Sponsor Presentation

Theravance, Inc.
Alan Hopkins, Ph.D., Theravance, Inc.
G. Ralph Corey, M.D., Duke University

Targanta Therapeutics Corp.
Dr. Alan Forrest, Senior Scientist, Pharmacometrics,
Ordway Research Institute

Arpida AG
Khalid Islam, Ph.D., Former CEO, Board Member
Statistical Consultants
Charles Davis, Ph.D.
LJ Wei, Ph.D.

Guest Speaker Presentations
Infectious Diseases Society of America (IDSA) presentation

Brad Spellberg, M.D.
Los Angeles Biomedical Research Institute
at Harbor-UCLA Medical Center

Questions to the Presenters

Open Public Hearing

Questions to the AIDAC
and AIDAC Discussion

Adjourn

Questions to the committee:

1. Are non-inferiority trials acceptable for the indication of cSSSI? Please vote Yes/No.

Vote : **Yes= 20 No = 0 Abstain = 0**

- If Yes, please discuss the following points and provide your rationale:
 - What margin is acceptable?

Discussion

Committee members felt that a 10% margin was a reasonable compromise as long as major abscesses are excluded and there are safety, cost, and/or antimicrobial benefits associated with the innovator.

- What is the appropriate primary endpoint?

Discussion

Committee members considered the following endpoints:

- *Completion of therapy*
 - *Response to therapy (e.g., resolution of fever, how quickly patients returned to work)*
 - *Test of cure*
- What is the appropriate timing of assessment of the primary endpoint (e.g. on therapy, at the end of therapy, or at a fixed time point after completion of therapy)?

Discussion

Committee members had various perspectives including the appropriate timing would be at 10-14 days to capture greater sensitivity and to justify an evidence based margin and others advocated assessment at end of therapy.

- If No, please provide your rationale and advice you may have on alternative trial designs.
None of the committee members voted no to the first question.

2. Please discuss if it is acceptable to justify a NI margin for cSSSI as a group or should the margin be justified by specific infection type, i.e. cellulitis, wound infections, or abscesses.

- If it is acceptable to study cSSSI as one group, should the number of any one type of infection be limited?

Discussion

Committee members discussed the pros and cons of separating major abscesses from other types of cSSSI such as cellulitis, erysipelas, and wound infections.

- Should patients with diabetic foot infections be studied in a separate clinical trial or should they be included in cSSSI trials?

Discussion

Committee members felt that diabetic foot infections should generally be studied in a separate clinical trial because of differences in epidemiology, microbiology, compliance, radiologic requirements, wound care, and concomitant illnesses (e.g., neuropathy) associated with this type of infection. Please see the transcript for detailed discussion.

3. Given that the data evaluated for determining treatment effect in skin infections includes data from various types of skin infections, are non-inferiority trials acceptable for the indication of uSSSI? Please vote Yes/No.

Vote(as displayed) : Yes = 4 No = 16 Abstain = 0

Due to difficulties with the voting system, three of the “yes” votes were later changed to “no” votes during the discussion session. The final vote on this question is, therefore,

Vote(after corrections) : Yes = 1 No = 19 Abstain = 0

Please see the transcript for detailed discussion.

- If Yes, please discuss the following points and provide your rationale:

Discussion

The Committee member who voted “yes” to the question commented on the need to be flexible and allow for the option of a non-inferiority trial. Please see the transcript for detailed discussion.

- What margin is acceptable?
Committee members did not comment on this question.
- What is the appropriate primary endpoint?
Committee members did not comment on this question.
- What is the appropriate timing of assessment of the primary endpoint (e.g. on therapy, at the end of therapy, or at a fixed time point after the completion of therapy)?

Committee members did not comment on this question.

- If No, please provide your rationale and advice you may have on alternative trial designs.

Discussion:

Committee members who voted “no” felt that a superiority trial was justified by the limited historical data available for uSSSI and the unfavorable risk/benefit ratio with treating uSSSI such as impetigo.

4. Should uSSSI studies only enroll patients with infections such as impetigo, erysipelas, and cellulitis and exclude those with abscesses?

Due to previous discussions of uncomplicated skin and skin structure infections, the overwhelming “no” vote for question 3, and limited time, the Committee and the FDA decided not to vote on this question.

Please see the transcript for detailed discussion.

The session adjourned @ approximately 4:56 p.m.