

**Food and Drug Administration  
Center for Drug Evaluation and Research**

**Summary Minutes of the Anti-Infective Drugs Advisory Committee Meeting  
November 2, 2012**

Location: DoubleTree by Hilton Hotel Washington, DC-Silver Spring,  
8727 Colesville Road, Silver Spring, Maryland 20910

Issue: The committee discussed biologics licensing application (BLA) 125349,  
raxibacumab injection, a humanized monoclonal antibody against protective  
antigen of *Bacillus anthracis*, by Human Genome Sciences, Inc. for the proposed  
indication of treatment of inhalational anthrax.

These summary minutes for the November 2, 2012 Anti-Infective Drugs Advisory Committee  
meeting were approved on November 26, 2012.

I certify that I attended the November 2, 2012 Anti-Infective Drugs Advisory Committee  
meeting and that these minutes accurately reflect what transpired.

\_\_\_\_\_/s/\_\_\_\_\_  
Philip Bautista, PharmD  
Acting Designated Federal Officer, AIDAC

\_\_\_\_\_/s/\_\_\_\_\_  
Thomas Moore, MD, FACP, FIDSA  
Chairperson, AIDAC

## Summary Minutes of Meeting of the Anti-Infective Drugs Advisory Committee November 2, 2012

The following is the final report of the Anti-Infective Drugs Advisory Committee (AIDAC) meeting held on November 2, 2012. A verbatim transcript will be available in approximately six weeks, sent to the Division of Anti-Infective Products and posted on the FDA website at:

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm293600.htm>

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

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The Anti-Infective Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on November 2, 2012 at the DoubleTree by Hilton Hotel Washington DC-Silver Spring, Silver Spring, Maryland. Prior to the meeting, members and temporary voting members were provided copies of the briefing materials from the FDA and Human Genome Sciences, Inc. The meeting was called to order by Thomas A. Moore, MD, FACP, FIDSA (Chairperson); the conflict of interest statement was read into the record by Philip Bautista, PharmD (Acting Designated Federal Officer). There were approximately 175 people in attendance. There were no Open Public Hearing speakers.

**Issue:** The committee discussed biologics licensing application (BLA) 125349, raxibacumab injection, a humanized monoclonal antibody against protective antigen of *Bacillus anthracis*, by Human Genome Sciences, Inc. for the proposed indication of treatment of inhalational anthrax.

### **Attendance:**

#### **AIDAC Members Present (Voting):**

Diane Cappelletty, PharmD; Christopher Carpenter, MD, FACP, FIDSA; Thomas Moore, MD, FACP, FIDSA (*Chairperson*); Michael Neely, MD; CAPT Monica Parise, MD; Kurt Stevenson, MD, MPH

#### **AIDAC Members Not Present (Voting):**

Paul Auwaerter, MD; Archana Chatterjee, MD, PhD; Sheldon Kaplan, MD; Yu Shyr, PhD; Melvin Weinstein, MD, MPH; Kathleen Young (*Consumer Representative*)

#### **AIDAC Member Not Present (Non-Voting):**

Patrick A. Robinson, MD (*Industry Representative*)

#### **Temporary Members (Voting):**

Wallace Kemper Alston, MD, MPH; Elizabeth Bell-Perkins, MPH (*Acting Consumer Representative*); Dean Follman, PhD; Matthew Goetz, MD; Philip Hanna, PhD; Peter Katona, MD, FACP, FIDSA; Joseph Kosler, PhD; Steve Leppla, PhD; COL Christian Ockenhouse, MD, PhD (*Patient Representative*); Lyman Barth Reller, MD, DTM&H; Nicholas Vietri, MD, MS; Mary Wright, MD, MPH

**FDA Participants (Non-Voting):**

Edward Cox, MD, MPH; John Farley, MD, MPH; Yuliya Yasinskaya, MD; Terry Miller, PhD;  
Jingyu Yu, PhD

**Acting Designated Federal Officer (Non-Voting):** Philip Bautista, PharmD

**Open Public Hearing Speakers:** None

*The agenda proceeded as follows:*

Call to Order and Introduction of Committee

**Thomas A. Moore, MD, FACP, FIDSA**  
Chairperson, AIDAC

Conflict of Interest Statement

**Philip Bautista, PharmD**  
Acting Designated Federal Officer, AIDAC

FDA Introductory Remarks

**John Farley, MD, MPH**  
Acting Director  
Division of Anti-Infective Products (DAIP)  
Office of Antimicrobial Products (OAP)  
Office of New Drugs (OND), CDER, FDA

**BIOMEDICAL ADVANCED RESEARCH AND DEVELOPMENT  
AUTHORITY (BARDA) PRESENTATION**

HHS Anthrax Medical Countermeasure Program  
(Anthrax Antitoxins)

**Gerald R. Kovacs, PhD**  
Director  
Division of Chemical, Biological, Radiological, and  
Nuclear Countermeasures  
BARDA, Office of the Assistant Secretary for  
Preparedness and Response

Clarifying Questions to BARDA

**SPONSOR PRESENTATIONS**

**Human Genome Sciences, Inc.**

Introduction

**Sally Bolmer, PhD**  
Senior Vice President  
Development and Regulatory Affairs  
Human Genome Sciences, Inc.

Inhalational Anthrax Public Health Need

**Dan Hanfling, MD**  
Special Advisor for Emergency Preparedness and  
Response, Inova Health System  
Clinical Professor of Emergency Medicine  
George Washington University

Mechanism of Action, Efficacy, Nonclinical Safety

**Thi-Sau Migone, PhD**  
Vice President, Research  
Human Genome Sciences, Inc.

November 2, 2012  
Meeting of the Anti-Infective Drugs Advisory Committee

**SPONSOR PRESENTATIONS (cont.)**

Nonclinical and Clinical Pharmacokinetics

**Al Corey**  
Senior Pharmacokineticist  
Human Genome Sciences, Inc.

Human Safety

**Brian Oscar Porter, MD, PhD, MPH**  
Associate Director, Clinical Research  
Human Genome Sciences, Inc.

Benefit/Risk

**Dan Hanfling, MD**

Clarifying Questions to the Sponsor

**BREAK**

**FDA PRESENTATIONS**

Raxibacumab: Regulatory and Clinical Overview

**Yuliya Yasinskaya, MD**  
Medical Officer  
DAIP, OAP, OND, CDER, FDA

Nonclinical Safety Assessment of Raxibacumab in Anthrax  
Infected Rabbits

**Terry J. Miller, PhD**  
Pharmacology/Toxicology Reviewer  
DAIP, OAP, OND, CDER, FDA

Determination of Pediatric Dose of Raxibacumab  
for the Treatment of Inhalational Anthrax

**Jingyu Yu, PhD**  
Reviewer  
Division of Pharmacometrics  
Office of Clinical Pharmacology  
Office of Translational Sciences, CDER, FDA

Clarifying Questions to the FDA

**LUNCH**

Open Public Hearing Session

Charge to the Committee

Questions to the Committee/Committee Discussion

**BREAK**

Questions to the Committee/Committee Discussion

**ADJOURNMENT**

**Questions to the Committee:**

Considering the information described for raxibacumab in the rabbit and monkey animal model studies and safety trials in healthy human volunteers:

1. **VOTE:** Do the results from the therapeutic studies of raxibacumab with and without antimicrobials in two animal models of inhalational anthrax provide substantial evidence that raxibacumab (40 mg/kg IV single dose in adults) is reasonably likely to produce clinical benefit for the treatment of humans with inhalational anthrax?

**YES: 16            NO: 1            ABSTAIN: 1**

**Committee Discussion:** *The majority of the committee agreed that the results from the therapeutic studies of raxibacumab with and without antimicrobials in two animal models of inhalational anthrax provided substantial evidence that raxibacumab (40mg/kg IV single dose in adults) is reasonably likely to produce clinical benefit for the treatment of humans with inhalational anthrax. The committee agreed that the results of the animal studies were statistically significant when comparing raxibacumab monotherapy to placebo. Although the results of the combination studies (raxibacumab + antibiotic vs. antibiotic alone) were not statistically different (p-value 0.0874), the committee agreed that these results were of clinical significance. The committee members stated that 0.05 is an arbitrary cut-off and that this drug has a 92% chance of having added benefit. Given the lack of an antagonistic effect on antibiotics and the lethality of anthrax disease, the majority of the committee agreed that this drug had clinical value, especially for patients infected with multi-drug resistant anthrax and patients with multiple antibiotic allergies. The committee member who voted “no” stated that if this product was approved, providers will think that this drug has added benefit, despite not demonstrating statistically significant evidence of this. This committee member further added that in the case of an emergency, this product would still be available via an Emergency Use Authorization (EUA) or treatment IND despite not being approved by the FDA. Please see the transcript for details of the committee discussion.*

- a. **DISCUSSION:** If yes, do you have any recommendations regarding labeling of the product, or if not, what additional studies are needed?

**Committee Discussion:** *The committee recommended several additions to the labeling if this product were to be approved. These additions include 1) clear guidance and protocols on which patients should receive this product; 2) guidance on the logistical use of this product during a large-scale emergency event; and 3) labeling emphasizing that this product will not protect against central nervous system infections such as meningitis due to its inability to penetrate the blood-brain barrier. The committee suggested additional trials be conducted to study the following: 1) potential interactions with anthrax vaccinations; 2) shorter infusion times or more concentrated infusions; 3) dosing in obese patients or those with large amounts of edema/ fluid retention (dosing based on actual body weight vs. ideal body weight); 4) efficacy of doses greater than 40mg/kg and 5) effective dosing during different stages of disease progression. Please see the transcript for details of the committee discussion.*

2. **VOTE:** Do the results from raxibacumab safety trials in healthy volunteers and studies in animals support an acceptable risk benefit profile given the benefits of the therapy discussed in Question 1?

**YES: 18            NO: 0            ABSTAIN: 0**

**Committee Discussion:** *The committee unanimously agreed that the results from the raxibacumab safety trials in healthy volunteers and studies in animals support an acceptable risk benefit profile given the benefits of the therapy discussed in question #1. The committee agreed that the deficiencies in the previous BLA submission have been sufficiently addressed and the lack of dose response regarding the central nervous system events suggest that this product is safe and does not contribute to the death of patients. Please see the transcript for details of the committee discussion.*

- a. **DISCUSSION:** If yes, do you have any recommendations regarding labeling of the product, or if not, what additional studies are needed?

**Committee Discussion:** *The committee stated that labeling should reinforce the fact that the safety of this drug was evaluated in healthy humans rather than patients with inhalational anthrax. Additionally, the committee recommended further studies to evaluate the following: 1) safety of doses greater than 40mg/kg; 2) higher concentration and shorter infusion times; and 3) effect of raxibacumab on pre-exposure or postexposure vaccination. Please see the transcript for details of the committee discussion.*

3. **DISCUSSION:** Please discuss any recommendations regarding the proposed dosing of 40 mg/kg for adults and the pediatric proposed dosing based on body weight:

<b>WT (Kg)</b>	<b>IV Dose (mg/kg)</b>
≤15	80
>15 to ≤50	60
>50	40

**Committee Discussion:** *The majority of the committee agreed with the proposed dosing of 40mg/kg for adults. However, some of the committee members stated that this dose may not be the maximum effective dose. Therefore, the committee recommended additional studies to evaluate the efficacy and safety of doses higher than 40mg/kg. The committee suggested that these additional studies would also provide information about the safety and efficacy of the proposed weight-based dosing in pediatric patients that is higher than proposed for adults. When using the proposed pediatric dosing, the committee noted that pediatric patients who have weights that approach 15kg or 50kg will receive doses larger than patients with weights greater than these values while acknowledging that the simplicity of pediatric dosing is an important factor under emergency. In addition, the committee suggested evaluating alternative body surface area (BSA) or lean body weight (LBW) based dosing for pediatric patients. Please see the transcript for details of the committee discussion.*

The meeting was adjourned approximately 2:35 p.m.