Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Antimicrobial Drugs Advisory Committee Meeting
May 2, 2018

Location: DoubleTree by Hilton Hotel Bethesda – Washington DC, Grand Ballroom 8120 Wisconsin Avenue Bethesda, Maryland

Topic: The committee discussed new drug application (NDA) 210303 for plazomicin, sponsored by Achaogen Inc., for the proposed indications for the treatment of complicated urinary tract infections and blood stream infections in adults.

These summary minutes for the May 2, 2018 meeting of the Antimicrobial Drugs Advisory Committee of the Food and Drug Administration were approved on 6/19/18.

I certify that I attended the May 2, 2018 meeting of the Antimicrobial Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/
Cindy Chee, PharmD
Acting Designated Federal Officer
Antimicrobial Drugs
Advisory Committee (AMDAC)

/s/
Lindsey R. Baden, MD
Acting Chairperson, AMDAC

Summary Minutes of the Antimicrobial Drugs Advisory Committee Meeting
May 2, 2018

The Antimicrobial Drugs Advisory Committee (AMDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on May 2, 2018, at the DoubleTree by Hilton Hotel Bethesda – Washington DC, Grand Ballroom 8120 Wisconsin Avenue Bethesda, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Achaogen, Inc. The meeting was called to order by Lindsey R. Baden, MD (Acting Chairperson). The conflict of interest statement was read into the record by Cindy Chee, PharmD (Acting Designated Federal Officer). There were approximately 160 people in attendance. There were nine Open Public Hearing (OPH) speaker presentations.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

Agenda: The committee discussed new drug application (NDA) 210303 for plazomicin, sponsored by Achaogen Inc., for the proposed indications for the treatment of complicated urinary tract infections and blood stream infections in adults.

Attendance:
AMDAC Members Present (Voting): Nina M. Clark, MD; Demetre C. Daskalakis, MD, MPH; Dean A. Follmann, PhD; Michael D. Green, MD, MPH; Barbara M. Gripshover, MD; Jonathan R. Honegger, MD; Vincent Lo Re, MD, MSCE; Joanna M. Schaenman, MD, PhD; Peter Weina, PhD, MD, FACP, FIDSA

AMDAC Members Not Present (Voting): Amanda H. Corbett, PharmD, BCPS, FCCP; Ighovwerha Ofotokun, MD, MSc

AMDAC Member Present (Non-Voting): Nicholas A. Kartsonis, MD (Industry Representative)

Temporary Members (Voting): Lindsey R. Baden, MD (Acting Chairperson); Debra Dunn (Patient Representative); Randy W. Hawkins, MD (Acting Consumer Representative); Jennifer Le, PharmD, MAS; Paul Palevsky, MD; Robert Rej, PhD; Jurgen Venitz, MD, PhD

FDA Participants (Non-Voting): Edward Cox, MD, MPH; Sumathi Nambiar, MD, MPH; Shrimant Mishra, MD, MPH; Daniel Rubin, PhD

Acting Designated Federal Officer (Non-Voting): Cindy Chee, PharmD

Open Public Hearing Speakers: Barrett Thornhill (Antimicrobial Innovation Alliance); Shoshana Shendelman, PhD; Armando Nahum (Safe Care Campaign); Thomas Lodise, PharmD, PhD (Albany College of Pharmacy and Health Sciences); Michael S. Gelfand, MD (UT Methodist Physicians); Yoav Golan, MD, MS, FIDSA (Tufts Medical Center); Steven Burdette, MD (Miami Valley Hospital); Juan Diaz, DO, FACP (statement read by Armando Nahum); Danielle Shapiro, MD, MPH (National Center for Health Research)

The agenda was as follows:

Call to Order and Introduction of Committee	**Lindsey R. Baden, MD** Acting Chairperson, AMDAC
Conflict of Interest Statement	**Cindy Chee, PharmD,** Acting Designated Federal Officer, AMDAC
FDA Opening Remarks	**Sumathi Nambiar, MD, MPH** Director Division of Anti-Infective Products (DAIP) Office of Antimicrobial Products (OAP) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Achaogen Inc.**
Introduction	**Anne Keane, PA-C, JD** Head of Regulatory Affairs and Clinical Quality Assurance Achaogen, Inc.
Unmet Need	**James McKinnell, MD** Assistant Professor of Medicine, Infectious Disease Specialist David Geffen School of Medicine University of California, Los Angeles
Microbiology and Clinical Pharmacology	**Kevin Krause** Head of Microbiology Achaogen, Inc.
Efficacy	**Ian Friedland, MD** Clinical Consultant Friedland Strategic Consulting
Safety	**Lynn Connolly, MD, PhD** Clinical Consultant Achaogen, Inc.
Concluding Remarks Clarifying Questions to the Presenters	**Lynn Connolly, MD, PhD**
BREAK	
FDA PRESENTATIONS	
Presentation of Clinical Efficacy	**Hengrui Sun, DrPH** Statistical Reviewer Division of Biometrics IV (DBIV) Office of Biostatistics (OB) Office of Translational Sciences (OTS), CDER, FDA

	Daniel Rubin, PhD Statistical Reviewer DBIV, OB, OTS, CDER, FDA
	Shrimant Mishra, MD, MPH Medical Officer DAIP, OAP, OND, CDER, FDA
Presentation of Clinical Safety	**Shrimant Mishra, MD, MPH**
Clinical Pharmacology	**Luning (Ada) Zhuang, PhD** Pharmacometrics Reviewer Division of Pharmacometrics Office of Clinical Pharmacology (OCP) OTS, CDER, FDA
	Kunyi Wu, PharmD Clinical Pharmacology Reviewer Division of Clinical Pharmacology 4 OCP, OTS, CDER, FDA
Clarifying Questions	
LUNCH	
OPEN PUBLIC HEARING	
Questions to the Committee/Committee Discussion	
BREAK	
Questions to the Committee/Committee Discussion (cont.)	
ADJOURNMENT	

Questions to the Committee:

1. **VOTE:** Has the applicant provided substantial evidence of the safety and effectiveness of plazomicin for the treatment of complicated urinary tract infections in patients with limited or no treatment options?
    a. If yes, please provide any recommendations regarding labeling.
    b. If no, what additional studies/analyses are needed?

Vote Result: Yes: 15 No: 0 Abstain: 0 No-Voting: 1

Committee Discussion: *The committee unanimously agreed that the applicant provided substantial evidence of the safety and effectiveness of plazomicin for the treatment of complicated urinary tract infections in patients with limited or no treatment options.*

The members commented that the animal studies also support efficacy. The clinical data did not show any patern of serious adverse events. The development of plazomicin will prove to be valuable, given continued emergence of microbial resistance to currently available therapies. The panel also commented on the limited safety data and suggested additional exploration on dosing and markers for nephrotoxicity. Furthermore, the committee recommended additional post marketing safety studies and labeling to include guidance on therapeutic drug monitoring. Members also expressed concern with potential ototoxicity given antimicrobial class considerations and future monitoring for this is prudent. One panel member was not present to vote as noted for the record. Please see the transcript for details of the committee discussion.

2. **VOTE:** Has the applicant provided substantial evidence of the safety and effectiveness of plazomicin for the treatment of bloodstream infections in patients with limited or no treatment options?
    a. If yes, please provide any recommendations regarding labeling.
    b. If no, what additional studies/analyses are needed?

Vote Result: Yes: 4 No:11 Abstain: 0 No-Voting: 1

Committee Discussion: *The majority of the committee voted that the applicant has not provided substantial evidence of the safety and effectiveness of plazomicin for the treatment of bloodstream infections in patients with limited or no treatment options. The panel members who voted "Yes"commented that the study showed some efficacy and safety for those with truly limited or no treatment options. They also commented that although there are many issues with the study, the totality of the data are compelling, and demonstrates efficacy and safety especially in the context of few to no treatment options for this life-threatening infection. The members who voted "No" commented on the very small sample size and inadaquency of the non-inferiority analysis as a basis for approval. Members commented that the data were not convincing and did not meet the FDA's standards for substantial evidence of efficacy. Committee members suggested monitoring cardiac side effects and evaluating off-label uses of plazomicin for bloodstream infections if the drug is approved for complicated urinary track infections. The committee also suggested a larger study population. One panel member was not present to vote as noted for the record. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 4:10 p.m.