FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE (AMDAC)

Wednesday, May 2, 2018

8:30 a.m. to 4:09 p.m.

DoubleTree by Hilton Hotel Bethesda

The Grand Ballroom

8120 Wisconsin Avenue

Bethesda, Maryland

1   Meeting Roster

2   **ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)**

3   **Cindy Chee, PharmD**

4   Division of Advisory Committee and Consultant

5   Management

6   Office of Executive Programs, CDER, FDA

7

8   A**NTIMICROBIAL DRUGS ADVISORY COMMITTEE MEMBERS**

9   **(Voting)**

10 **Nina M. Clark, MD**

11 Associate Professor

12 Director, Transplant Infectious Disease Program

13 Division of Infectious Diseases

14 Loyola Medical Center

15 Maywood, Illinois

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17 **Demetre C. Daskalakis, MD, MPH**

18 Acting Deputy Commissioner

19 Division of Disease Control

20 New York City Department of Health and

21 Mental Hygiene

22 Long Island City, New York

1   **Dean A. Follmann, PhD**

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3   Chief Biostatistics Research Branch

4   National Institute of Allergy and

5   Infectious Diseases

6   National Institutes of Health (NIH)

7   Bethesda, Maryland

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9   **Michael D. Green, MD, MPH**

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11   Translational Science

12   University of Pittsburgh School of Medicine

13   Division of Infectious Diseases

14   Director, Antimicrobial Stewardship & Infection

15   Prevention

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University Hospitals Cleveland Medical Center

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Assistant Professor of Pediatrics

The Ohio State University College of Medicine

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12   Division of Infectious Diseases

13   David Geffen School of Medicine at UCLA

14   Los Angeles, California

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16   **Peter Weina, MD, PhD, FACP, FIDSA**

17   Colonel, Medical Corps, USA

18   Chief, Department of Research Programs

19   Walter Reed National Military Medical Center

20   Division of Education, Training and Research

21   Bethesda, Maryland

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1   **ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEMBERS**

2   **(Non-Voting)**

3   **Nicholas A. Kartsonis, MD**

4   *(Industry Representative)*

5   Acting Section Head, Antibacterials/CMV

6   Vice President and Therapeutic Area Head

7   Infectious Diseases, Clinical Research

8   Merck Research Laboratories

9   North Wales, Pennsylvania

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11 **TEMPORARY MEMBERS (Voting)**

12 **Lindsey R. Baden, MD**

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14 Director of Clinical Research

15 Division of Infectious Diseases

16 Brigham and Women's Hospital

17 Director, Infectious Disease Service

18 Dana-Farber Cancer Institute

19 Associate Professor, Harvard Medical School

20 Boston, Massachusetts

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1   **Debra Dunn**

2   *(Patient Representative)*

3   Libertyville, Illinois

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5   **Randy Hawkins, MD**

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15   Research Scientist, Wadsworth Center

16   New York State Department of Health

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1 **Jurgen Venitz, MD, PhD**

2 Professor and Vice Chairman

3 Virginia Commonwealth University

4 School of Pharmacy

5 Department of Pharmaceutics

6 Richmond, Virginia

7

8 **FDA PARTICIPANTS (Non-Voting)**

9 **Edward Cox, MD, MPH**

10 Director

11 Office of Antimicrobial Products (OAP)

12 Office of New Drugs (OND), CDER, FDA

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14 **Sumathi Nambiar, MD, MPH**

15 Director

16 Division of Anti-Infective Products (DAIP)

17 OAP, OND, CDER, FDA

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19 **Shrimant Mishra, MD, MPH**

20 Medical Officer

21 DAIP, OAP, OND, CDER, FDA

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1   **<u>Daniel Rubin, PhD</u>**

2   Statistical Reviewer

3   Division of Biometrics IV (DBIV)

4   Office of Biostatistics (OB)

5   Office of Translational Sciences (OTS), CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

1   P R O C E E D I N G S

2   (8:30 a.m.)

3   **Call to Order**

4   **Introduction of Committee**

5   DR. BADEN: It is 8:30. We shall begin the

6   day's work.

7   Good morning. I would like to remind

8   everyone to please silence your cell phones,

9   smartphones, and any other devices if you've not

10   already done so. I would also like to identify the

11   FDA press contact, Teresa Eisenman, who is in the

12   back at the left.

13   My name is Dr Lindsey Baden. I am

14   chairperson of the Antimicrobial Drug Advisory

15   Committee, and I will be chairing this meeting. I

16   will now call this meeting to order. We'll start

17   by going around the table and introduce ourselves.

18   We'll start with the FDA on the left.

19   DR. COX: Good morning. Ed Cox, director of

20   the Office of Antimicrobial Products at CDER, FDA.

21   DR. NAMBIAR: Good morning. Sumathi

22   Nambiar, director, Division of Anti-Infective

Products, CDER, FDA.

DR. MISHRA: Shrimant Mishra, clinical reviewer for FDA.

DR. RUBIN: Dan Rubin, Office of Biostatistics, CDER, FDA.

DR. PALEVSKY: Paul. Palevsky. I'm a nephrologist from the University of Pittsburgh and the VA Pittsburgh Healthcare System.

DR. LE: Jennifer Le, pharmacy from UC San Diego.

DR. VENITZ: Jurgen Venitz, clinical pharmacologist and professor at Virginia Commonwealth University.

DR. SCHAENMAN: Joanna Schaenman, infectious diseases, David Geffen School of Medicine at UCLA.

DR. LO RE: Good morning. Vin Lo Re, Division of Infectious Diseases, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania.

DR. DASKALAKIS: Demetre Daskalakis, infectious diseases, New York City Department of Health, deputy commissioner for disease control.

1   DR. CHEE: Cindy Chee, acting designated

2 federal officer for AMDAC.

3   DR. BADEN: Lindsey Baden, infectious

4 diseases physician at Brigham Women's Hospital,

5 Dana Farber Cancer Center, and Harvard Medical

6 School.

7   DR. WEINA: Peter Weina, infectious disease

8 physician and director of research at the Walter

9 Reed National Military Medical Center.

10   DR. HONEGGER: Jonathan Honegger, pediatric

11 infectious diseases, Ohio State University.

12   DR. GREEN: Michael Green, pediatric

13 infectious diseases, Children's Hospital,

14 Pittsburgh and the University of Pittsburgh School

15 of Medicine.

16   DR. GRIPSHOVER: Barb Gripshover, adult

17 infectious diseases from University Hospitals

18 Cleveland Medical Center at Case Western Reserve

19 University.

20   DR. CLARK: Nina Clark, infectious diseases,

21 Loyola University Medical Center in Maywood,

22 Illinois.

1   DR. FOLLMANN: Dean Follmann, head of

2 biostatistics at the National Institute of Allergy

3 and Infectious Diseases.

4   DR. HAWKINS: Barney Randy Hawkins, internal

5 medicine and pulmonary medicine, Los Angeles,

6 California.

7   MS. DUNN: Debra Dunn, patient

8 representative.

9   DR. REJ: Good morning. I'm Bob Rej,

10 clinical chemist and hematologist, New York State

11 Department of Health in Albany in the School of

12 Public Health at the State University of New York

13 at Albany.

14   DR. KARTSONIS: Good morning. I'm the

15 industry rep. I'm Nick Kartsonis, and I represent

16 Merck Research Company.

17   DR. BADEN: I would like to thank all the

18 committee members for making the time and joining

19 us both yesterday and today.

20   For topics such as those being discussed at

21 today's meeting, there are often a variety of

22 opinions, some of which are quite strongly held.

1   Our goal is that today's meeting will be a fair and

2   open forum for discussion of these issues and that

3   individuals can express their views without

4   interruption. Thus as a gentle reminder,

5   individuals be allowed to speak into the record

6   only if recognized by the chairperson. We look

7   forward to a productive meeting.

8   In the spirit of the Federal Advisory

9   Committee Act and the Government in the Sunshine

10   Act, we ask that the advisory committee members

11   take care that their conversations about the topic

12   at hand take place in the open forum of the

13   meeting. We are aware that members of the media

14   are anxious to speak with the FDA about these

15   proceedings, however, FDA will refrain from

16   discussing the details of this meeting with the

17   media until its conclusion.

18   Also, the committee is reminded to please

19   refrain from discussing the meeting topic during

20   breaks or lunch. Thank you.

21   I'll now pass to Dr Cindy Chee, who will

22   read the Conflict of Interest Statement.

Conflict of Interest Statement

1

DR. CHEE: The Food and Drug Administration

is convening today's meeting of the Antimicrobial

Drugs Advisory Committee under the authority of the

Federal Advisory Committee Act of 1972. With the

exception of the industry representative, all

members and temporary voting members of the

committee are special government employees or

regular federal employees from other agencies and

are subject to federal conflict of interest laws

and regulations.

The following information on the status of

this committee's compliance with federal ethics and

conflict of interest laws, covered by but not

limited to those found at 18 USC Section 208, is

being provided to participants in today's meeting

and to the public.

FDA has determined that members and

temporary voting members of this committee are in

compliance with federal ethics and conflict of

interest laws. Under 18 USC Section 208, Congress

has authorized FDA to grant waivers to special

1 government employees and regular federal employees

2 who have potential financial conflicts when it is

3 determined that the agency's need for special

4 government employees' services outweighs his or her

5 potential financial conflicts of interest, or when

6 the interest of a regular federal employee is not

7 so substantial as to be deemed likely to affect the

8 integrity of the services which the government may

9 expect from the employee.

10   Related to the discussions of today's

11 meeting, members and temporary voting members of

12 this committee have been screened for potential

13 financial conflict of interest of their own as well

14 as those imputed to them, including those of their

15 spouses or minor children, and for purposes of 18

16 USC, Section 208, their employers. These interests

17 may include investments, consulting, expert witness

18 testimony, contracts, grants, CRADAS, teaching,

19 speaking, writing, patents and royalties, and

20 primary employment.

21   Today's agenda involves discussion of new

22 drug application 210303 for plazomicin sponsored by

1   Achaogen, Inc. for the proposed indications for the

2   treatment of complicated urinary tract infections

3   and blood stream infections in adults. This is a

4   particular matters meeting during which specific

5   matters related to Achaogen's NDA will be

6   discussed. Based on the agenda for today's meeting

7   and all financial interests reported by the

8   committee members and temporary voting members, no

9   conflict of interest waivers have been issued in

10   connection with this meeting. To ensure

11   transparency, we encourage all standing committee

12   members and temporary voting members to disclose

13   any public statements that they have made

14   concerning the product at issue.

15   With respect to FDA's invited industry

16   representative, we would like to disclose that

17   Dr. Nicholas Kartsonis is participating in this

18   meeting as a nonvoting industry representative

19   acting on behalf of regulated industry.

20   Dr. Kartsonis' role at this meeting is to represent

21   industry in general and not any particular company.

22   Dr. Kartsonis is employed by Merck and Co.

1   We would like to remind members and

2 temporary voting members that if the discussions

3 involve any other products or firms not already on

4 the agenda for which an FDA participant has a

5 personal or imputed financial interests, the

6 participants need to exclude themselves from such

7 involvement and their exclusion Will be noted for

8 the record. FDA encourages all other participants

9 to advise the committee of any financial

10 relationships that they may have with the firm at

11 issue. Thank you.

12   DR. BADEN: We will now proceed with the

13 FDA's introductory remarks from Dr. Sumathi

14 Nambiar, director of the Office of the

15 Anti-Infective Products.

16   **FDA Opening Remarks - Sumathi Nambiar**

17   DR. NAMBIAR: Thank you, Dr. Baden.

18   Good morning everybody, and welcome to

19 today's meeting of the Antimicrobial Drugs Advisory

20 Committee convened to discuss NDA 210303,

21 plazomicin sulfate injection. The applicant is

22 Achaogen. The product has qualified infectious

1   disease product designation for the following

2   indications: complicated urinary tract infections,

3   catheter related bloodstream infections, hospital

4   acquired bacterial pneumonia, ventilator-associated

5   bacterial pneumonia, and complicated

6   intra-abdominal infections.

7   The product was also granted breakthrough

8   therapy designation for the treatment of blood

9   stream infections caused by certain

10   enterobacteriaceae in patients who have limited or

11   no alternative treatment options. The applicant

12   has requested review of the BSI indication under

13   Section 506(h) of the Federal Food, Drug, and

14   Cosmetic Act, or the LPAD pathway, which I'll touch

15   upon in subsequent slides. The NDA was granted

16   priority review, as the product has QIDP

17   designation.

18   The applicant is seeking the following two

19   indications, as a single agent in patients 18 years

20   of age or older for the treatment of complicated

21   urinary tract infections, including pyelonephritis

22   caused by the following susceptible organisms. The

1   second indication is for patients aged 18 years or

2   older for the treatment of BSIs caused by

3   Klebsiella pneumoniae and Escherichia coli.

4   For both indications, the applicant is

5   proposing including the following language in

6   labeling, "As only limited clinical safety and

7   efficacy data for plazomicin are currently

8   available, plazomicin should be reserved for use in

9   patients who have limited or no alternative

10   treatment options."

11   The proposed dosing is based on creatinine

12   clearance, and the dosing intervals could be every

13   24 hours, every 48 hours, and the dose could be 10

14   or 15 mgs per kg. In addition, the applicant's

15   proposing therapeutic drug monitoring. An

16   AUC-based approach is proposed for bloodstream

17   infections and a Cmin-based approach for patients

18   with a cUTI if they have moderate to severe renal

19   impairment or the anticipated duration of therapy

20   is greater than 5 days.

21   I'll spend the next couple of minutes

22   talking about the 21st Century Cures Act and LPAD,

1   signed into law on December 13th of 2016, and

2   Section 3042 is the limited population pathway for

3   antibacterial and antifungal drugs, otherwise known

4   as the LPAD pathway. The requirements for LPAD are

5   as follows. The drug should be intended to treat a

6   serious or life-threatening infection in a limited

7   population of patients with unmet needs. It's

8   important to know that the standards for approval

9   still need to be met under the LPAD pathway, and

10   the sponsor needs to submit a written request that

11   the drug be approved as a limited population drug.

12   To meet the standards for approval, the

13   sponsor must provide substantial evidence of

14   effectiveness for the drugs intended use and

15   sufficient information to conclude that it is safe

16   for use under the conditions prescribed,

17   recommended, or suggested in the proposed labeling.

18   In our determination if a product is safe and

19   effective, we require substantial evidence of

20   effectiveness for treatment of the proposed

21   indication, and the benefits for the proposed

22   population must outweigh the risks.

1   Substantial evidence requires evidence

2   consisting of adequate and well-controlled

3   investigations, and the criteria for adequate and

4   well-controlled trials are described in 21

5   CFR 314.126. We might consider data from one

6   adequate and well-controlled trial with other

7   confirmatory evidence to constitute substantial

8   evidence.

9   Accepting greater uncertainty or higher risk

10   in patients with serious disease and with an unmet

11   need is an appropriate approach to risk-benefit

12   assessment, however, it's important to note that

13   flexibility in regulations do not allow for

14   marketing approval prior to demonstration of

15   substantial evidence of effectiveness.

16   Additional requirements under LPAD relate to

17   labeling and promotional materials. All

18   advertising and labeling will include a limited

19   population in a prominent manner and the

20   prescribing information will also contain a

21   statement that this drug is indicated for use in a

22   limited and specific population of patients.

1   Promotional materials need to be submitted at least

2   30 days prior to dissemination of such materials.

3   Moving on to the plazomicin development

4   program, the applicant has conducted six phase 1

5   studies, including a lung penetration study,

6   thorough QT study, and a renal impairment study.

7   There's a phase 2 trial and the phase 3 trial in

8   adults with cUTI/acute pyelonephritis and a phase 3

9   trial in adults with bloodstream infection or a

10 HABP/VABP.

11   Briefly, the phase 2 UTI trial, study 002,

12 evaluated two doses of plazomicin 10 milligram per

13 kilogram or 15 milligram per kilogram, and

14 plazomicin was compared to levofloxacin.

15 Plazomicin was administered for 5 days. There was

16 no option to switch to oral therapy. Patients with

17 creatinine clearance less than 60 mL per minute

18 were excluded from this trial. The primary

19 endpoint was microbiologic eradication of the test

20 of cure visit. In general, the group that received

21 15 mgs per kg were similar in terms of outcomes

22 compared to the levofloxacin arm.

1   Study 009 is the phase 3 cUTI trial. It's a

2   randomized, double-blind NI trial where plazomicin

3   was compared to meropenem. In general, the trial

4   design was consistent with our cUTI guidance.

5   After a minimum of 4 days of blinded IV therapy,

6   patients in both arms of the study could be

7   switched to open-label, oral levofloxacin for an

8   additional 3 to 6 days. The co-primary endpoint

9   was a composite of clinical cure rate and

10   microbiologic eradication. The primary analysis

11   population was the microbiologic modified

12   intent-to-treat population, and the co-primary

13   assessments were made at day 5 in the test of cure

14   visits.

15   The prespecified NI margin was 15 percent,

16   which is wider than what we typically accept for

17   development programs, and that was because if the

18   product were to be approved, labeling would include

19   a statement that it be reserved for use in patients

20   who have limited or no alternative treatment

21   options. In this trial, dose adjustment was based

22   on creatinine clearance. Therapeutic drug

1   monitoring was not performed.

2   In general, plazomicin was noninferior to

3   meropenem at the day 5 and TOC visits in the

4   primary analysis population, and the prespecified

5   NI margin of 15 percent was met.

6   The second phase 3 trial, study 007, was in

7   patients with bloodstream infections or HABP/VABP.

8   This was a randomized, open-label superiority trial

9   where plazomicin was compared to colistin and

10   patients had to have carbapenem resistant

11   enterobacteriaceae. In both arms of the trial,

12   patients could receive concomitant tigecycline or

13   meropenem, and this was based on the susceptibility

14   of the baseline organism.

15   The primary efficacy endpoint when the trial

16   was originally designed was 28-day all-cause

17   mortality. The primary analysis population was the

18   microbiologic modified intent-to-treat population,

19   which included all randomized patients who had

20   received at least one dose of study drug and had

21   CRE isolated from an acceptable study qualifying

22   baseline specimen. The original sample size for

1   the study was 286 patients with confirmed CRE. The

2   statistical significance level that was agreed to

3   was the one-sided alpha of 0.05, and Dr. Rubin will

4   discuss this further in his presentation.

5   There were two protocol amendments. The

6   first amendment changed the primary efficacy

7   endpoint from 28-day all-cause mortality to a

8   composite of 28-day all-cause mortality or

9   significant disease related complications such as

10   new or worsening ARDS, a new lung abscess, empyema,

11   onset of septic shock, and persistent CRE

12   bacteremia. In the second amendment, and

13   uncontrolled cohort 2 was created, and this would

14   include patients who were not eligible for cohort

15   1.

16   This study was stopped after two years, as

17   the applicant encountered difficulties in enrolling

18   patients in this trial. The final sample size in

19   the randomized cohort to cohort 1 was 37 in the

20   primary analysis population. The statistical

21   analysis plan was finalized after enrollment was

22   completed, but before they were unblinding of the

1   results, and the SAP stated that no formal

2   hypothesis testing was to be performed.

3   The initial dose and dosing interval in the

4   study were adjusted based on baseline estimated

5   creatinine clearance or the type of renal

6   replacement therapy, and subsequent doses were

7   adjusted as needed based on therapeutic drug

8   monitoring using measured plazomicin plasma

9   concentrations and dose adjustment equations.

10   If you look at the clinical outcomes in

11   study 007, using the 28-day all-cause mortality or

12   SDRCs, which was the endpoint following the first

13   amendment, the mortality rates in the plazomicin

14   arm were lower than what was seen in the colistin

15   arm and it provided the 90 percent confidence

16   intervals and the p-value for that. Similarly, for

17   the 28-day all-cause mortality, the mortality rates

18   in the plazomicin treated patients were lower than

19   what was seen in the colistin arm, and similarly,

20   the 90 percent confidence intervals here extend

21   from 1 to 52 percent and provided the p-value.

22   If you look at the outcomes by subgroups,

1   the first row has the results I just showed you,

2   which is the overall population, which includes

3   patients with bloodstream infections as well as

4   HABP/VABP, and then specifically of the subgroup of

5   BSI and the subgroup of HABP/VABPs, in the overall

6   population, the treatment difference was 26 percent

7   with the lower mortality seen in plazomicin treated

8   patients. The exact 90 percent CI spread from

9   minus 1 to 51 percent, and the one-sided exact

10   p-value is .09. In the BSI subpopulation, the

11   treatment difference of 39 percent and the

12   confidence intervals from 9 percent to 66 with a p

13   of 0.03.

14   Looking at it for the other endpoint, which

15   was the 28-day all-cause mortality, the mortality

16   rates in the plazomicin patients were lower than

17   the colistin treated patients and provided the

18   confidence intervals and p-value here as well.

19   The primary safety assessment in this NDA

20   was based on the phase 3 cUTI trial with some

21   supportive evidence from the phase cUTI trial,

22   where a few patients received the proposed 15 mgs

1   per kg dose. Safety from study 007, which was the

2   BSI HABP/VABP study, was assessed separately

3   because there were inherent differences between

4   patients in this trial and the other trials; for

5   example, the duration of treatment, the patient

6   population use of concomitant medications. In

7   general, the safety of plazomicin is consistent

8   with what's known about the aminoglycoside class.

9   There is a signal for nephrotoxicity, and the

10 potential for ototoxicity cannot be ruled out.

11   So we'll have presentations by the applicant

12 followed by presentations by the FDA. The FDA

13 presentations will be as follows. Dr. Sun will

14 discuss the efficacy seen in the cUTI trial.

15 Dr. Rubin and Dr. Mishra will discuss the efficacy

16 findings in study 007, which is the BSI HABP/VABP

17 study. Dr. Mishra will then provide a summary of

18 the safety inflammation for this NDA. And then we

19 have two presentations from clinical pharmacology

20 primarily focused on aspects of therapeutic drug

21 monitoring as it relates to the cUTI indication.

22 Dr. Zhuang and Dr. Wu will each have their

1   presentations, one for cUTI and one for BSI. We

2   have time for clarifying questions following both

3   the applicant presentation and the FDA

4   presentation. After lunch, we have an open public

5   hearing followed by questions for the committee.

6   We have two voting questions for the

7   committee today. The first one is, has the

8   applicant provided substantial evidence of the

9   safety and effectiveness of plazomicin for the

10   treatment of complicated urinary tract infections

11   in patients with limited or no treatment options?

12   If yes, please provide any recommendations for

13   labeling. If no, please discuss additional studies

14   or analyses that are needed.

15   The second question is, has the applicant

16   provided substantial evidence of the safety and

17   effectiveness of plazomicin for the treatment of

18   bloodstream infections in patients with limited or

19   no treatment options? If yes, please provide any

20   recommendations for labeling. If no, please

21   discuss additional studies or analyses that are

22   needed.

1   With that, thank you and look forward to the

2   discussions today.

3   DR. BADEN: Thank you, Dr. Nambiar for an

4   overview of the day's data discussions.

5   We'll now move to the applicant

6   presentations.

7   Both the FDA and the public believe in a

8   transparent process for information-gathering and

9   decision-making. To ensure such transparency at

10   the advisory committee meeting, FDA believes that

11   it is important to understand the context of an

12   individual's presentation. For this reason, FDA

13   encourages all participants, including the

14   applicant's non-employee presenters, to advise the

15   committee of any financial relationships that they

16   may have with the applicant such as consulting

17   fees, travel expenses, honoraria, and interest in a

18   sponsor, including equity interests and those based

19   upon the outcome of the meeting.

20   Likewise, FDA encourages you at the

21   beginning of your presentation to advise the

22   committee if you do not have any such financial

1   relationships. If you choose not to address this

2   issue of financial relationships at the beginning

3   of your presentation, it will not preclude you from

4   speaking.

5   We'll now proceed with Achaogen's

6   presentations.

7   **Applicant Presentation - Anne Keane**

8   MS. KEANE: Thank you.

9   Good morning. My name is Anne Keane, and

10   I'm head of regulatory affairs and clinical quality

11   assurance at Achaogen. I'd first like to take this

12   opportunity to thank the division. Throughout the

13   plazomicin development program, you have been

14   unfailingly generous and collaborative with your

15   time and expertise, and the plazomicin program has

16   benefited greatly from both. I'd also like to

17   thank BARDA. Without your support, plazomicin

18   development would never have been possible. And

19   finally, I'd like to thank the members of the

20   committee for this opportunity to present the

21   plazomicin data today.

22   Plazomicin is a new aminoglycoside intended

1   for systemic use. It was engineered to overcome

2   the common mechanisms of resistance to the approved

3   aminoglycosides. The key target pathogens for

4   plazomicin are the enterobacteriaceae, including

5   drug-resistant strains. The clinical development

6   of plazomicin began in 2008 and is focused on the

7   treatment of serious infections due to multidrug

8   enterobacteriaceae, including CRA, for patients

9   with limited or no alternative treatment options.

10   Study 007, the first of its kind superiority

11   study of plazomicin in patients with bloodstream

12   infections or HABP/VABP due to CRE, was open in

13   early 2014. Over the next two years, Achaogen met

14   with the division several times to discuss

15   study 007 enrollment challenges and study

16   feasibility, amending the study twice in an attempt

17   to increase enrollment. In spite of those efforts

18   and due to the continued slow enrollment, an

19   alternative pathway to approval based on a single

20   phase 3 cUTI study was agreed upon with the

21   division. And in December of 2015, Achaogen opened

22   study 009.

1   Enrollment in study 009 proceeded very

2 quickly. In the spring of 2016, as completion of

3 study 009 approached, enrollment projection

4 suggested that study 007 would not be completed in

5 a relevant time frame with earliest possible NDA

6 submission toward the end of 2022. Achaogen then

7 agreed with the division on a stopping rule for

8 study 007 that would allow the data from 007 to be

9 included in an initial plazomicin NDA based on the

10 results of study 009.

11   In August of 2016, study 009 was completed

12 and study 007 was closed to enrollment. Top-line

13 data from both studies became available in December

14 of 2016. In May of 2017, FDA granted breakthrough

15 therapy designation for the BSI indication because

16 the findings in study 007 demonstrated preliminary

17 evidence of a substantial improvement over existing

18 therapies.

19   In October of 2017, Achaogen submitted the

20 NDA for plazomicin requesting indications for cUTI

21 and BSI both for patients with limited treatment

22 options. We've requested review of the data

1   supporting the BSI indication under the new limited

2   population antibacterial drug or LPAD pathway.

3   Study 009 was designed in accordance with

4   FDA's 2013 unmet need guidance, which lays out a

5   streamlined development program available for

6   antibiotics intended to treat patients with unmet

7   need. Antibiotics approved via this pathway will

8   have a limited treatment option statement in the

9   indication section of the label.

10   These programs are still required to meet

11   the normal statutory standard for efficacy and

12   safety, but there is some flexibility in the

13   statistical requirements for the study; for

14   example, a wider noninferiority margin or a

15   superiority study with less stringent statistical

16   requirements may be acceptable. Importantly, the

17   study can be conducted in patients who have

18   alternative treatment option significantly

19   increasing enrollment feasibility for these

20   studies. However, all of these options still

21   require a fairly large trial in the hundreds of

22   patients.

1   In 2016, Congress passed the 21st Century

2   Cures Act, creating a new pathway called the

3   limited population antibacterial drug, or LPAD

4   pathway. This legislation was the result of many

5   years of effort on the part of professional

6   societies, the antibiotic industry, and government

7   agencies, and it was intended to create a feasible

8   pathway to approval to advance and incentivize the

9   development of antibiotics against the most urgent

10   antibacterial needs, including the need for new

11   antibiotics for infection due to MDR pathogens.

12   Its passage reflects recognition by Congress

13   that large clinical trials are not possible for

14   serious and life-threatening infections, which

15   occur in limited populations and that physicians

16   and patients are generally willing to accept

17   greater uncertainty from drugs that treat

18   life-threatening and severely debilitating

19   illnesses. The plazomicin BSI indication will be

20   the first application reviewed under the LPAD

21   pathway.

22   The statute permits flexibility to approve

1   an antibiotic, alone or in combination, if the

2   antibiotic is intended to treat a serious or

3   life-threatening infection in a limited population

4   of patients. While this substantial evidence

5   standard must be met, the statute states that the

6   determination of safety and effectiveness must

7   reflect the benefit-risk profile of the drug in the

8   limited population, and it must take into account

9   the severity and rarity or prevalence of the

10 infection the drug is intended to treat and the

11 availability of alternative treatment options.

12   Antibiotics approved by this pathway will

13 require prior review of all promotional materials

14 by the FDA and a limited population statement will

15 be placed prominently next to the drug name on all

16 promotional and labeling materials.

17   My colleagues will describe the totality of

18 the evidence that supports the approval of

19 plazomicin for the BSI indication via the LPAD

20 pathway. This includes data from studies 007 and

21 009, extensive in vitro and relevant animal data,

22 and PKPD data that supports a high probability of

1   target attainment, and exposures achieved in our

2   clinical trials. The data package provides

3   substantial evidence of efficacy and safety and

4   describes a positive benefit-risk for plazomicin

5   for the treatment of BSI in patients who have

6   limited or no treatment options in accordance with

7   the LPAD statute.

8   Our proposed indications for plazomicin will

9   include a limitations-of-use statement, advising

10   prescribers that limited safety and efficacy data

11   are currently available and to reserve plazomicin

12   for use in patients who have limited or no

13   alternative treatment options. The limited-use

14   statement will apply to both the treatment of

15   urinary tract infection, including pyelonephritis

16   due to the pathogens listed here, and the treatment

17   of bloodstream infections caused by Klebsiella

18   pneumoniae and E coli.

19   Turning to the agenda for the rest of

20   Achaogen's presentation, Dr. Jamie McKinnell, an

21   infectious disease specialist and researcher from

22   the David Geffen School of Medicine at UCLA, will

1 discuss the current unmet medical need. Kevin

2 Krause, Achaogen's head of microbiology, will

3 presents the microbiology and clinical pharmacology

4 of plazomicin. Dr. Ian Friedland, a clinical

5 consultant, will review the efficacy data, and

6 Dr. Lynn Connolly, clinical consultant, will

7 present the safety data and then conclude with a

8 benefit-risk assessment.

9   We have several additional experts with us

10 today. All outside experts have been compensated

11 for their time and travel to today's meeting.

12 Thank you. It's my pleasure now to turn the lectern

13 over to Dr. McKinnell.

14   **Applicant Presentation - James McKinnell**

15   DR. McKINNELL: Good morning. My name is

16 James McKinnell. I'm an infectious disease

17 physician based in Los Angeles, California. My

18 research focuses on treatment of CRE infections and

19 the epidemiology of CRE in the United States. I

20 will focus my presentation today on

21 enterobacteriaceae. When I look at this list of

22 organisms and try to remember which organisms fall

1   into the family of enterobacteriaceae, I tend to

2   think of them as all of the healthcare-associated

3   gram-negative rods that aren't pseudomonas,

4   acinetobacter, and stenotrophomonas.

5   E. coli is the most common cause of

6   bacterial infection in man and is a driving factor

7   in the epidemiology of extended-spectrum

8   beta-lactamase or ESBL producing infections.

9   Enterobacter and klebsiella are driving forces of

10   carbapenem resistant enterobacteriaceae or CRE.

11   ESBL are considered a serious public health threat

12   by the CDC largely because of the overall burden of

13   disease and the impact of ESBL on carbapenem

14   consumption.

15   ESBL infections are notoriously difficult to

16   treat. ESBLs degrade many cephalosporins,

17   including ceftriaxone and antipseudomonal

18   cephalosporins like cefepime and ceftazidime. They

19   also frequently carry cross-class resistance to

20   other antibiotics, including fluoroquinolones and

21   aminoglycosides. As a result, delayed appropriate

22   therapy is common, which leads to initial

1   antibiotic failure, higher infection related

2   mortality, and higher infection related

3   readmissions.

4   ESBL is becoming common. On the left, you

5   see community acquired prevalence of ESBL E. coli.

6   So on the left is ESBL E. coli from the community,

7   and on the right hospital-associated prevalence.

8   These data are concerning. By the end of 2014,

9   16 percent of community and 28 percent of hospital

10 E. coli were ESBL producers. A common strategy to

11 mitigate morbidity and mortality is to use

12 carbapenem therapy often including carbapenems

13 during empiric regimens.

14 I'm again showing you the prevalence of ESBL

15 among hospital-associated UTI due to E. coli.

16 These are the number of UTI in patients treated

17 with a carbapenem between 2004 and 2009. You can

18 see it stays stable at approximately a 100,000

19 patients per year. After 2009, we see an increase

20 in carbapenem use coincident with the rise in

21 prevalence of ESBL UTIs. The rise in carbapenem

22 use has led to another problem, carbapenem

1   resistance.

2   CRE are the worst of the MDR

3   enterobacteriaceae. They are classified by the

4   World Health Organization as a priority pathogen

5   for research and drug development. The CDC calls

6   them an urgent public health threat. The concern

7   with CRE is that first CRE is spreading. Second,

8   we have limited treatment options and high

9   mortality.

10   CRE first emerged largely in the Mid

11   Atlantic states and began to spread through

12   transfer of patients from one healthcare setting to

13   another. We now document CRE in all 50 states.

14   Not only do we see geographic spread, we also see

15   rising burden of disease with increasing CRE

16   hospitalizations over the last few years. The

17   particular studies shown here use patient level

18   data from nearly 300 hospitals to project national

19   estimates. The results mirror findings from other

20   studies supporting arise in CRE hospitalizations.

21   CRE infections have consequences. CRE

22   infections have attributable mortality rates of 30

1   to 40 percent for serious infections such as

2   intra-abdominal infections, pyelonephritis,

3   pneumonia, and worst of all, bacteremia. Among all

4   of the CRE infections, bloodstream infections are

5   clearly the most lethal.

6   For multiple publications around the world,

7   CRE bloodstream infections are associated with 40

8   to 50 percent mortality by day 30. CRE BSI

9   frequently occurs in complex, critically ill

10   patients. Source of bacteremia can be difficult to

11   determine either because an individual patient has

12   multiple potential sources, including intravascular

13   catheters, or the patient may be immunosuppressed.

14   When no source is found, these patients are deemed

15   to have primary bacteremia.

16   In published studies and in clinical

17   experience, primary bacteremia and

18   catheter-associated bacteremia are common and

19   associated with high mortality. In studies that

20   report mortality for primary and

21   catheter-associated bacteremia, we see a range of

22   mortality from 32 to 79 percent.

1   Optimal treatment strategies for CRE have

2   previously been defined by clinical experience and

3   non-randomized observational data. The current

4   treatment mantra for CRE has been combination

5   therapy or double coverage. The original data

6   comes largely from clinical experience of failures

7   with monotherapy and meta-analyses of observational

8   studies. You can clearly see the observed survival

9   benefit of combination therapy in this reference.

10   Crafting a combination therapy regimen can

11   be challenging. These are data from a national

12   selection of long-term acute care hospitals. You

13   can see here that fluoroquinolone resistance among

14   CRE is 98 percent, essentially eliminating this

15   class of antibiotics. Gentamicin or tobramycin

16   resistance is again 98 percent; again, little use

17   in treatment. Amikacin is slightly better at 66

18   percent, but that means it's an option for only

19   about a third of patients.

20   Antimicrobial susceptibility of colistin and

21   tigecycline are good, but these are considered

22   agents of last resort. The PKPD profile of

1   tigecycline does not support its use for

2   septicemia, and the FDA has a black box warning

3   that tigecycline has poor efficacy and severe

4   infections.

5   Colistin is an agent that was abandoned for

6   decades due to known issues of toxicity,

7   particularly nephrotoxicity. Dosing of colistin is

8   challenging oftentimes requiring ID pharmacist

9   help, and automated susceptibility testing for

10   colistin is unreliable. Despite the known

11   limitations of tigecycline and colistin, we see

12   broad use of these agents simply because we've had

13   nothing else for CRE infections.

14   The new beta-lactam beta-lactamase inhibitor

15   combinations are recently approved CRE active

16   agents that utilize novel beta-lactamase inhibitors

17   to protect traditional beta-lactam antibiotics from

18   inactivation. For example, beta-lactam protects

19   ceftazidime and vaborbactam protects meropenem.

20   The audience should be aware that CRE can

21   develop carbapenem resistance through one of two

22   mechanisms. CRE can produce a carbapenemase. The

1 novel beta-lactamase inhibitors primarily target

2 KPC. Carbapenem resistance can also develop

3 through expression of a cephalosporinase in

4 combination with a porin mutation or efflux pump

5 overexpression, but the novel beta-lactamase

6 inhibitors do not help in this second scenario.

7   While the newer BL/BLI combinations provide

8 an option, particularly for KPC producing

9 organisms, they have variable or no activity for

10 the non-KPC CRE. Even for KPC, we've observed the

11 emergence of resistance on therapy highlighting the

12 need for additional agents. Unfortunately, non-KPC

13 CRE appears to be on the rise. At ID week last

14 year, LA County Department of Public Health

15 presented data that more than 20 percent of their

16 CRE isolates were non-KPC. In another report from

17 Vancouver, greater than 90 percent of the CRE were

18 non-KPC producers.

19   In summary, we recognize that there is unmet

20 clinical need for ESBL treatment and CRE

21 management. A reliable carbapenem sparing agent

22 for ESPN infections has value from an antibiotic

1 stewardship and resistance perspective. In terms

2 of CRE, a non-beta-lactam agent is a potential

3 combination option with novel BL/BLI agents to

4 prevent on-treatment emergence of resistance and as

5 an alternative when novel beta-lactamases may not

6 be the best choice, either for resistance reasons,

7 deep salvage scenarios, or tolerability issues. In

8 light of the high mortality and lack of effective

9 treatment options, we need antibiotics for patients

10 with these serious infections.

11   Thank you very much for your attention.

12 I'll now turn the podium over to Kevin Krause.

13   **Applicant Presentation - Kevin Krause**

14   DR. KRAUSE: Thank you. My name is Kevin

15 Krause, and I will now review some of the key

16 microbiology and clinical pharmacology attributes

17 of plazomicin. Plazomicin is a new aminoglycoside

18 with activity against enterobacteriaceae, including

19 isolates resistant to currently available

20 aminoglycosides as well as ESBL producers and CRE.

21 Plazomicin inhibited greater than 95 percent of

22 enterobacteriaceae collected in global surveillance

1   studies at an MIC of less than or equal to

2   4 micrograms per milliliter, which is the tentative

3   breakpoint applied during the plazomicin

4   development program. In addition, plazomicin

5   inhibited greater than 90 percent of

6   enterobacteriaceae nonsusceptible amikacin,

7   gentamicin, and/or tobramycin when applying this

8   interpretive criteria.

9   Exposures associated with human doses

10   prevent the emergence of plazomicin resistance in

11   both in vitro and in vivo studies, thereby limiting

12   the potential for clinical resistance development.

13   And finally, efficacy has been demonstrated against

14   target pathogens in a variety of animal models of

15   infection.

16   Aminoglycoside modifying enzymes, or AMEs,

17   which inactivate current aminoglycosides, are the

18   most common form of aminoglycoside resistance.

19   This mechanism is responsible for more than 99

20   percent of aminoglycoside resistance amongst

21   enterobacteriaceae in the United States. AMEs are

22   often found in combination with other resistance

1   elements such as ESBL and carbapenemases, making

2   these isolates multidrug resistant.

3   Plazomicin was designed to overcome AME

4   based resistance and therefore remains active

5   against multidrug resistant enterobacteriaceae. A

6   second less common mechanism of resistance is

7   target-site modification due to 16S rRNA

8   methyltransferases or RMTs. These enzymes result

9   in pan-aminoglycoside resistance, including

10   resistance to plazomicin. However, RMTs are rare

11   and their prevalence is not increasing in the

12   United States despite decades of clinical use of

13   aminoglycosides. Specifically, only 5 RMT

14   producers were found amongst approximately 6500

15   enterobacteriaceae isolates collected in the United

16   States between 2014 and 2016 in the plazomicin

17   surveillance program.

18   Here we show the structure of plazomicin

19   with the major AME classes and their associated

20   sites of action on most aminoglycosides. However,

21   plazomicin lacks the 3-prime and 4-prime hydroxyl

22   groups found in many aminoglycosides, which are

1   targets of several AMEs. In addition, the

2   hydroxyethyl group at 6 prime position blocks the

3   action of AAC 6-prime AMEs, and the HABA group at

4   the N1 position blocks the action of AAC 3 AMEs as

5   well as less common but clinically important AME

6   classes.

7   As a result, plazomicin is active against

8   multidrug resistant enterobacteriaceae, including

9   aminoglycoside nonsusceptible isolates, ESBL

10   producers, and CRE. In addition, plazomicin

11   maintains inhibition of protein synthesis, the

12   rapid concentration-dependent bactericidal

13   activity, and the prolonged post antibiotic effects

14   that are key features of the amino glycoside class.

15   We evaluated the activity of plazomicin

16   against 6,459 enterobacteriaceae in prospective

17   U.S. surveillance studies. Plazomicin was broadly

18   active against these isolates within an MIC 90 of

19   1 microgram per milliliter. Plazomicin retained

20   activity against isolates nonsusceptible to

21   amikacin, gentamicin, and/or tobramycin, and this

22   includes isolates that are nonsusceptible to 2 or

more aminoglycosides when no RMT is present. MIC

90 values ranged from 2 to 4 micrograms per

milliliter against these isolate groups. And as

with the other aminoglycosides, plazomicin is

inactive against 5 isolates containing an RMT.

Plazomicin is active against CRE collected

from global surveillance studies irrespective of

the underlying mechanism of carbapenem resistance.

Plazomicin MICs are less than or equal to

4 micrograms per milliliter against 93 percent of

KPC producers and against 80 percent of

metallo-carbapenemase producers collected from

around the world, including two-thirds of isolates

with an NDM 1 carbapenemase. In addition,

plazomicin retains activity against 80 percent of

OXA 48 carbapenemase producers and 92 percent of

isolates that are a carbapenem resistance in the

absence of a carbapenemase.

Let's now turn to data for plazomicin

against CRE specifically from U.S. surveillance.

Many of these isolates are multidrug resistant,

including to the currently available

1   aminoglycosides through co-expression of AMEs. As

2   a result, only 67 percent of these CRE isolates are

3   susceptible to amikacin, only 53 percent are

4   susceptible to gentamicin, and only 13 percent are

5   susceptible to tobramycin. However, plazomicin

6   retains its potent activity against the CRE

7   isolates because of its stability against AMEs.

8   Overall, 99 percent of these CRE isolates were

9   inhibited by a plazomicin MIC of less than or equal

10   to 4 micrograms per milliliter.

11   Like other aminoglycosides, in vitro synergy

12   between plazomicin and beta-lactams has been

13   demonstrated against enterobacteriaceae. Here we

14   show a synergy time-kill curve of plazomicin in

15   combination with ceftazidime against a multidrug

16   resistant Klebsiella pneumoniae isolate encoding an

17   AME, a KPC, and an ESBL. As expected, ceftazidime

18   alone was inactive.

19   When plazomicin was tested at a

20   concentration of one-quarter of the MIC,

21   bactericidal effects were not maintained through 24

22   hours. However, when plazomicin was tested at this

1   same concentration in combination with ceftazidime,

2   an approximate 6 to 8 log improvement in

3   bactericidal activity was observed at 24 hours

4   compared to either drug tests at alone.

5   The potential for the development of

6   plazomicin resistance was assessed in both in vitro

7   and in vivo models. The enterobacteriaceae

8   isolates were examined in an in vitro chemostat

9   model to understand plazomicin exposures in

10   relation to suppression of resistance development.

11   At plazomicin AUCs of less than or equal to 66,

12   which are well below those achieved with the

13   clinical dose of 15 milligrams per kilogram,

14   resistant isolates were selected with phenotypes

15   similar to those observed in the in vitro passage

16   selection studies demonstrating that these results

17   could be recreated in this model. However, no

18   resistant mutants were observed when exposures were

19   increased to an AUC of 132 or more.

20   Therefore, the mean plazomicin AUC of 236

21   associated with the clinical dose is above the

22   mutant prevention concentration. These results

1   correlate with the results of animal models of

2   infection where no resistance was observed out to

3   96 hours when animals were treated with exposures

4   at or near target exposures in patients.

5   In the phase 3 program, emergence of

6   resistance to plazomicin was infrequent. No

7   resistance development was observed amongst 44

8   plazomicin treated patients in study 007. In

9   study 009, resistance development was observed in 7

10 post-baseline isolates from 6 of 191 plazomicin

11 treated patients. Only 2 of these patients were

12 clinical failures and only 1 required additional

13 antibiotics

14   The majority of the recovered isolates had

15 an identical genetic background to the baseline

16 isolate with the addition of a plasmid containing

17 multiple resistance elements, including an RMT.

18 These isolates were found in patients from eastern

19 Europe, which is a region known to have a higher

20 prevalence of RMTs than any in the United States.

21 Most of these isolates were recovered at or before

22 the end of IV visit, suggesting that they existed

1   at baseline and represent outgrowth of a resistance

2   subpopulation after rapid elimination of the

3   susceptible bacterial population.

4   Now, I'd like to switch to plazomicin PK,

5   PKPD, and nonclinical efficacy. Like other

6   aminoglycosides, plazomicin has predictable and

7   linear PK with low protein binding of approximately

8   20 percent. The plazomicin half-life is

9   approximately 4 to 5 hours in the patient

10   population studied with more than 97 percent of the

11   dose eliminated via the kidney as unchanged drug.

12   And finally, there is a low potential for drug-drug

13   interactions as determined by a comprehensive

14   preclinical package and data from a phase 1

15   drug-drug interaction study.

16   The proposed plazomicin dose is 15

17   milligrams per kilogram once daily administered as

18   a 30-minute intravenous infusion for patients with

19   normal renal function or mild renal impairment. As

20   shown in this dosing table, dose adjustments are

21   recommended for patients with moderate or severe

22   renal impairment as plasma clearance of plazomicin

significantly decreases with decreasing renal

function.

To ensure adequate therapy while minimizing

unnecessary exposure, the proposed duration of

treatment is 4 to 7 days of IV therapy for patients

with cUTI, including those with pyelonephritis, and

7 to 14 days of treatment for patients with

bloodstream infection.

Therapeutic drug management is standard

practice for aminoglycosides and therefore also

recommended for a subset of plazomicin treated

patients. For patients with bloodstream

infections, and AUC based TDM approach is

recommended. This approach requires 2 blood

samples and is designed to decrease the risk of

poor outcomes due to under exposures in this

critically ill patient population while also

reducing the potential for toxicity due to

overexposure. In the subset of cUTI patients at

increased risk for nephrotoxicity, a Cmin or trough

based approach is recommended. This approach

requires a single blood draw and is designed to

1   reduce the potential for toxicity due to

2   overexposure.

3   Additionally, a plazomicin specific assay

4   has been developed. Overall, these TDM based dose

5   adjustments are intended to maintain exposures

6   within a target range associated with efficacy

7   while avoiding sustained high exposures that may

8   lead to toxicity. As with other amino

9   aminoglycosides, the ratio of the AUC to MIC is the

10   PKPD driver of efficacy.

11   The probability of target attainment by MIC

12   is shown here by the blue line for patients with

13   cUTI when applying a stasis target. A stasis

14   target is appropriate for use in cUTI because

15   plazomicin concentrates at the effect site, and

16   this infection type is associated with fewer

17   comorbidities and low attributable mortality.

18   These values are overlaid on the MIC distributions

19   of enterobacteriaceae isolates collected from

20   urinary tract infections during U.S. surveillance,

21   shown in dark blue, and the baseline isolates from

22   study 009, shown in light blue.

1   The substantial overlap in these data

2   suggests that the isolates with the described

3   clinical and microbiological outcomes from

4   study 009 are similar to enterobacteriaceae

5   collected from across the United States. These

6   PKPD analyses show that there is a greater than 90

7   percent probability of target attainment in

8   patients with cUTI due to enterobacteriaceae with

9   MICs of less than or equal to 4 micrograms per

10   milliliter.

11   A similar analysis was conducted for

12   patients with bloodstream infections. In red is

13   the probability of target attainment for the 1 log

14   kill target, which is appropriate for patients with

15   bloodstream infection when source control is

16   challenging, when effective combination partner

17   antibiotics aren't available, or in the presence of

18   significant underlying comorbidities.

19   In blue is the probability of target

20   attainment by MIC for the stasis target, which is

21   appropriate for use in patients when used

22   combination therapy or in the setting of available

1   source control. Both of these sets of data or

2   overlaid on the MIC distributions of

3   enterobacteriaceae isolates from bloodstream

4   infections collected during U.S. surveillance,

5   again shown in dark blue, and the baseline isolates

6   from study 007 shown in light blue.

7   As with study 009, the isolates collected in

8   study 007 have a similar MIC distribution with

9   those from U.S. surveillance with the exception of

10   the RMC containing isolates found in this clinical

11   program that had MICs of greater than or equal to

12   128 micrograms per milliliter.

13   These PKPD analyses show that like cUTI,

14   there's a greater than 90 percent probability of

15   target attainment for patients with BSI due to

16   enterobacteriaceae across the vast majority of the

17   MIC distribution. These data support the adequacy

18   of the plazomicin dosing regimen for target

19   pathogens in these patient groups.

20   Additional support for the plazomicin dose

21   comes from in vivo infection models where efficacy

22   was established in various sites of infection and

1   evaluated using human simulated exposures. Initial

2   investigations focus on efficacy against

3   enterobacteriaceae, including aminoglycoside and/or

4   carbapenem resistant strains in the mouse urinary

5   tract, thigh, and lung infection models. These

6   models were associated with reductions in bacterial

7   burden against a diversity of isolates with various

8   resistance mechanisms. Additionally, the efficacy

9   of human simulated exposures of plazomicin were

10 studied in a mouse model of septicemia caused by

11 enterobacteriaceae with a range of plazomicin MICs.

12   This study was designed to provide

13 supportive evidence to the clinical study data for

14 the bloodstream infection indication and was

15 consistent with observed plazomicin exposures and a

16 probability of target attainment analyses.

17 Overall, a single dose of plazomicin monotherapy at

18 a human equivalent exposure led to significant

19 improvements in survival up to 96 hours and rapid

20 clearance of bacteremia. Dr. Dr. Friedland will

21 discuss more detailed results of the study and the

22 clinical efficacy section describing patients with

1   bloodstream infections.

2   In summary plaza, plazomicin is a new

3   aminoglycoside that has potent activity against the

4   majority of enterobacteriaceae, including most

5   aminoglycoside resistant isolates, ESBL producers,

6   and CRE. Plazomicin efficacy has been established

7   in a number of animal models of infection,

8   including in studies using human simulated

9   exposures against target pathogens. Plazomicin

10   pharmacokinetics are predictable and similar to

11   those observed for the aminoglycoside class

12   overall. And finally, the probability of target

13   attainment calculated using plazomicin PKPD targets

14   and Monte Carlo simulations shows that the

15   plazomicin dosing regimen is expected to result in

16   plasma exposures consistent with efficacy against

17   target pathogens in cUTI and BSI patients. Similar

18   results were observed when applying the recommended

19   dose adjustments for patients with impaired renal

20   function.

21   Thank you. I'll now turn the presentation

22   over to Dr. Friedland.

Applicant Presentation - Ian Friedland

DR. FRIEDLAND: Thank you. I'm Ian

Friedland. I was involved in the development of

plazomicin as the chief medical officer at

Achaogen. I'll first review the efficacy results

for the cUTI indication. Overall, the results of

the cUTI study showed plazomicin was non inferior

to meropenem in patients with cUTI, including acute

pyelonephritis. Study 009, also called the EPIC

study, was a randomized, multicenter, double blind

study to evaluate the efficacy and safety of

plazomicin compared to meropenem in adult patients

with complicated urinary tract infection. Patients

received a minimum of 4 days and a maximum of

7 days of IV therapy, and there was an option to

switch to oral therapy in patients sufficiently

improved. The total duration of treatment was 7 to

10 days.

Levofloxacin was a preferred oral switch

agent, but in cases of quinolone resistance or

patient intolerance, other agents were allowed.

There were two follow-up visits, the test of cure

on approximately day 17 and the late follow-up

visit at approximately 4 weeks. The primary

efficacy endpoint was a composite of

microbiological eradication and clinical cure and

was assessed at day 5 and the test of cure visit.

The primary endpoint was assessed in mMITT

population, which consisted of all patients who

received any amount of study drug and had at least

one qualifying baseline uropathogen with growth

exceeding 10 to the 5 organisms per mL.

Of note, in contrast to other recent cUTI

studies, the mMITT population included only

patients whose baseline pathogens were susceptible

to both study drug and comparator, ensuring no

undue bias against meropenem.

Study 000 was a noninferiority study based

on a 15 percent noninferiority margin at both day 5

and the test of cure visit. The 15 percent

noninferiority margin is in accordance with the FDA

unmet need guidance for patients with limited or no

alternative therapies.

The distribution of patients in the various

1   analysis populations was similar in the two

2   treatment groups. 609 patients were randomized,

3   306 to plazomicin and 303 to meropenem. The most

4   frequent reason for exclusion from the mMITT

5   population was lack of a study qualifying baseline

6   pathogen, which is common to cUTI studies.

7   Approximately 64 percent of patients were included

8   in the primary analysis population, the mMITT.

9   Patient demographics and baseline disease

10   characteristics of the mMITT population overall was

11   similar in the two treatment groups and consistent

12   with an acutely ill population with cUTI. Patients

13   were on average 60 years old and approximately

14   40 percent had acute pyelonephritis. Approximately

15   70 percent of patients had mild or moderate renal

16   impairment at baseline, and 12 percent had

17   concomitant bacteremia.

18   The duration of IV and oral treatment was

19   comparable between arms. Patients received a

20   median titled treatment duration of 10 days by

21   which a median of 6 days were IV treatment.

22   Approximately 80 percent of patients switched to

oral therapy, which was mostly levofloxacin. The

proportion of patients who switched to oral

therapy, the type of oral therapy used, and the

duration of use was consistent between plazomicin

and meropenem treated patients.

Plazomicin demonstrated noninferiority to

meropenem with respect to the composite cure rates

at both day 5 and the test of cure visit. At both

time points, the lower bound of the 95 percent

competence interval for the difference between

treatment arms was well above the 15 percent

margin. At the test of cure visit, the lower bound

of the composite interval exceeded zero, suggesting

a statistically higher response rate for plazomicin

over meropenem at this visit.

This figure plots the cumulative proportion

of patients achieving composite cure by study day

and at the two follow-up visits. On IV therapy,

the last of the two treatment groups overlapped.

However, the response rates diverged in favor of

plazomicin at the test of cure and late follow-up

visits.

1   The primary endpoint of composite cure was

2   assessed in important subgroups, and this forest

3   plot shows differences between treatment groups at

4   the test of cure represented by the blue circles

5   with the 95 percent confidence intervals.

6   Treatment differences directionally favorite

7   plazomicin across patient subgroups such as age and

8   renal function, and in both cUTI and acute

9   pyelonephritis. Of note, the comparison favored

10   plazomicin whether or not patients received oral

11   switch therapy.

12   The most common bacterial pathogens where E.

13   coli and Klebsiella, and approximately one-quarter

14   of pathogens had an ESBL phenotype, and a similar

15   proportion were nonsusceptible to other

16   aminoglycosides. Per pathogen microbiological

17   eradication rates were high for plazomicin across

18   the most common species. Importantly, favorable

19   eradication rates were observed for plazomicin in

20   common resistant subgroups such as ESBL-producing

21   pathogens and pathogens not susceptible to

22   currently marketed aminoglycosides.

1   The high cure rates for plazomicin seen in

2   test of cure were maintained at the late follow-up

3   visit conducted at approximately 4 weeks. Both

4   microbiological recurrence and clinical relapse

5   were less common with plazomicin therapy than

6   meropenem therapy, indicating that the benefit of

7   plazomicin was sustained out to the late follow-up

8   visit.

9   In conclusion, plazomicin was noninferior to

10   meropenem based on the co-primary endpoints at day

11   5 and the test of cure, where the statistically

12   higher response rate for plazomicin suggested at

13   test of cure, which was maintained through the late

14   follow-up visit. Subgroup analyses supported the

15   primary plazomicin response observed. And finally,

16   plazomicin demonstrated high eradication rates at

17   test of cure compared to meropenem against the most

18   common gram-negative pathogens, including important

19   resistance subgroups. The outcomes are shown and

20   support the benefit of plazomicin for patients with

21   cUTI who have limited or no alternative treatment

22   options.

1   Let me now review the data supporting

2   efficacy in the BSI indication, including results

3   of the 007 study, also known as CARE. study 007

4   was the first of its kind resistant pathogen focus

5   study. It was intended to demonstrate superiority

6   and be sufficient for registration. Data from that

7   study demonstrated that plazomicin was associated

8   with reduced mortality or significant disease

9   related complications in patients with confirmed

10   CRE BSI compared to standard of care agent

11   colistin.

12   Despite concerted efforts, study 007 proved

13   challenging to enroll. We screened over 2100

14   patients to randomize 39 over a two and a half year

15   period, which is consistent with the experience of

16   other sponsors conducting CRE studies. One of the

17   most challenging barriers to enrollment is

18   obtaining consent in critically ill patients.

19   Other barriers include unpredictable changes in CRE

20   prevalence, which can occur naturally or through

21   infection control measures, and the time required

22   for confirmation of CRE infection that can

1   disqualify patients due to early death or excessive

2   prior antibiotic therapy.

3   In addition, towards the end of the trial,

4   the prevalence of resistance to the comparator

5   colistin was increasing at high enrolling sites.

6   Given the limited size of the clinical data set

7   that could be feasibly obtained in the key target

8   population, the totality of the data generated in

9   the clinical and nonclinical program must be

10   considered.

11   The data I'll be sharing includes efficacy

12   from the randomized cohort of study 007, which

13   provides the primary clinical evidence of

14   plazomicin efficacy in patients with BSI due to

15   CRE, and study 009, the cUTI study, which provides

16   additional randomized control data in patients with

17   BSI from a urinary source. Further supportive

18   clinical data derived from efficacy in the

19   nonrandomized BSI subset from cohort 2 of study 007

20   and nonclinical efficacy from a mouse septicemia

21   model. In all, clinical efficacy data were

22   generated in more than 50 plazomicin treated

1   patients with enterobacteriaceae BSI from a variety

2   of sources.

3   Study 007 consisted of two cohorts,

4   cohort 1, a randomized, controlled, open-label

5   cohort comparing plazomicin to colistin in patients

6   with BSI or HABP/VABP due to CRE, and cohort 2, a

7   single-arm cohort, which was added later in the

8   study, allowing access to plazomicin therapy for

9   patients not eligible for enrollment in cohort 1.

10   Patients with suspected or confirmed

11   infections due to CRE were randomized 1 to 1 to

12   plazomicin or colistin, each in combination with

13   either high dose extended infusion meropenem or

14   tigecycline as chosen by the investigator.

15   Plazomicin 50 milligrams per kilogram doses was

16   subsequently adjusted based on TDM to target the

17   prespecified AUC range. In addition, colistin

18   dosing was optimized, including the use of a

19   loading dose.

20   Patients received 7 to 14 days of IV therapy

21   with a test of cure visit approximately 7 days

22   after the last dose of study therapy and end of

1   study visit at day 28, and a long-term safety visit

2   at day 60. Study 007 was designed to demonstrate

3   superiority of plazomicin compared to colistin in

4   cohort 1 with a primary endpoint of all-cause

5   mortality at day 28 or significant disease related

6   complications.

7   Our original assumptions were that the event

8   rate in the colistin arm would 35 percent with a 12

9   percent absolute reduction in the plazomicin arm.

10   As agreed to with the FDA, in the context of the

11   high unmet need for new treatments for MDR or

12   enterobacteriaceae infections, superiority was to

13   be tested against a one-sided alpha 5 percent

14   corresponding to a 90 percent confidence interval.

15   The results I'll be sharing with you today are

16   descriptive in nature due to the smaller than

17   anticipated sample size.

18   Thirty nine patients were enrolled in cohort

19   1; 18 patients were randomized to plazomicin and 21

20   to colistin. An additional 30 patients were

21   enrolled in cohort 1. In cohort 1, all but one

22   patient in each treatment group had confirmed CRE

infection based on central laboratory testing, and

were thus included in the mMITT, which was the

primary efficacy analysis population. The majority

of these patients across treatment groups and

cohorts had BSI. Due to the low number of

HABP/VABP patients enrolled, conclusions regarding

advocacy in this indication could not be drawn, and

we are thus not seeking an indication for this

patient population.

The demographics and baseline

characteristics of patients enrolled in cohort 1 of

study 007 were reflective of an acutely ill patient

population with serious infections due to CRE. The

majority were male and elderly, and APACHE II

scores were well balanced between treatment arms.

As I mentioned, the majority of patients,

approximately 80 percent, had to be assigned. A

greater proportion of patients in the plazomicin

group had renal impairment or were on continuous

renal replacement therapy at baseline. Most

patients received tigecycline as initial adjunctive

therapy. Because the majority of patients enrolled

1   had BSI, the general demographics for this

2   subpopulation was similar to those in the overall

3   patient population.

4   Here I'll focus on additional

5   characteristics of importance for this key

6   subpopulation of bloodstream infections.

7   Consistent with the literature describing CRE BSI,

8   primary bacteremia was common in both treatment

9   groups. The urinary tract and abdomen were the

10 most common sources of secondary bacteremia.

11 Although most patients did have indwelling

12 intravascular catheters, only one patient in each

13 study arm had an intravascular catheter related

14 infection.

15   Here are the results of the primary

16 endpoints 28-day all-cause mortality or significant

17 disease related complications and a key secondary

18 endpoint all-cause mortality alone in both the full

19 mMITT population and the BSI subgroup. In the full

20 population, plazomicin based therapy was associated

21 with a 26.5 percent absolute reduction in all-cause

22 mortality or SDRCs. The majority of events were

1   driven by deaths with plazomicin demonstrating a 28

2   percent absolute reduction in 28-day all-cause

3   mortality compared to colistin.

4   In the BSI subgroup, plazomicin based

5   therapy was associated with a 39 percent absolute

6   reduction in all-cause mortality or SDRCs and a 33

7   percent absolute reduction in all-cause mortality

8   alone compared to colistin.

9   The 28 day all-cause mortality rate of 40

10   percent in the colistin arm is consistent with our

11   assumptions and with outcomes described in the

12   literature with this agent, suggesting that the

13   comparator arm behaved as expected in this study.

14   Because we are seeking a BSI indication, the

15   remainder of my presentation will focus on

16   additional outcomes in this patient population.

17   Analysis of mortality through day 60

18   revealed that separation between the two treatment

19   groups was observed early in the treatment period

20   and sustained throughout the study with plazomicin

21   treatment associated with a lower rate of mortality

22   through day 60 compared with colistin. The hazard

1   ratio of 0.37 in favor of plazomicin, represented a

2   63 percent reduction in the estimated rate of

3   mortality in patients with BSI.

4   Plazomicin was also associated with faster

5   median time to clearance of CRE bacteremia and a

6   higher proportion of plazomicin treated patients

7   had documented clearance of CRE bacteremia by

8   day 5. No plazomicin treated patient had positive

9   CRE blood cultures after day 10 compared with 3

10   patients in the colistin group. Consistent with

11   results of the time to clearance of bacteremia

12   analysis, the per pathogen favorable

13   microbiological response at test of cure was higher

14   for plazomicin at 93 percent versus colistin at 53

15   percent for CRE pathogens, including those

16   nonsusceptible to currently available

17   aminoglycosides.

18   A number of baseline factors were raised by

19   FDA as having the potential to impact the primary

20   outcome, so I will examine these in the next couple

21   of slides. As expected, because of the time it

22   takes to confirm CRE infection, receipt of

1 antibiotic therapy prior to randomization was high

2 in both treatment arms. Based on susceptibility

3 data, a lower proportion of plazomicin treated

4 patients received potentially effective prior

5 antibiotics suggesting the prior therapy received

6 did not bias the study in favor of the plazomicin

7 group.

8   As required by the protocol, all BSI

9 patients had at least one positive blood culture in

10 the 96 hours prior to randomization. However, as a

11 result of prior therapy and the intimate nature of

12 gram-negative bacteremia, some patients had

13 negative blood cultures in the 24 hours prior to

14 randomization. The proportion of such patients was

15 balanced between the two groups.

16   Now, let's see how these factors impact the

17 primary outcome. Whether patients received

18 effective prior antibiotic therapy or not, the

19 outcomes favored plazomicin. Similarly, the

20 treatment difference favorite plazomicin regardless

21 of the adjunctive agent received. Looking at the

22 impact of negative cultures in the 24 hours prior

1   to enrollment that was observed in some patients,

2   such patients in the colistin arm still had poor

3   outcomes, suggesting that the short courses of

4   prior therapy were insufficient to impact the

5   primary endpoint.

6   Given that these factors were balanced by

7   treatment group or favored colistin and the lack of

8   clear impact on the treatment difference, none of

9   these factors appear to meaningfully impacted the

10   primary outcome or explain the large treatment

11   difference observed in favor of plazomicin therapy.

12   Next, let's turn to the results from study

13   009, which provides additional efficacy data in

14   patients with BSI from a urinary source.

15   Approximately 12 percent of patients enrolled in

16   the phase 3 009 study had bacteremia due to

17   enterobacteriaceae at baseline associated with

18   their urinary tract infection. In this subset of

19   patients, plazomicin demonstrated early and

20   sustained clearance of enterobacteriaceae from the

21   blood with 88 percent and 100 percent documented

22   clearance at day 5 and test of cure, respectively.

1   Next, I'll move to the results from cohort 2

2   of study 007. Cohort 2 patients reflected a more

3   heterogeneous population than cohort 1 patients.

4   Most were male and elderly with a wide range of

5   APACHE II scores. Half of the patients had

6   polymicrobial infection, including 4 patients with

7   coinfections involving pseudomonas or

8   acinetobacter, which are not target pathogens for

9   plazomicin. Half were primarily BSIs and all

10   secondary BSIs had a urinary source and 3 patients

11   had intravascular catheter related infections. The

12   majority again received tigecycline as adjunctive

13   therapy.

14   In this the subgroup of BSI patients in

15   cohort 2, the rate of all-cause mortality at day 28

16   or SDRCs was 36 percent with the majority of events

17   driven by SDRCs rather than mortality. The rate of

18   all-cause mortality alone, or 14 percent, is

19   supportive of the 7 percent rate observed in cohort

20   1 plazomicin treated patients. All SDRCs observed

21   were persistent bacteremia.

22   Additional supportive evidence of efficacy

1   in the BSI indication comes from data generated in

2   a mouse septicemia model. This study evaluated

3   survival using human simulated exposures in the

4   treatment of mouse septicemia due to

5   enterobacteriaceae. As demonstrated by the

6   untreated control group, this infection is nearly

7   100 percent lethal in the absence of therapy.

8   Tigecycline was also poorly effective in

9   this model even though all assets were susceptible,

10 showing that this model can detect poorly effective

11 therapies in septicemia. In contrast, substantial

12 improvements of the 96 hours survival were observed

13 in plazomicin treated mice compared with controls

14 for organisms with plazomicin MICs of 2 to 4.

15   In conclusion, the totality of data

16 including clinical outcomes data and more than 50

17 plazomicin treated patients with BSI provides

18 substantial evidence of plazomicin efficacy. In

19 the primary efficacy analysis of cohort 1 in study

20 007, plazomicin was associated with clinically

21 meaningful improvements in mortality based

22 endpoints compared to colistin. Due to the small

1   sample size in cohort 1, superiority could not be

2   statistically confirmed. However, the large

3   survival benefit in this limited data set should be

4   considered in the context of the severity and

5   rarity of CRE, BSI, and the lack of alternative

6   treatment options for this patient population.

7   The mortality benefit of plazomicin therapy

8   in study 007 was supported by the high and

9   sustained bacterial eradication rates in patients

10   with BSI, and similarly, bacteremia eradication

11   rates were high in the subset of cUTI patients with

12   concurrent bacteremia in study 009. Outcomes in

13   cohort BSI patients as well as a mouse septicemia

14   model provide additional supportive evidence of

15   efficacy in BSI due to enterobacteriaceae.

16   I'll now hand it over to Dr. Connolly to

17   present safety data.

18   **Applicant Presentation - Lynn Connolly**

19   DR. CONNOLLY: Thank you. I'm Lynn

20   Connolly, and as the head of late development at

21   Achaogen, I lead the clinical development of

22   plazomicin from the end of phase 2 through the NDA

1   submission and review. I'd now like to present the

2   safety data for plazomicin. I will first describe

3   for you the safety profile of plazomicin in

4   patients with cUTI based on pooled analyses of

5   safety data from our phase 2 and phase 3 studies in

6   this indication.

7   Pooling of data from the two cUTI studies

8   was felt to be appropriate as these patients had

9   the same infection types, similar dosing duration,

10   and comparable safety assessments. I will then

11   describe the safety profile of plazomicin in

12   patients with serious infections due to CRE. Due

13   to the relatively small numbers of BSI patients,

14   data for all patients, irrespective of their

15   baseline diagnosis, were included in this analysis.

16   And finally, I will present an analysis of topics

17   of special interest for the aminoglycoside class,

18   namely nephrotoxicity and ototoxicity.

19   In the cUTI population, the median duration

20   of IV study drug therapy was 5 days for both the

21   plazomicin and comparator group, which included

22   levofloxacin and meropenem. Across treatment

1   groups, approximately 90 percent of patients

2   received 4 to 7 days of IV study drug therapy. In

3   the 007 study, the median duration of IV treatment

4   was 12 days in both groups with the majority of

5   patients receiving 11 to 15 days of therapy. The

6   differences in study drug exposure support separate

7   analyses of the safety profile of plazomicin in

8   these two distinct patient populations.

9   Here is an overview of the safety profile

10   across the pooled phase 2 and phase 3 cUTI studies.

11   The overall incidence of adverse events, adverse

12   events leading to discontinuation, and serious

13   adverse events were similar between plazomicin and

14   comparative groups. A single death occurred in the

15   plazomicin arm study 009. This patient was a 63

16   old woman who presented with hematuria and lower

17   abdominal pain that was initially attributed to

18   acute pyelonephritis. She subsequently died on

19   study day 18 from metastatic uterine cancer that

20   was discovered within 48 hours following

21   enrollments. Plazomicin was discontinued after a

22   single dose.

1   The patient also experienced a serious

2   adverse event of acute kidney injury requiring

3   hemodialysis. This event was ongoing at the time

4   of death and was attributed to the patient's

5   underlying malignancy by the investigator. The

6   cancer, the acute kidney injury, and the death were

7   all considered unrelated to plazomicin.

8   Here I'm showing you adverse events and

9   greater than or equal to 2 percent of patients in

10   the plazomicin group. Adverse events generally

11   occurred with low frequency or mild to moderate in

12   severity and were balanced between plazomicin and

13   comparator groups with the exception of a higher

14   rate of adverse events due to renal function in the

15   plazomicin group. The types of events were typical

16   of a hospitalized patient population with cUTI,

17   with the most frequently reported events being

18   decreased renal function, diarrhea, and headache.

19   The imbalance in events related to renal

20   function is consistent with known toxicities of the

21   aminoglycoside class. I will describe the

22   nephrotoxicity risk in more detail, including tools

1   to mitigate this risk later in the presentation.

2   The incidence of serious adverse events was

3   low and similar between the plazomicin and

4   comparator groups. I'm showing you here only those

5   events that occurred in two or more patients in

6   either treatment group. All serious adverse events

7   resolved or were resolving at the end of study with

8   the exception of the ongoing acute kidney injury in

9   the patient who died from metastatic cancer. The

10   second serious adverse event of acute kidney injury

11   in the plazomicin group occurred after a single

12   dose of plazomicin, and the patient subsequently

13   experienced full recovery of renal function.

14   Next, I'll turn to safety in the 007 study.

15   In patients with serious infections due to CRE,

16   plazomicin demonstrated a favorable safety profile,

17   including a reduced incidence of nephrotoxicity

18   compared to colistin. Because cohort 2 was a

19   distinct patient population from cohort 2 and

20   lacked a comparator, I'll focus this section on the

21   patients in the randomized cohort.

22   As expected in this severely ill patient

1   population, nearly all patients experienced at

2   least one adverse event, and the majority

3   experienced at least one serious adverse event. In

4   all categories, adverse events were generally lower

5   or comparable in the plazomicin group relative to

6   the colistin group. Fewer plazomicin treated

7   patients died compared to colistin treated, and no

8   deaths were deemed related to study drugs.

9   Here are the reported adverse events by

10   preferred term that occurred in 10 percent or more

11   patients in the plazomicin group. The briefing

12   book includes additional details for events

13   occurring in 5 percent or more of patients. In

14   both groups, renal function events and sepsis where

15   the most common events reported with a higher

16   incidence reported in colistin treated patients

17   compared to plazomicin treated patients. A higher

18   proportion of the renal function events were

19   considered related to IV study drug in the colistin

20   arm.

21   Overall, fewer plazomicin treated patients

22   experienced a serious adverse event compared to

colistin treated patients. Similar types of events

were reported in each group with the most common

events in both groups being sepsis and cardiac

arrest, both of which are expected in the

underlying patient population. Fewer serious

adverse events associated with sepsis or renal

function were reported in the plazomicin than in

the colistin group.

Here's a listing of the causes of death

through day 60 with sepsis, including septic shock

being the most commonly reported event leading to

death. A higher proportion of patients in the

colistin group compared to the plazomicin group

died of sepsis. The majority of other fatal events

occurred in only one or two patients.

The overall safety profile of plazomicin in

cohort 2 patients was similar to that observed in

the plazomicin group of cohort 1 with a similar

overall rate of treatment-emergent adverse events,

serious adverse events, and adverse events leading

to discontinuation of study drugs. Similar To

cohort 1 plazomicin treated patients, the two most

common types of adverse events were those related
to renal function and sepsis. Forty percent of
patients died through day 60 with the most frequent
causes of death being septic shock, cardiac arrest,
and multiple organ dysfunction syndrome.

Next, I'd like to take a look at events of
special interest, namely nephrotoxicity and
ototoxicity. Based on data I'm about to share,
plazomicin carries the risk of these known class
related toxicities. First, let's focus on
nephrotoxicity. As an objective analysis of
nephrotoxicity, we determined the proportion of
patients experiencing a serum creatinine increase
of 0.5 milligrams per deciliter or greater at any
time on study. This magnitude of serum creatinine
increase is considered a clinically meaningful
change and has been associated with increased
morbidity in hospitalized patients.

In this analysis for cUTI patients,
7 percent of plazomicin treated patients compared
to 4 percent of comparator treated patients
experienced an increase in serum creatinine at

1   anytime post baseline. Most of these occurred

2   while on IV study drug therapy. In the subgroup of

3   events that occurred while on study drug therapy,

4   the majority in the plazomicin group recovered by

5   the end of therapy, and all but 3 patients

6   experienced full recovery. Each of these 3

7   patients had additional ongoing risk factors for

8   nephrotoxicity that potentially contributed to

9   their serum creatinine increases, and none of these

10   patients required renal replacement therapy.

11   We conducted additional analyses in the cUTI

12   population to characterize risk factors associated

13   with the development of nephrotoxicity. The risk

14   factors identified are similar to those established

15   for other aminoglycosides. The most important is

16   baseline renal function. Moderate renal impairment

17   at baseline had the strongest association with the

18   subsequent development of serum creatinine

19   elevations. Mild renal impairment was also

20   associated with a slight increased risk for

21   plazomicin treated patients versus comparator

22   treated patients, while patients with normal renal

1   function did not appear to be at increased risk for

2   nephrotoxicity with plazomicin therapy.

3   Similar to exposure response relationship

4   established for currently available

5   aminoglycosides, elevated Cmin or trough early in

6   therapy was associated with an increased risk of

7   nephrotoxicity, particularly in patients with renal

8   impairment of baseline. Based on these data,

9   therapeutic drug management targeting a Cmin value

10   less than 2 micrograms per milliliter is

11   recommended for cUTI patients with renal impairment

12   at baseline to help mitigate the risk of

13   nephrotoxicity.

14   Let's next examine nephrotoxicity in

15   patients with serious infections due to CRE.

16   Consistent with the lower incidence of adverse

17   events related to renal function reported in the

18   plazomicin group of cohort 1, the incidence of

19   serum creatinine increases in the plazomicin group

20   was lower than the colistin group both at anytime

21   post baseline and while on IV study drug therapy.

22   The single event shown here in the plazomicin group

1   in cohort 1 recovered by last visit compared to

2   half of the events in the colistin treated

3   patients.

4   Based on the associations observed in the

5   development program and decades of clinical

6   experience with other aminoglycosides, close

7   monitoring of renal function while receiving

8   plazomicin is recommended, particularly in patients

9   with renal impairment. Particular care should be

10   taken to ensure that plazomicin doses are

11   appropriately adjusted based on estimated renal

12   function, and therapeutic drug management for BSI

13   patients and the subset of cUTI patients at

14   increased risk of nephrotoxicity is also

15   recommended.

16   Next, I'll turn to ototoxicity. We

17   monitored for ototoxicity using both objective and

18   subjective assessments. In phase 1 and 2 studies,

19   we used the gold standard method, pure tone

20   audiometry including high frequency audiometry in

21   phase 1 to detect changes in cochlear function.

22   Based on an independent audiologist review of this

1   data, a similar proportion of patients in each

2   group or approximately 2 percent had changes in

3   audiometry for its treatment related effects could

4   not definitively be excluded.

5   In terms of subjective AE reporting, no AEs

6   consistent with potential cochlear or vestibular

7   toxicity were reported in study 007. The incidence

8   of AEs associated with cochlear or vestibular

9   function in the pooled cUTI studies was balanced

10   and low across treatment groups.

11   In terms of the validated questionnaires

12   used in study 009, no patients in either group met

13   criteria for potentially clinically significant

14   change in the hearing or tinnitus handicap

15   inventories. One plazomicin treated patient

16   demonstrated a potentially significant change at

17   end of IV therapy in the dizziness handicap

18   inventory. However, the DHI score returned back to

19   the baseline value of zero at the next scheduled

20   assessment.

21   Based on the data collected in the

22   development program, we cannot exclude the risk of

1 nephrotoxicity with plazomicin therapy. Therefore,

2 we recommend that when starting plazomicin, the

3 risk-benefit profile for patients possibly at

4 increased risk be considered. Based on established

5 risk factors of the aminoglycoside class, these

6 include patients with a family history of hearing

7 loss and patients with renal impairment at baseline

8 to minimize ototoxicity risks do not exceed the

9 recommended duration therapy.

10   In conclusion, in patients with cUTI,

11 plazomicin demonstrated a comparable safety to

12 non-nephrotoxic comparators with the exception of a

13 higher incidence of larger reversible

14 nephrotoxicity. In acutely ill patients with

15 infections due to CRE, plazomicin demonstrated a

16 favorable safety profile, including a reduced

17 incidence of nephrotoxicity compared to colistin, a

18 known nephrotoxic agent. A small number of events

19 potentially consistent with ototoxicity suggests

20 the plazomicin carries this class associated risk.

21 Taken together, the safety profile of plazomicin in

22 both indications support use in patients with

1   limited or no alternative therapies.

2   That concludes the data portion of this

3   presentation, and I'd now like to turn to some

4   concluding remarks.

5   **Applicant Presentation - Lynn Connolly**

6   DR. CONNOLLY: You've heard from Dr.

7   McKinnell that alternative therapies are needed for

8   infections due to MDR enterobacteriaceae. There

9   has been a steady increase in infections due to

10   these pathogens including ESBL producers and CRE in

11   the United States due to widespread use of broad

12   spectrum antimicrobial agents. These infections

13   are associated with poor outcomes largely due to

14   limitations of currently available treatment

15   options.

16   Older agents are associated with poor

17   efficacy and safety profiles as well as established

18   resistance. Newer BL/BLI agents are active against

19   only a subset of isolates and are not indicated for

20   use in all infection types, including the BSI. In

21   addition, emergence of resistance to one of these

22   agents has been described in clinical practice.

1   These limitations point to the need for

2   additional antibiotic classes with clinical

3   evidence of efficacy against these difficult to

4   treat pathogens. Microbiological benefits of

5   plazomicin include in vitro activity against

6   strains resistant to currently available

7   aminoglycosides and the fact that plazomicin is a

8   non-beta-lactam agent with potent activity against

9   a variety of ESBL producers and CRE. In addition,

10   plazomicin demonstrates rapid bactericidal

11   activity, including synergistic killing of bacteria

12   in vitro when used in combination with beta-lactam

13   agents.

14   Plazomicin has demonstrated clinical

15   benefits in the treatment of cUTI, including cases

16   caused by resistant organisms demonstrating

17   noninferiority to meropenem on the primary end

18   points as well as higher microbiological

19   eradication rates for ESBL-producing pathogens and

20   a lower risk of clinical relapse. Plazomicin

21   demonstrated a similar safety profile to meropenem

22   in cUTI patients with the exception of a higher

1   incidence of nephrotoxicity. Patient factors

2   associated with this increased risk of toxicity

3   have been identified and are the same as those

4   associated with other aminoglycosides, which have

5   been used clinically for many years. TDM guided

6   dose adjustments for this at-risk patient

7   population are designed to minimize the risk of

8   this toxicity.

9   In regards to the BSI indication, given the

10   challenges we have discussed in generating clinical

11   data in the target patient population, we have

12   asked that this indication be reviewed in the

13   context of the life-threatening nature of CRE BSI

14   and the lack of alternative treatment options for

15   this limited patient population.

16   LPAD was created to provide an approval

17   pathway for antibacterial drugs that treat

18   infections such as CRE BSI where it is not possible

19   to run traditional trials. While LPAD states that

20   the statutory approval standard must be met, it

21   allows for the approval of an antibiotic on the

22   basis of a favorable benefit-risk profile even when

1   there is greater uncertainty about the evidence due

2   to the small number of patients available for

3   study.

4   We believe that the totality of the data

5   package in support of the BSI indication provides

6   substantial evidence of efficacy and safety for

7   approval in this limited patient population at high

8   risk of death. The primary evidence of efficacy

9   for the BSI indication comes from clinical outcomes

10   in more than 50 patients with BSI treated with

11   plazomicin, including randomized controlled data.

12   Study 007 was designed to demonstrate

13   superiority. Though the sample size is too small

14   to confirm this statistically, the 33 percent

15   absolute reduction in 28-day all-cause mortality

16   for plazomicin compared to colistin is both

17   clinically meaningful and compelling. The high and

18   sustained rate of clearance of bacteremia with

19   plazomicin provides a biological plausibility to

20   the survival benefit observed.

21   In addition, supportive data from patients

22   with bacteremia from a urinary source and an

1   expanded population with CRE BSI, combined with

2   extensive in vitro data, evidence of efficacy from

3   relevant animal models, and a high probability of

4   target attainment at clinical exposures support the

5   conclusion that the efficacy observed in the

6   randomized cohort of study 007 was not by chance.

7   Plazomicin was also associated with an

8   overall favorable safety profile compared to

9   colistin with fewer SAEs, including those related

10   to renal function and sepsis or leading to death.

11   Notably, plazomicin was associated with a reduced

12   rate of nephrotoxicity compared to colistin

13   therapy.

14   Finally, TDM guided dose adjustments for

15   this patient population are designed to maintain

16   efficacious exposures while minimizing the risk of

17   potentially toxic levels. In conclusion, there is

18   an increasing burden of infections due to MDR

19   enterobacteriaceae in the United States. Although

20   we have seen recent approval of agents with

21   activity against a subset of these pathogens,

22   currently available treatment options continue to

1   have limitations. Based on the data presented here

2   today, plazomicin demonstrates a favorable

3   benefit-risk profile for patients who have limited

4   or no alternative due to resistance, intolerance,

5   or failure of other treatment options for cUTI and

6   BSI.

7   Thank you for your attention. We're now

8   happy to take your questions.

9   **Clarification Questions to the Presenters**

10   DR. BADEN: I would like to thank the

11   applicant for presenting a tremendous amount of

12   data very efficiently and clearly. We can now

13   begin clarifying questions from the committee to

14   the applicant. We have about 30 minutes at this

15   time before the break. I will remind the committee

16   to please remember to state your name for the

17   record. If you can direct questions to a specific

18   presenter, that will make it easier. I will start

19   with the first question, although to the committee

20   members, please get myself or Dr. Chee's attention.

21   We'll have a running list. If a line of

22   questioning emerges, please indicate if you already

1 follow-on question so we can develop a thought as

2 completely as possible while respecting the overall

3 order of questioning. So I will start with the

4 first question while we accrue the names of others.

5   In the two clinical studies 009 and 007, how

6 were catheters handled, both urinary and

7 intravenous?

8   DR. CONNOLLY: In both studies, catheters

9 were to be removed before -- so in the case of the

10 009 study, catheters were to be removed before

11 completion of therapy, removed or replaced. So

12 they were to be removed.

13   DR. BADEN: So let me rephrase it. Not what

14 was desired. What happened?

15   DR. CONNOLLY: Yes, of course. There was

16 high compliance with catheter management in the 009

17 study. And I believe we have some specific

18 information we can share. While we're waiting for

19 that, I will speak to catheter management in the

20 context of the 007 study. In the 007 study, if a

21 catheter was present at the time that the patient

22 presented, that catheter was to be removed. And

1   blood cultures qualifying the patients for

2   enrollment were to be drawn either through a

3   peripheral site or through the placement of a brand

4   new catheter. And we will probably have more

5   discussion around that.

6   In terms of the indwelling catheters in the

7   009 study, approximately 15 percent of patients in

8   both treatment groups did have indwelling catheters

9   at baseline. Of these 58 patients in total, albeit

10   8, so 6 in the plazomicin group and 2 in the

11   meropenem group had documented replacement or

12   removal of the catheter.

13   DR. BADEN: Dr. Venitz?

14   DR. VENITZ: I have some questions first

15   related to the information that you provided on PK

16   and then on the dosing strategies that you're

17   proposing. Let me start with PK then. In your

18   summary material, you're mentioning in your

19   population PK analysis that you found volumes of

20   distributions to be elevated in patients. Is that,

21   first of all, correct?

22   DR. CONNOLLY: That's correct.

1   DR. VENITZ: Do you have any rationale, any

2   explanation for that? Do you think that's an

3   artifact of the analysis or do you think there's

4   any biological reasons why the volumes doubled or

5   tripled based on average?

6   DR. CONNOLLY: This is actually commonly

7   observed in patients with infection, particularly

8   the more serious infection types, that the volume

9   of distribution is larger due to fluid shifts in

10   these patients. And I would like to ask one of our

11   experts, one of our clinical pharmacology experts,

12   provide additional detail around that.

13   DR. BHAVNANI: Sujata Bhavnani from the

14   Institute for Clinical Pharmacodynamics, consultant

15   Achaogen. Our group developed the population PK

16   model based on healthy volunteer data and the

17   patient data that you've seen presented today.

18   Specifically, with regard to your question about

19   volumes, we did see an infection type difference

20   that was applicable to the PK parameters. We can

21   provide more information about these volume

22   differences and estimates, if that would be

1   helpful.

2   DR. VENITZ: No, that's okay. I just wanted

3   to confirm that I read it right. Now, just to

4   follow up, did you see any changes in clearance in

5   those patients not related their renal function?

6   DR. BHAVNANI: We also saw an infection

7   related type effect on clearance parameters as

8   well.

9   DR. VENITZ: And which way did it go and by

10 how much?

11   DR. BHAVNANI: That I will need to provide

12 more detail.

13   DR. VENITZ: Was it more or less than the

14 kidney contributed to this variability in

15 clearance?

16   DR. BHAVNANI: There was an increased

17 clearance.

18   DR. VENITZ: Unrelated to their renal

19 dysfunction.

20   DR. BHAVNANI: There was an increased

21 clearance related to infection type, and we saw

22 differences between patients with urinary tract

1   infections and bloodstream infections. And we can

2   provide, again, more clarity around the direction

3   relative to infection type.

4   DR. VENITZ: And which way would the

5   half-life go? Would the half-life be prolonged

6   than in those patients relative to healthy

7   volunteers without infections?

8   DR. BHAVNANI: Well, the most important

9   effect was related to clearance. So we, as you

10   would expect, saw increased half-life in those

11   renally impaired patients. But with regard to

12   infection type again, just to get back to you, I

13   will have to provide more information.

14   DR. VENITZ: Thank you.

15   DR. BADEN: One detail I can provide around

16   the clearances, that it was increased by 13 percent

17   in patients with acute pyelonephritis and then

18   decreased by about 11 percent in patients with

19   bloodstream infections.

20   DR. VENITZ: So relatively small compared to

21   what the kidney contributes.

22   DR. CONNOLLY: Yes, it's relatively small

1   compared to the impact of creatinine clearance.

2   DR. VENITZ: All right. Maybe we can use

3   slide CO-45 as prop, because now I want to discuss

4   with you what you're proposing in terms of dosing

5   strategy. So the first adjustment, if I understand

6   you correctly, is at baseline, you're going to

7   measure renal function creatinine clearance --

8   DR. CONNOLLY: Correct.

9   DR. VENITZ: -- and you're going to

10   categorize the patients into three categories based

11   on dosing interval and milligram per kilogram.

12   DR. CONNOLLY: Correct.

13   DR. VENITZ: Now, are you going to do any

14   further renal assessments while they are on drug to

15   adjust the dose?

16   DR. CONNOLLY: So we do recommend that renal

17   function be assessed during the course of therapy,

18   particularly in patients who have renal impairment

19   at baseline. We are in the patients with cUTI

20   recommending a trough based type of monitoring that

21   could be used instead of creatinine clearance to

22   adjust the dose if that trough is elevated.

1   DR. VENITZ: Have you actually done that?

2   So my first question is that's what you're

3   proposing, but what have you actually done and what

4   are you proposing that hasn't been done yet?

5   DR. CONNOLLY: Exactly. So we actually

6   specifically decided not to do TDM in the 009

7   study, and that was in conversation with the FDA,

8   so that we could develop exposure-response

9   relationships for plazomicin that could be used to

10   provide rationale for TDM for this drug

11   specifically. It wasn't felt to be appropriate to

12   use other relationships from other aminoglycosides.

13   So this is why we didn't conduct TDM and why

14   we enrolled patients with a broader range of renal

15   function to allow for that type of variability so

16   that we could identify both the risk factors and

17   thresholds of concern to use for TDM based dose

18   adjustments.

19   DR. VENITZ: Right. So that would be a

20   second strategy for cUTIs, right?

21   DR. CONNOLLY: Exactly. That is correct.

22   DR. VENITZ: But if I understand you

1   correctly, you're saying you can either measure

2   trough levels or you can measure renal function as

3   a proxy. Is that what I heard you say?

4   DR. CONNOLLY: So we did use renal function

5   to guide dose adjustments during the course of the

6   study. So we know if we dose adjust with that type

7   of strategy, we see that 7 percent rate of

8   nephrotoxicity, and that is higher in patients with

9   renal impairment at baseline.

10   So now that we have established a

11   relationship between -- I'll go ahead and put this

12   up. Te patients with lower renal impairment, we

13   see that rate of nephrotoxicity, 14 percent in the

14   moderates, 6 percent in the milds, is higher than

15   what would be expected at baseline, so 4 percent.

16   And that's using the creatinine clearance guided

17   dose adjustment.

18   So consistent with other aminoglycosides,

19   we've now established a relationship between trough

20   and that increased risk of nephrotoxicity for those

21   patients. So that's why we're suggesting for those

22   patients, that trough be used in a similar manner

1   as it is used for other aminoglycosides to try and

2   lower their exposures early on to prevent

3   nephrotoxicity.

4   DR. VENITZ: Instead of having to do daily

5   renal assessments for the purposes of the adjusting

6   the dose.

7   DR. CONNOLLY: Right.

8   DR. VENITZ: And that makes sense to me.

9   But let's look at the area method that you're

10   proposing for the BSI.

11   DR. CONNOLLY: So the AUC based?

12   DR. VENITZ: Right. My first question is,

13   you're right now proposing to take two samples, if

14   I understand it correctly --

15   DR. CONNOLLY: That's correct.

16   DR. VENITZ: -- and use two samples to

17   estimate the area under the curve.

18   DR. CONNOLLY: Yes.

19   DR. VENITZ: Any idea how well two points

20   are going to predict the 24-hour area?

21   DR. CONNOLLY: Yes. So let me step back and

22   provide some of the rationale for why we approached

1   dosing this way in the 007 study. When we began

2   this study, we only had PK data from patients with

3   urinary tract infections in normal healthy

4   volunteers, but we knew that AUC was the driver of

5   efficacy for these patients based on our

6   preclinical models and lots of work done with

7   aminoglycosides.

8   So the dose we chose was designed to achieve

9   and AUC value projected to be associated with

10 efficacy based on probability of target attainment

11 analyses. And then because we suspected, based on

12 what we've observed for other aminoglycosides, that

13 we would see a lot of fluctuating PK in these

14 patients, a lot more variability in PK. And PK

15 that is not as easily projected simply by

16 creatinine clearance, we wanted to have TDM in

17 place to try and assure that those AUC values were

18 maintained within a reasonable precision of that

19 efficacy target for these patients.

20   So the TDM designed for these patients was

21 largely to ensure that we didn't have wide

22 variability in PK and that we maintained

efficacious exposures. So this type of TDM does

require two time points. The two time points are

taken around that dosing interval. For patient on

q24 hour, that's a 2-hour and a 10-hour time point.

So in the context of a hospital that has these in

their clinical laboratory, that information can be

available for dose adjustments by the second and

certainly by the third dose.

So the precision with which we were able to

calculate those AUCs with two time points, I would

ask one of our clinical pharmacology experts to

come to the podium.

DR. SEROOGY: Julie Seroogy, director of

clinical pharmacology with DMPK. As Lynn

mentioned, during the course of development of the

algorithm, ICPD looked at different sampling times

in order to best estimate and predict clearance

that would then best estimate and project AUC. So

within the course of that, we ran modeling and

simulations across those different time points to

understand the performance there.

Subsequent to that, we did do analyses to

1 understand how the TDM predicted AUCs from those

2 algorithms and compared those to the AUCs from the

3 population PK model. And those shows good

4 agreement in the predicted exposures from the

5 algorithm based on those two time points, and then

6 the AUCs that were achieved in the trial. And I

7 could just show you some of the outcomes of the AUC

8 across days.

9   So here you see we're targeting an AUC 262,

10 as Dr. Connolly mentioned, and on day 1, we're

11 achieving a mean of roughly 262. And then

12 throughout the course of conducting TDM in this

13 patient population, maintaining good AUC exposures

14 around that time, and then also decreasing the

15 variability in the exposures and the patient

16 population.

17   DR. CONNOLLY: Thank you. I think one

18 other --

19   DR. VENITZ: And just to make sure that I

20 understand this table, this is the simulation that

21 you run on your patients after the fact where you

22 used your two point method to predict an area, and

1   then you use that area to adjust the dose on those

2   various days. Is that what I'm looking at?

3   DR. SEROOGY: So this is population PK data,

4   so it's the post hoc estimated exposures showing

5   that as we utilize TDM in the course of this study,

6   that we were able to maintain exposure, so showing

7   that the algorithms providing the tool to adjust

8   the exposures got us into a good exposure.

9   DR. VENITZ: But did you actually use the

10   algorithm in this study or was this done all

11   in silico?

12   DR. SEROOGY: The algorithm was used in this

13   study.

14   DR. VENITZ: Okay.

15   DR. SEROOGY: So data was received for each

16   patient back for those two time points. They were

17   put into an algorithm based on the protocol, and

18   then doses were adjusted within this study based on

19   that algorithm.

20   DR. VENITZ: Okay. Thank you.

21   DR. BADEN: Dr. Le, did you have a follow-on

22   question?

1   DR. LE: Yes. First, I wanted to go back on

2   the volume distribution with that variability that

3   you see in healthy versus the BSI patients. Did

4   you consider the use of loading dose in this

5   scenario?

6   DR. CONNOLLY: We did not consider use of a

7   loading dose. Our initial dose is actually

8   designed to try and achieve those efficacious

9   exposures from the very beginning.

10   DR. LE: The second question I had relates

11   to the use of Bayesian estimation for during the

12   TDM process here. Generally, I wanted to see when

13   you were conducting TDM by this Cmin versus AUC,

14   was Bayesian estimation considered in the

15   estimation of these exposures?

16   DR. CONNOLLY: One thing I can state, while

17   Dr. Bhavnani comes to the microphone, we did

18   consider developing like a Bayesian calculator, so

19   taking advantage of the pop PK model to guide the

20   dose adjustment. But the challenge that came with

21   that was that would be considered an

22   investigational device. We already had a second

1   investigational device that we were using in the

2   context of this study, the TDM assay. So for study

3   purposes, we did not use Bayesian estimation. We

4   used these equations that were developed in order

5   to estimate AUC.

6   DR. SEROOGY: I concur with Dr. Connolly.

7   DR. BADEN: Dr. Palevsky, you have a

8   follow-on?

9   DR. LE: I have a few more related to this.

10   For the nephrotoxicity margin, did you consider the

11   use of renal biomarkers at all? Because there's

12   the nag to creatinine ratio that has been studied

13   for aminoglycoside class.

14   DR. CONNOLLY: Yes, but none of those have

15   actually been validated for use in humans for this

16   purpose. They're still considered experimental or

17   investigational.

18   DR. LE: Okay. One other question relates

19   to the toxicity as well. As a class, you mentioned

20   on your slides in the BSI trial, that there were

21   cardiac effects, which is not seen with the other

22   aminoglycosides. For example, we saw 11 percent

1   hypotension, atrial fibrillation, and I believe

2   12.5 percent deaths on cardiac effects.

3   Can you elaborate on that more in terms of

4   was it dose or exposure related?

5   DR. CONNOLLY: Sure. So let's start with

6   the events of cardiac arrest. Those occurred in

7   007 study, and it's important to remember this is a

8   patient population who is already hospitalized with

9   significant comorbidities, often cardiovascular

10   disease. Those events of cardiac arrest that

11   occurred late in the course of that study, we

12   followed out to day 60. So all but one of those

13   occurred beyond day 28 well distant from the

14   receipt of plazomicin therapy. In the eyes of the

15   investigator, these were all considered unrelated,

16   and as I mentioned, these were all elderly subjects

17   with underlying cardiac disease. We have also

18   conducted a dedicated TQT study with plazomicin

19   where we do not see clinically significant effects

20   or impacts on the QT syndrome.

21   In terms of the hypotensive events, what we

22   observed in a phase 1 study, we had a small number

1   of subjects who did experience hypotension near or

2   at the end of IV infusion, and this was associated

3   with a 10-minute IV infusion. There wasn't a clear

4   exposure-response relationship to those events, but

5   we did decide because of that to increase the

6   infusion duration to 30 minutes, which is more

7   standard for other aminoglycosides, which tend to

8   be 30 minutes to an hour.

9   Since we have extended that infusion

10   duration, we have not seen additional events

11   occurring around or near the end of infusion in

12   plazomicin treated patients. We did see events of

13   hypotension in the 007 study. Again, none of those

14   occurred in relation to dosing, and in one of those

15   patients, the event occurred in the setting of

16   ongoing septic shock.

17   DR. BADEN: Dr. Palevsky?

18   DR. PALEVSKY: So I have a follow-up

19   question regarding the TDM and the AUC method. The

20   effect of kidney function on what the AUC curve is

21   going to look like is going to be very dramatic,

22   someone with normal kidney function versus someone

1   with markedly impaired kidney function. Have you

2   figured out how one size can fit all in terms of

3   the AUC with those differences? If you're aiming

4   for similar peaks, you're going to get very, very,

5   very, very different troughs, and therefore very

6   different AUCs.

7   DR. CONNOLLY: Actually, this is part of the

8   reason why we're not aiming for peaks and troughs

9   because absolutely we do see more variation in

10   those values, and also because those values, unless

11   you precisely draw that blood draw at that peak or

12   trough, you get misguided information. So actually

13   we think that the AUC, even in these patients with

14   renal impairment and varying renal function, can be

15   estimated more accurately or precisely than either

16   the trial for the peak.

17   DR. PALEVSKY: But if your dosing interval

18   has to change, and if I read what your guidance is,

19   you're going to have dosing intervals going out to

20   48 hours with patients with markedly impaired

21   kidney function. How are you basing your dosing

22   then on an AUC of 0 to 24 hours?

1   DR. CONNOLLY: I see. This is the Cmin

2   guided dose adjustment for patients with cUTI. I'm

3   just clarifying we're just AUC --

4   DR. PALEVSKY: Maybe I'm misunderstanding.

5   You're dosing recommendation based on in a patient

6   with markedly impaired kidney function, how are you

7   going to change it?

8   DR. CONNOLLY: I think I understand now.

9   DR. PALEVSKY: So let's take the patient not

10   on dialysis with an eGFR of less than -- or

11   creatinine clearance of less than 15 with a

12   bloodstream infection. Explain how you're going to

13   dose that and how that compares to a patient who

14   has normal kidney function.

15   DR. CONNOLLY: So that patient with that

16   very low GFR would get that 10 milligram per

17   kilogram dose and then have TDM conducted after

18   that first dose to estimate the AUC. And we do

19   provide instructions that if that dose -- if the

20   adjusted dose required for that patient is either

21   above or below 15, that we would also change the

22   dosing interval.

1   I think for additional detail around this, I

2   would ask one of our clinical pharmacology experts

3   to come to the microphone.

4   DR. PALEVSKY: It might be helpful if you

5   have curves of the different AUCs for those

6   characteristics. Have you developed those?

7   DR. SEROOGY: This is Julie Seroogy,

8   clinical pharmacology at Achaogen. For the

9   different dosing intervals, there's a possibility

10 for a patient to also go on q12 hour dosing. So we

11 have different -- the second time point is

12 different based on those patients. So that first

13 time point is at 2 hours post- start of infusion,

14 and the second time point is at 8, 10, or 18 hours

15 post start of infusion.

16   So specific to your example where it's poor

17 renal function on a q48 hour dosing, that patient

18 would get a TDM sample collected at 2 hours and at

19 18 hours. There are three different algorithms

20 based on the dosing interval, so it is normalized

21 to that q24 hour AUC.

22   So based on the dosing that we've achieved

1   in the study, as Dr. Connolly mentioned, we're

2   really targeting an AUC range consistent across

3   renal function, so that's done with dose

4   adjustments and duration adjustments. So what you

5   see here in our phase 2 and phase 3 patients are

6   observed AUC ranges based on renal function.

7   DR. CONNOLLY: I think I understand what

8   you're getting at now as well, is that in that q48

9   hour dosing, that shape of the AUC means that it's

10   front-loaded for those patients.

11   DR. PALEVSKY: Well, you have to maintain

12   your level at a much higher level -- well, let me

13   phrase it differently. To achieve the same AUC,

14   since you don't have a steep decline, you're going

15   to have a level that is, shall we say, more

16   constant over time.

17   Is that what you're aiming for with this?

18   This is a drug that has sustained killing after the

19   level falls, as other aminoglycosides do, and

20   maintaining a sustained level for a prolonged

21   period of time may not make the most sense and may

22   actually be augmenting toxicity.

1   DR. CONNOLLY: Yes, I see what you're

2   saying. And I think the important thing to

3   remember is this would only be used in a scenario

4   where there's no alternative option. So we're not

5   talking about broad use for patients. And then

6   only for a patient like that, again, where there's

7   no alternative option and where a physician can

8   make that determination about whether that

9   risk-benefit profile is appropriate for that

10   patient.

11   DR. BADEN: It seems that more discussion,

12   not necessarily at this table, need to go on about

13   the dosing. The point is well taken.

14   Dr. Daskalakis, you had the next question.

15   DR. DASKALAKIS: I actually have two

16   questions. The first is, could you share race and

17   ethnicity data on your studies?

18   DR. CONNOLLY: Sure. We have a side that

19   looks at race and ethnicity as included in our

20   population PK model because that would encompass

21   all studies. Within the context of the best model,

22   we have included -- let me go ahead and just show

1   you the whole thing.

2   The majority, as you can see here, were

3   white. Approximately 9 percent of patients were

4   black or African American; 4 percent Asian. This

5   American-Alaskan Native is unfortunately an

6   artifact of the way data was collected in our phase

7   2 cUTI study where patients in Latin America marked

8   the box Americas, which then mapped -- that's

9   largely patients from Latin America in the American

10 Indian-Alaskan Native. So this provides the

11 information on race and ethnicity across studies,

12 which were included in our final population PK

13 model.

14   DR. DASKALAKIS: In your clinical 007 and

15 009 studies, specifically, could you show those

16 data as well?

17   DR. CONNOLLY: Yes, so very few patients.

18 The vast majority of patients in those studies were

19 white. The patients with the more variability in

20 race come largely from the phase 2 cUTI study and

21 from one of our phase 1 studies, the TQT study

22 actually.

1   DR. DASKALAKIS: And then one brief

2   clarifying question. On slide 74, when you have

3   the option of positive or no culture obtained, can

4   you comment as to how many were positive and how

5   many had no culture?

6   DR. CONNOLLY: Yes. Actually, they were

7   about split in half, so we had a third positive, a

8   third no culture, and a third negative at the time

9   of enrollment.

10   DR. DASKALAKIS: Thank you.

11   DR. BADEN: Dr. Schaenman, a follow-on

12   question.

13   DR. SCHAENMAN: Just a follow-up question

14   regarding the race and ethnicity. Not only were

15   the majority of the patients in 009 white, they

16   were from eastern Europe.

17   DR. CONNOLLY: Correct.

18   DR. SCHAENMAN: That just seems unusual for

19   a study that's spanning multiple continents. I was

20   just wondering if the applicant could explain why

21   the enrollment was so lopsided for what's a

22   relatively common cause of complicated UTI in

1   nursing home patients in the U.S.

2   DR. CONNOLLY: Oh, certainly. So this is

3   actually a very common issue in registrational

4   studies in the cUTI indication. Several drugs who

5   have recently come for registration have largely

6   enrolled these studies in eastern Europe. Even

7   though we had the same number of sites open in the

8   U.S. as we had open at countries in eastern Europe,

9   the enrollment is just different.

10   We do think that despite the low U.S.

11   enrollment, the data collected can be generalized

12   to a U.S. patient population, particularly because

13   the primary analysis excluded pathogens resistant

14   to study drugs, thus in voiding imbalances due to

15   geographic differences in resistance. We also know

16   that plazomicin is not metabolized. It's cleared

17   by the kidneys. And in our pop PK analysis, which

18   did have greater racial diversity than this 009

19   study, we did not see an impact of race on

20   plazomicin exposure or clearance.

21   In addition, we do have some patients from

22   the U.S., and that was large in the phase 2 cUTI

1   study. And this study does also illustrate the

2   challenges we had in enrolling. Although we had a

3   quarter of the number of patients enrolled in the

4   phase 2 studies and the phase 3, it took more than

5   twice as long to enroll. We had 78 U.S. patients

6   actually in that study, and in terms of

7   microbiologic eradication at test of cure, if we

8   look in the ME patient populations, which are more

9   similar, we saw similar response rates. So again,

10   the phase 2 outcomes do support the notion that

11   this data can be generalized to the U.s.

12   population.

13   DR. BADEN: And a follow-on. In the 007

14   study, with enrollment largely coming from a

15   relatively small geographic area, the isolates that

16   were recovered, anything about them that makes them

17   less susceptible to colistin or more homogeneous in

18   their genetic background in terms of responsiveness

19   to plazomicin?

20   DR. CONNOLLY: So in terms of plazomicin

21   responsiveness, not particularly. So the majority

22   of isolates and the majority of patients that was

1   driven by the epidemiology of CRE being very high

2   in Greece, most of those are KPC producers. They

3   mostly are the ST-258 background, and that is

4   similar to what we see in the U.s. for CRE

5   epidemiology.

6   DR. BADEN: And in relation to colistin?

7   DR. CONNOLLY: The relation to colistin, one

8   issue we did encounter during the study, which led

9   to our challenges in enrolling, is that over time,

10   we began to see increasing resistance to colistin.

11   So at certain sites, resistance rates as high as

12   40 percent. We have seen reports or heard of

13   reports of colistin resistance rate as high as 20

14   percent in KPC producers in the U.S. at certain

15   centers.

16   DR. BADEN: Dr. Green?

17   DR. GREEN: Thank you. Michael Green. I

18   have a couple of questions relating to resistance

19   that will have a general theme and maybe to the

20   durability of the effectiveness of this drug. So

21   my first question is I believe you provided some

22   data that amongst NDM producing carbapenemases,

1   only 66 percent of the isolates were susceptible I

2   guess at baseline to plazomicin.

3   Have you characterized that mechanism of

4   resistance?

5   DR. CONNOLLY: Yes, we have. In NDM

6   producers from certain geographic areas tend to

7   also carry a ribosomal methyltransferase. So in

8   those NDM producers that are not susceptible to

9   plazomicin because of the ribosomal

10   methyltransferase, that renders them resistant to

11   all aminoglycosides.

12   DR. GREEN: And to clarify, is that gene

13   located on a transposon or plasmid, or is it

14   chromosomally based?

15   DR. CONNOLLY: Generally, these are plasmid

16   mediated.

17   DR. GREEN: Okay. Then the second question

18   that I have is, do you understand why plazomicin

19   doesn't work against pseudomonas, thetamonas [ph],

20   and acinetobacter?

21   DR. CONNOLLY: Sure. We suspect this is due

22   to efflux permeability issues with those pathogens.

1   So the plazomicin MICs for those organisms are

2   actually fairly similar to other aminoglycosides.

3   And the issue there usually is related to simply

4   uptake or penetration of the drug into those

5   pathogens.

6   DR. GREEN: And then I guess the follow-on

7   question to those is in terms of durability,

8   particularly for plasmid mediated resistance, I

9   know that you're going to restrict -- your labeling

10   is going to suggest restricting. And hopefully

11   antimicrobial stewardship, with the increased

12   attention it's getting by Joint Commission, CMS, is

13   going to work. But I mean, I guess one wonders

14   what the durability of effectiveness will be when

15   it is a mechanism that is easily -- since it's

16   plasmid based, resistance that's plasmid based

17   transmits in hospitals that are pretty high rate

18   and transmits between hospitals at a pretty high

19   rate. So I don't know if you've had any

20   speculation on that.

21   DR. CONNOLLY: No. Sure. Absolutely. I

22   think when we look at the data that we have for the

1   U.S. over our three-year surveillance period and

2   over 6,000 isolates, we found only 5 RMT producers.

3   And that is despite decades of use of

4   aminoglycosides in the U.S., which should be able

5   to -- any aminoglycoside should be able to select

6   for an RMT producer.

7   So we think the differences between places

8   like the U.S. and eastern Europe where we see

9   higher rates of resistance in general to

10 aminoglycosides and where we picked up some of

11 these, is that massive burden of aminoglycoside

12 use. And I can show you some data.

13   This is publicly available data from the

14 European centers for disease control and

15 prevention. If you look across Europe at the

16 countries that have these high rates of

17 aminoglycoside resistance, there is a correlation

18 with aminoglycoside consumption. So these are

19 countries where aminoglycosides are being used more

20 as frontline agents for multiple infection types.

21 So one issue that we think will limit the emergence

22 of resistance is the way that these drugs are used

1   and that we propose plazomicin be used in a very

2   limited patient population.

3   In addition, another difference may be

4   infection control procedures that may differ

5   between the U.S. and some of these other places

6   where we see very high rates of resistance.

7   DR. BADEN: Thank you. We will now take a

8   10-minute break. Panel members, please remember

9   that there should be no discussion of the meeting

10   topic during the break amongst yourselves or with

11   any member of the audience. We'll resume at 10:52

12   with the agency's presentations.

13   (Whereupon, at 10:42, a recess was taken.)

14   DR. BADEN: We will now proceed. I just

15   wanted to have a comment towards the end of the

16   last session. There are many more questions from

17   the committee members for the applicant. We will

18   resume with the further clarifications after the

19   agency's presentation and clarifying questions with

20   the agency, and then we will resume the many other

21   questions and clarifications that the committee

22   would like.

1   So we will now proceed with the FDA

2   presentations.

3   Dr. Sun?

4   **FDA Presentation - Hengrui Sun**

5   DR. SUN: Thank you for the opportunity to

6   present on the efficacy of plazomicin for the

7   treatment of complicated urinary tract infection.

8   I will discuss the design of study 009, followed by

9   patient disposition, demographics, and the baseline

10   characteristics. Then I will present efficacy

11   results and provide a summary.

12   This was a phase 3 randomized, double-blind,

13   noninferiority trial to compare plazomicin and

14   meropenem regimens for the treatment of a cUTI,

15   including acute pyelonephritis. Patients were

16   randomized 1 to 1 to plazomicin or meropenem group

17   to receive IV therapy. After a minimum of 4 days

18   of blinded IV therapy, there was an option to

19   switch patients to open-label, oral levofloxacin

20   for an additional 3 to 6 days to complete therapy.

21   The maximum duration of therapy was 7 days.

22   Clinical response and in a microbiological response

1   were assessed at day 5, end of IV test of cure, and

2   late follow-up.

3   The co-primary endpoint were the composites

4   of microbiological eradication and the clinical

5   cure rate at day 5 or at the end of ivy you

6   patients stops ivy before or on day 5 or at end of

7   IV if patient stops IV before or on day 5, and at

8   ToC visit. The term co-primary for this study

9   means that noninferiority needs to be shown with

10 the primary endpoint at both day 5 and in ToC in

11 order to conclude efficacy.

12   The results of the composite endpoint was

13 defined so that the worst response from the two

14 components would be the result of the composite.

15 For example, if either clinical or microbiological

16 endpoint was a failure, then the composite would be

17 a failure. Another example, if one endpoint was a

18 success and the other was indeterminate, then the

19 composite would be indeterminate.

20   The primary analysis population was the

21 microbiological modified intent-to-treat

22 population, which was defined as all randomized

1   patients who received any dose of study drug and

2   have at least one qualified baseline pathogens.

3   The pathogen needs to be susceptible to both

4   plazomicin and meropenem.

5   The prespecified NI margin was 15 percent on

6   the risk of difference scale, which is wider than

7   the 10 percent margin recommended in FDA guidance

8   for cUTI. This was agreed by the agency because

9   this is an unmet need. For each of the two

10   treatment groups, cure rates were computed. The

11   difference of the cure rates in 95 percent

12   confidence interval were calculated using

13   continuity corrected disease statistics.

14   A total of 6 009 patients were randomized to

15   the study, and the mMITT population included 388

16   patients with 191 in the plazomicin group and 197

17   in the meropenem group. About 99 percent of

18   patients completed the study in both groups. For

19   the patients who discontinued study drug early, the

20   reasons for the premature discontinuation was

21   generally comparable between the two groups.

22   This table shows that demographics in mMITT

population were generally balanced between the two

groups. The majority of patients were from eastern

European countries, that is 98.5 percent, which is

shown here as region 2. Patients were

predominantly white, which is 99.5 percent of the

population.

Baseline characteristics were also generally

balanced between the two groups. 58 of study

patients had a cUTI and 42 percent had AP.

Baseline uropathogens were mostly gram-negative

enterobacterial ACA such as E. coli and Klebsiella

pneumoniae. Approximately 25 of the patients had

aminoglycosides resistant pathogens. About

4 percent had carbapenem resistant pathogens.

Almost 28 percent of patients had pathogens that

produced ESBL.

For both treatment arms, about 80 percent of

patients switched to oral therapy after receiving

IV study drug. This figure shows the distribution

of duration of treatment. The upper row is for

plazomicin group and the bottom row is for

meropenem. The first column shows the duration of

1   IV therapy, the second column is for oral therapy,

2   and the last column is for the total duration of

3   therapy. The distribution is generally comparable

4   between the two groups.

5   Results for the primary efficacy endpoint at

6   day 5 in ToC are shown in the table. Again, for

7   patients who stopped IV before or on day 5, end of

8   IV response was used as day 5 response. Response

9   at ToC reflects the treatment effect of both IV and

10   oral therapy. Compared to the prespecified NI

11   margin of 15 percent, both lower limits of the 95

12   percent confidence intervals at day 5 in ToC were

13   larger than NI margin.

14   For this analysis indeterminate outcomes

15   were treated as failure. To see whether the

16   results are sensitive to the handling of

17   indeterminate data, we conducted additional

18   analysis that treat indeterminates as failure in

19   the plazomicin group and as a success in meropenem

20   group. Results of this analysis are not shown

21   here. They also supported the noninferiority of

22   plazomicin to meropenem.

1   The forest plot shows the risk difference in

2   95 percent confidence interval and each of the

3   visits for the composite endpoints in the two

4   components, which are the clinical response and the

5   microbiologic response. The two blue boxes

6   indicate the co-primary efficacy endpoint. The

7   numerical values are in the table above. The red

8   vertical line represents the 15 percent margin.

9   From the plot, we can see that the composite

10   results were driven by the microbiological

11   response.

12   This table shows the microbiological

13   eradication rates at ToC by baseline pathogen in

14   mMITT population. The numeric value of the

15   eradication rates for plazomicin group are

16   generally higher compared to the meropenem group.

17   The forest plot shows the results for the composite

18   endpoint at day 5 and ToC for some important

19   baseline subgroups in mMITT population. The

20   results are generally consistent across the

21   subgroups.

22   Since the maturity of patients were from

1   region 2 and white, subgroups of region and the

2   race are not included in the plot. Also, because

3   the sample size for some of the subgroups were are

4   small, we observed the wider confidence intervals

5   for those subgroups; for example, patients with

6   indwelling catheter or with diabetes.

7   To summarize, study 009 results supported

8   the conclusion that a plazomicin regimen is

9   noninferior to a meropenem regimen based on a

10   prespecified NI margin of 15 percent. The efficacy

11   findings were robust to the handling of

12   indeterminate data. This study was mainly

13   conducted in eastern European countries in white

14   patients.

15   My colleague Dr. Rubin will discuss the

16   efficacy for the study of bloodstream infections.

17   Thank you.

18   **FDA Presentation - Daniel Rubin**

19   DR. RUBIN: Thank you for the opportunity to

20   present on the efficacy of plazomicin for the

21   treatment of bloodstream infections. I will

22   discuss the design and results of study 007,

1   statistical issues limiting superiority

2   conclusions, an alternative analysis and

3   consideration of noninferiority, and provide a

4   summary.

5   This was a randomized, open-label comparison

6   between plazomicin and colistin regimens for the

7   treatment of infections due to carbapenem resistant

8   enterobacteriaceae. In the original study design,

9   this was to be a superiority trial. The original

10   primary endpoint was day 28 all-cause mortality.

11   Key secondary efficacy endpoints were clinical

12   response at a test of cure visit approximately 7

13   days after the end of therapy, day 14 all-cause

14   mortality, and time to death through day 28.

15   The primary analysis population was the

16   microbiological modified intent-to-treat population

17   with CRE confirmed by a central laboratory. The

18   originally planned sample size was 286 patients in

19   this primary analysis population with confirmed

20   CRE. The superiority testing was to be at the

21   one-sided 0.05 statistical significance level

22   rather than the usual two-sided 0.05 level.

1   We agreed with the significance level

2 because of the high cost of failing to detect an

3 effective treatment in an unmet needs setting. In

4 addition, a trial providing some evidence of

5 superiority to colistin likely would provide

6 persuasive evidence of superiority compared to a

7 hypothetical placebo.

8   We agreed to several features of the trial

9 because this was a superiority design. These

10 features included the combining of patients with

11 serious diseases of BSI or HABP/VABP. Patients

12 could be enrolled if they had a positive culture in

13 the 96 hours before randomization even if they had

14 negative cultures immediately before randomization.

15 Prior antibacterial therapy could be given for up

16 to 72 hours. Concomitant meropenem or tigecycline

17 was to be given for the entire 7 to 14 day duration

18 of therapy to provide additional CRE coverage.

19 Patients who were enrolled with unbeknownst

20 colistin nonsusceptible infections could be

21 included in the primary analysis. In addition, the

22 intention-to-treat efficacy analysis did not

1   consider study drug discontinuations.

2   There were two protocol amendments in this

3   study. The first changed the primary endpoint from

4   day 28 all-cause mortality to a composite of either

5   day 28 all-cause mortality or significant disease

6   related complications. The second protocol

7   amendment added an uncontrolled cohort to make

8   plazomicin available to patients who were

9   ineligible for randomization.

10   There were enrollment challenges in this

11   trial. The study was halted after two years due to

12   the pace of enrollment, and the final sample size

13   was 37 patients in the primary analysis population

14   of the randomized cohort. This was much smaller

15   than the originally planned sample size of 286

16   patients.

17   The statistical analysis plan was finalized

18   after enrollment had completed, but before the

19   sponsor became unblinded to results of this

20   open-label study. It stated that "while the

21   protocol specified primary and secondary endpoints

22   will be analyzed and traditional statistical

inference measures such as p-values and/or

confidence intervals will be included for

descriptive purposes, no formal hypothesis testing

is to be performed in this limited sample size."

The final primary endpoint and original primary

endpoint were to be presented in parallel.

Descriptive presentations were to use 90 percent

confidence intervals and one-sided p-values.

This figure shows the design scheme for the

randomized cohort, the planned 7 to 14 day duration

of therapy, and the study schedule. This diagram

shows the study disposition. There were

39 patients in the randomized cohort, and from the

allocation boxes, you can see that 21 patients were

randomized to the colistin group and 18 were

randomized to the plazomicin group.

There was only one patient in each group

excluded from the mMITT primary analysis population

because they did not have a confirmed CRE pathogen.

Thus, from the analysis boxes, the primary analysis

population had 20 patients in the colistin group

and 17 patients in the plazomicin group. From the

1   bottom most infection site boxes, you can see that

2   in the colistin group, there were 15 patients with

3   BSI and 5 with HABP/VABP, and in the plazomicin

4   group, there were 14 patients with BSI and 3 with

5   HABP/VABP.

6   This table shows demographics in the primary

7   analysis population of the randomized cohort, which

8   includes both BSI patients and HABP/VABP patients.

9   Due to the small sample size, the colistin and

10   plazomicin groups were imbalanced on some baseline

11   factors. For instance, the colistin group was

12   50 percent male and female [sic], while the

13   plazomicin group was 70 percent male. The study

14   was mostly conducted in Greece. The colistin group

15   had 3 patients from sites in Italy and Turkey and

16   none from the U.S., while the plazomicin group had

17   one patient from the U.S. and none from Italy or

18   Turkey. Most patients in each treatment group were

19   over 65 years old.

20   As previously mentioned, there were 29 BSI

21   patients and 8 HABP/VABP patients. The inclusion

22   criteria restricted the baseline APACHE II score to

be at least 15, and thus most patients had

significant comorbidities. Adjunctive meropenem or

tigecycline was to be given to all subjects for the

duration of therapy, and the majority received

tigecycline. The infecting CRE pathogen was almost

exclusively Klebsiella pneumoniae. Prior

antibacterial therapy could be given for up to

72 hours in this trial. You can see that almost

all patients received prior treatment. The most

common prior antibacterial therapies were

polymyxins and meropenem.

Here are the efficacy results for the

primary endpoints in the final protocol and the

original protocol. Numerical trends for both

primary endpoints favorite plazomicin. The rate of

day 28 all-cause mortality or significant disease

related complications was 10 out of 20 in the

colistin group compared to 4 out of 17 in the

plazomicin group. The rate of 28 all-cause

mortality was 8 out of 20 in the colistin group

compared to 2 out of 17 in the plazomicin group.

There were no missing data for these analyses.

1   For each primary endpoint, the one-sided

2   p-value was slightly above 0.05, and thus

3   plazomicin would not have met criteria for

4   declaring statistically significant superiority

5   under either the original or amended protocol. The

6   lower 90 percent confidence limits for differences

7   in event rates were near zero. Note that the 90

8   percent confidence interval for the day 28

9   all-cause mortality treatment effect exceeded zero

10   even though the one-sided p-value was above 0.05.

11   This was due to different methods being used to

12   construct the confidence interval and p-value.

13   There were only two patients in each group

14   who survived with a failure triggered by a

15   significant disease related complication. The two

16   colistin group patients had persistent bacteremia

17   and the two respective plazomicin group patients

18   had persistent bacteremia and septic shock.

19   Here are results for the three key secondary

20   efficacy endpoints. Rates of clinical care were 35

21   percent in both the colistin and plazomicin groups.

22   There were very few events for the day 14 all-cause

mortality secondary endpoint. Time to death

through day 28 favored plazomicin compared to

colistin. Note that time to microbiological

eradication was not one of the primary endpoints or

key secondary efficacy endpoints in this trial, so

is de-emphasized in our review.

Here you can see results for the two

infection types of BSI and HABP/VABP. In the

subgroup with BSI, the results favored plazomicin

compared to colistin for both primary endpoints.

To summarize the results of the planned

statistical analyses of the randomized cohort 1,

there were several issues limiting superiority

conclusions. There was a very small sample size,

implying substantial uncertainty for the plazomicin

treatment effect. The statistical analysis plan

specified use of only descriptive statistics. If

superiority testing had been kept in place,

statistical superiority would not have been

achieved for the final primary endpoint or original

primary endpoint at the protocol specified

one-sided 0.05 significance level, although with

1   the original all-cause mortality endpoint, the

2   results would have been near the boundary of

3   superiority. Uncertainty was expressed using 90

4   percent confidence intervals. Finally, there is an

5   issue with multiplicity when considering two

6   primary endpoints and the BSI subgroup. Focusing

7   on particularly favorable results such as the

8   apparent mortality benefit in BSI could unduly

9   favor plazomicin.

10   This figure shows the design for cohort 2,

11   which was the uncontrolled cohort. Patients could

12   have BSI, HABP/VABP, cUTI, and were all to be

13   treated with plazomicin. There were 30 patients

14   enrolled. All were enrolled in Greece, and like

15   the cohort 1 patients, they had significant

16   comorbidities, and 27 of these 30 patients had

17   confirmed CRE infections, which were all due to

18   Klebsiella pneumoniae. Of the 27 patients with

19   CRE, there were 14 with BSI, 9 with HABP/VABP, and

20   4 with cUTI.

21   The mortality results for the uncontrolled

22   cohort 2 were similar to those in the plazomicin

group of the randomized cohort 1. From the bottom

right cell of the table, you can see that only 6

out of the 27 patients treated with plazomicin died

by day 28. However, this was heavily influenced by

the low mortality in patients who are ineligible

for randomization because their APACHE II score was

below 15 or because they had a CRE due to a

complicated urinary tract infection. Consequently,

our thinking is that it would be inappropriate to

synthesize results by combining plazomicin treated

patients from cohort 1 and 2.

In our analysis of the data, we made several

choices. First, we focused on the randomized cohort

and the entire mMITT primary analysis population,

which included the 29 patients with BSI and 8

patients with HABP/VABP. Second, we focused on the

primary endpoint from the final protocol amendment,

which was day 28 all-cause mortality or significant

disease related complications. Third, we focused

on exact 95 percent confidence intervals because as

described earlier, the previous acceptance of 90

percent intervals had been due to the original

1   superiority design.

2   Our rationale was that this was the closest

3   achievable to having the statistical protection of

4   prespecification and represented an analysis of a

5   mortality driven endpoint and a BSI driven study

6   population. Drawbacks to this analysis were that

7   the disease related complications in the composite

8   might make this a less meaningful endpoint than

9   mortality, the applicant is only seeking an

10   indication for the BSI subgroup, and it is possible

11   to envision more efficient analyses.

12   Here are the results of our analysis. The

13   95 percent confidence interval provides evidence

14   that the plazomicin efficacy decrement compared to

15   colistin for day 28 all-cause mortality, or

16   significant disease related complications, is no

17   worse than 6 percent. The question then becomes

18   whether one can conclude that plazomicin is

19   effective based on this comparison to colistin.

20   There are several reasons why noninferiority

21   might be considered. The lower confidence limit of

22   negative 6 percent was based on conservative

1   choices in that other choices for the endpoint and

2   analysis population would have been more favorable

3   to plazomicin. In addition, so called exact 95

4   percent confidence intervals are also conservative

5   in that they will tend to cover the true treatment

6   effect in more than 95 percent of repeated trials.

7   In addition, noninferiority could still, in

8   principle, imply a favorable benefit-to-risk

9   profile if a very small efficacy detriment was

10   counterbalanced by much better safety than

11   colistin. However, any nontrivial increase in

12   mortality risk would likely offset improved rates

13   of reversible nephrotoxicity.

14   There are limitations of noninferiority

15   analysis. An efficacy conclusion based on

16   noninferiority would require reasonable confidence

17   in there being a large effect of colistin beyond a

18   hypothetical placebo in the setting of this study.

19   There are limited data with which to quantify this

20   colistin effect. Further, no noninferiority margin

21   had been prespecified for this trial, although from

22   a statistical perspective, this is an issue of

1   regulatory best practices rather than statistical

2   multiplicity.

3   In addition, several design features that I

4   will discuss in more detail on the next slide were

5   agreed to when planning a superiority trial and may

6   have impacted the magnitude of the colistin effect.

7   To further assess noninferiority, here are

8   selected baseline characteristics in the primary

9   analysis population of the randomized cohort.

10   There are several types of patients who were

11   enrolled in whom one might not expect an extremely

12   large difference between colistin and a

13   hypothetical placebo. There were only 4 patients

14   in each group with bloodstream infections who had

15   positive CRE blood cultures in the 24 hours before

16   randomization. My colleague Dr. Mishra will

17   describe this issue in more detail in his

18   assessment of causality from examining the

19   individual cases.

20   You can also see from this table that most

21   patients received more than 36 hours of prior

22   antibacterial therapy. From the third set of rows

1   in the table, it has been mentioned that all

2   subjects were to receive concomitant meropenem or

3   tigecycline for the duration of therapy. The last

4   row in the table shows that 12 patients had

5   colistin nonsusceptible Klebsiella pneumoniae.

6   Here are results for the primary endpoint of

7   day 28 all-cause mortality or significant disease

8   related complications in these subgroups. There

9   were no notable patterns between the timing of

10   baseline cultures and efficacy outcomes. In

11   patients with longer durations of prior therapy,

12   the plazomicin group had numerically better

13   outcomes. From the third set of rows in the table,

14   there was no noticeable impact of concomitant

15   meropenem or tigecycline, but it's unknown what

16   would have occurred had this double coverage been

17   withheld. Finally, from the last row in the table,

18   you can see that the plazomicin group had

19   numerically better results than the colistin group

20   in patients with colistin nonsusceptible

21   klebsiella.

22   Nonadherence can also impact noninferiority

1   analysis. There were two patients in each

2   treatment group with very early study drug

3   discontinuations. The two patients in the

4   plazomicin group discontinued on day 1 due to

5   microbiology indicating aminoglycoside resistance

6   and switched to regimens that included polymyxin

7   therapy, but were counted as successes for the

8   plazomicin group for both primary endpoints. The

9   two colistin group patients with early

10   discontinuations both died and were counted as

11   failures for the colistin group.

12   This table shows that if excluding the two

13   plazomicin patients who discontinued on day 1 from

14   this small study, the confidence intervals and

15   p-values become slightly less favorable to

16   plazomicin.

17   To summarize efficacy, numerical trends

18   favored plazomicin compared to colistin. There are

19   statistical limitations to concluding that

20   plazomicin has superior efficacy, including the

21   small sample size, use of descriptive statistics

22   and multiplicity from consideration of two primary

1   endpoints in the BSI subgroup. A conservative

2   analysis is to focus on the primary endpoint and

3   analysis population from the final protocol using

4   95 percent confidence intervals.

5   This provides evidence that the difference

6   in rates of day 28 all-cause mortality, or

7   significant disease related complications between

8   plazomicin and colistin is no worse for plazomicin

9   than 6 percent. However, noninferiority assessments

10   are complicated by design features agreed to when

11   planning a superiority trial. This summarizes our

12   assessment of the statistical evidence of efficacy

13   from this trial

14   My colleague Dr. Mishra will now discuss

15   additional clinical analyses of both efficacy and

16   safety. Thank you.

17   **FDA Presentation - Shrimant Mishra**

18   DR. MISHRA: Good thing is that it's summer

19   outside, but it's still winter in this room.   I

20   should have brought my snuggie.

21   (Laughter.)

22   DR. MISHRA: So I'm here to talk a little

1   bit about the clinical review issues that came up

2   with this NDA. I'm the main clinical reviewers.

3   I'm just going to highlight some of the main points

4   that we found that led to a little bit of concern

5   about the data with the BSI indication.

6   Because there was a very small sample size

7   for the BSI trial, particularly in cohort 1, we

8   were actually able to look at all the case report

9   forms pretty extensively. Besides just looking at

10   the basic demographic comparisons, we were actually

11   really able to look deeply into the blood culture

12   records. We were able to look at the presence of

13   lines and when they were changed. We were able to

14   look at the source workup, dates of the study drug

15   administration, any prior drug therapy

16   classification, and success and failures. So we

17   were really able to take a very comprehensive look

18   at each of the individual cases.

19   What we found were two main issues. The

20   first was there was uncertainty regarding this

21   definition of primary bacteremia. If you look at

22   the protocol, it very clearly outlines these

1   definitions, what's a primary bacteremia, what's a

2   secondary bacteremia, what's a central line

3   associated bacteremia? And this is all documented

4   in the CRF.

5   What's missing is there was really no

6   standardized procedure for source workup, and there

7   may be practicality issues associated with that.

8   But what happens is you actually have investigators

9   who sort of did different things when they were

10   doing their workup. So what you might have as you

11   might have bacteremias that were defined as primary

12   despite a fairly limited workup.

13   Here are two examples. There was a subject

14   who had a femoral line in. Their only qualifying

15   culture was a peripheral culture, which is one set.

16   There's none taken from the femoral line, and the

17   patient sort of characterizes as a primary

18   bacteremia.

19   In another case, you have a subject with

20   Klebsiella pneumoniae from the catheter as well as

21   from a peripheral culture, and here is sort of a

22   converse issue. The patient is actually still

1   called the primary bacteremia, and that's primarily

2   because there were some different resistance

3   patterns between the Klebsiella and the

4   [indiscernible] in the peripheral culture.

5   So there's a little bit of uncertainty

6   regarding these primary bacteremias. Again, this

7   just shows you the protocol definitions that they

8   had. And again, if you look at the central line

9   associated BSIs, the one thing that you'll note is,

10   typically these are defined you have to obtain

11   either blood or catheter site exudate cultures or

12   blood or catheter tip culture, central line and

13   peripheral cultures that match with timing as well

14   as in terms of differentials in colony counts.

15   This really is very dependent on the

16   investigator actually obtaining this information,

17   so what I want to show you is that we did have,

18   again, limited source determination. So of the 14

19   subjects in the plazomicin arm who had BSI, 10 of

20   them were counted as having primary bacteremias.

21   In the colistin arm, again, of the 15 subjects who

22   had BSI, again, 10 of them were counted as having

1   primary bacteremias. And if you look at the

2   workup, at least in the plazomicin arm, 5 out of 10

3   of those subjects had a line, had peripheral

4   cultures, but they really weren't done in

5   conjunction, and yet they were called primary

6   bacteremias.

7   In the colistin arm, it's even more so; 9

8   out of the 10 subjects had a line in, and line and

9   peripheral cultures were not done in conjunction,

10   and they were still called primary bacteremias.

11   Again, this is just looking at one aspect of source

12   workup, but again led to considerable uncertainty

13   in how to categorize these cases.

14   The second main issue that we determined was

15   beyond this issue of categorizing the bacteremias

16   was whether some of these patients were actually

17   bacteremic at all at baseline. In several

18   subjects, when we looked at their CRFs, we found

19   that in the plazomicin arm, 8 of the 14 cases, so

20   57 percent, and at least 3 of the 15 cases in the

21   colistin arm , 20 percent of subjects, had negative

22   or no cultures done at the time of starting

treatment, and they remain essentially culture

negative for the baseline CRE pathogen throughout

the rest of the study.

Now the question with these patients is,

well, was there still some little bacteremia that

was present at the time of starting treatment and

they were still adequately treated by the this

study drug, whether it's plazomicin or colistin.

But the other issue is really they are infected by

the time they started treatment at all. And the

reason why we want to consider this is that these

patients could have prior therapy. So they could

have prior therapy up to 72 hours prior to starting

study drug, and they could also have things done

such as removal and replacement of the line.

So to illustrate that, if you look at these

8 subjects who had negative cultures from day 1 and

throughout the rest of the study, 6 of them at

least had prior gram-negative therapy and 3 of them

had their lines removed or replaced around the time

of starting therapy. And only one of those

patients would have met this primary endpoint of

1   death or significant disease related complications.

2   So we're counting all these patients as success

3   when there's a little bit of uncertainty in terms

4   of how infective the patient was at baseline. And

5   you see a similar thing at the lower level with

6   colistin patients.

7   Now, the sponsor has pointed out that

8   despite whether you start with negative cultures on

9   day 1, that's still the colistin arm still seems to

10   have a higher rate of bacteremia as the study goes

11   on. The one thing that I'll say is that those

12   patients are a little bit difficult to interpret.

13   If you look at some of these patients, they may

14   have become transiently bacteremic for one day and

15   there's no change in therapy. So to call those

16   patients failures strictly on a basis of a positive

17   culture down the line is I think a little bit

18   tenuous. But it also still just doesn't answer the

19   central question of you have a significant group of

20   patients in the plazomicin arm who essentially

21   remained negative throughout the entire study, and

22   what do we do with those patients?

1   So to just quickly summarize, again, I'll

2   just point out what my colleague Dr. Rubin said.

3   The bottom line is the noninferiority assessments,

4   they're complicated by design features that greet

5   you in planning a superiority trial. So here we

6   have this confluence of events, where we have a

7   very small sample size that could lead to

8   heterogeneity both in measured and unmeasured

9   factors. You have the complication of prior

10   therapy, and you have the heterogeneity in terms of

11   how these patients were worked up leading to

12   complications and uncertainty interpreting the

13   data.

14   **FDA Presentation - Shrimant Mishra**

15   DR. MISHRA: I will now I guess hand it

16   over to myself --

17   (Laughter.)

18   DR. MISHRA: -- to go into safety. A lot of

19   the safety data has already been presented by the

20   sponsor, and some of the other safety issues are

21   going to be presented by some of the agency

22   colleagues a little bit later, particularly related

1   to the nephrotoxicity and trough issues. So I'm

2   just going to give a very brief overview of the

3   clinical safety data and just highlight some of the

4   things that we saw.

5   Again, we're going to just quickly talk

6   about a drug exposure, the safety population,

7   demographics, major safety results, and of course

8   drug associated adverse events of interest in the

9   aminoglycoside class, nephrotoxicity and

10   ototoxicity.

11   As has been noted before, there were 6 phase

12   1 studies. Four of them, the clinical study reports

13   came to us prior to the NDA submission, and this

14   was, again, two studies in healthy volunteers that

15   were primarily PK safety studies. There was a

16   study in subjects with renal impairment, and there

17   was a thorough QT study. And there were two more

18   studies that were done, and we received the final

19   report after the NDA submission, and these were

20   studies looking at the mass balance as well as a

21   drug interaction study with metformin. There's one

22   phase 2 study in complicated urinary tract

1   infection, as already been discussed, and there

2   were two phase 3 studies of complicated UTI as well

3   as blood bloodstream infection.

4   I'm going to focus primarily on the phase 2

5   and 3 safety findings primarily in complicated UTI.

6   I think it's been discussed earlier the bloodstream

7   infection safety information, first of all, it's a

8   very small sample size, and the subjects are

9   heavily confounded by a lot of their comorbidities,

10   which make interpreting safety data in that

11   population a little bit more difficult. So again,

12   I'm going to focus primarily on the phase 2 and 3

13   safety findings in cUTI.

14   We look at drug exposure. Basically the

15   highlights to note here is that in the phase 3

16   studies and phase 2 cUTI studies, there was roughly

17   377 patients that were exposed to the 15 mg per kg

18   dose. In the phase 3 BSI studies, there were 48

19   subjects that were exposed to the 15 mg per kg

20   plazomicin dose. And there were several subjects

21   in the phase 1 studies as well.

22   Again, looking at drug exposure, again,

1   these are not subjects who really take a

2   aminoglycosides for a long period of time. The

3   median duration of treatment in cUTI trials was

4   5 days. It was a bit longer in the BSI study.

5   The median duration of treatment was 12 days, but

6   by and large, the duration of treatment for these

7   subjects with aminoglycosides is a little bit less

8   than what we might see in clinical practice, so

9   it's good to interpret the safety data in that

10   context.

11   If we look at the subject disposition in the

12   phase 2 and 3 cUTI trials, a quarter of the

13   patients in the phase 3 trials in both arms

14   discontinued IV study drug. And again, as that has

15   been noted, that's primarily due to a lack of study

16   qualifying pretreatment baseline culture. So this

17   may be a subject who may have had a COAG negative

18   staph only in their culture or streptococci only in

19   their urine culture or had a negative urine

20   culture. So they were discontinued from treatment.

21   However, it's important to note that even though

22   there was this discontinuation from study

1   treatment, roughly 98 percent of subjects in all

2   the arms in and the phase 2 and phase 3 studies

3   continued their visit out to the late fall.

4   Subject disposition in the BSI trial, again,

5   you had a quarter of subjects discontinue IV study

6   drug in the plazomicin arm, a third in the colistin

7   arm. And the most important thing to note here is

8   that the discontinuations were for slightly

9   different reasons. In the plazomicin arm, it was

10   primarily due to adverse effect or a concern about

11   resistant pathogens, whereas in the colistin arm,

12   it was primarily due to an insufficient therapeutic

13   effect as well as death. Now, of course, these are

14   very small numbers, so again, you have to view

15   these numbers with caution. But anyway, these were

16   the trends.

17   Now, if we look at following out patients

18   out to day 60, obviously death was primarily the

19   major reason for withdrawing from the study, and

20   you saw that that happened more in the colistin

21   arm.

22   I briefly just want to point out the

1   demographics of the phase 2 and phase 3 cUTI

2   trials. And again, although the sponsor has pooled

3   the safety data, again, we elected not to do that.

4   And the reason why is the demographics of the two

5   studies are different in our view. If you look at

6   the 002 study, again, most of the patients came

7   from both Asia as well as Latin America, whereas if

8   you look at 009 study, almost all the patients came

9   from eastern Europe. So obviously, that led to a

10   little bit of differences in terms of racial makeup

11   in the two studies.

12   Also, 002 study, the vast majority of

13   patients were below the age of 65, whereas if you

14   look at the 009 study, the patients were split more

15   evenly between younger and older patients. Again,

16   if you look at infection type, you see that the 002

17   study primarily skewed toward acute pyelonephritis,

18   whereas in the 009 study, you saw more complicated

19   UTI patients that were enrolled. So because of

20   these differences, we elected not to pool the

21   safety data for these two studies and look at them

22   individually.

1   As has already been mentioned, there was

2   only one death in the phase 2 and 3 cUTI trials.

3   Again, this involved a patient, a 63-year-old woman

4   admitted for pyelonephritis. She received a dose

5   of plazomicin. This was discontinued from the

6   study drug due to acute kidney injury, and then

7   switched to piperacillin and tazobactam, and then

8   meropenem. At the time of discontinuation, she was

9   found to have metastatic uterine cancer with

10   possible involvement of the lungs and liver. She

11   went on hemodialysis, but on day 17 she refused,

12   and she died the following day.

13   So we tend to agree with the sponsor that

14   this patient had significant comorbidities that

15   probably led to her death. Of course, we can't

16   fully exclude an effect of plazomicin given its

17   potential nephrotoxic effects and given that the

18   patient had acute renal deterioration at the time

19   of her death. But again, we would agree with the

20   sponsor that there were significant comorbidities

21   involved in this patient's death.

22   If you look in the BSI trial, the 007 trial,

1   again, most of the deaths are related to either

2   newly acquired or prior existing infection, or to

3   end-of-life events like cardiac arrest and

4   cardiorespiratory arrest. If you look at serious

5   adverse events in the phase 2 and 3 cUTI trials,

6   the one thing that we want to note is that,

7   actually, the serious adverse event rate is very

8   low. In terms of the plazomicin arm, really, the

9   most noticeable thing is that there were a couple

10   of serious adverse events related to acute kidney

11   injury, again, highlighting the potential

12   nephrotoxic effects of this aminoglycoside.

13   Now, if we look at treatment-emergent

14   adverse events that are related to plazomicin in

15   the phase 3 cUTI study, they fall into three

16   categories. The first category would be just your

17   general complaints that we see in drug trials in

18   general, complaints of diarrhea, headache,

19   vomiting, nausea. The second category would be the

20   nephrotoxic events. You see a few patients who had

21   events of blood creatinine increased, creatinine

22   renal clearance decreased, acute kidney injury.

1   And the third category would be local effects, so a

2   couple of patients with infusion site phlebitis and

3   injection site erythema.

4   In the BSI trial, you saw the same thing,

5   again, in terms of looking at treatment-emergent

6   adverse events related to plazomicin. The main

7   thing to note, again, in the plazomicin arm, you

8   did have a few patients who had nephrotoxic related

9   events, acute kidney injury, and renal impairment

10   that were attributed to plazomicin.

11   So looking at this issue more broadly with

12   the nephrotoxicity, again, for nephrotoxicity that

13   is measured essentially, as has been done in prior

14   trials, by looking at subject of serum creatinine

15   greater than or equal to 0.5 milligrams per dL

16   above baseline. So if you look at this at these

17   patients who had had this increase -- and this

18   could be at any time after starting treatment -- so

19   it could be during treatment.

20   It could have been post-treatment -- again,

21   reinforcing what we've already heard earlier, you

22   see increases occurring, particularly in the UTI

1 trials, at a slightly larger rate in the plazomicin

2 arm relative to the comparator, whereas in the 007

3 study you see these increases happening at a

4 slightly lower rate relative to colistin. And for

5 the most part, when you look at the plazomicin arm,

6 most of the increases seem to be relatively mild in

7 that point 0.5 to 1 milligram per dL range.

8   Again, most of this was reversible, so if

9 you look at study 009, 9 of the 11 subjects, or 82

10 percent of the plazomicin subjects who had had

11 serum increases while on therapy had improvement in

12 their serum creatinine by the last follow-up visit.

13   If you look in nephrotoxicity by the RIFLE

14 classification, again, you see a similar thing. In

15 the UTI studies, it looks like a little bit more

16 nephrotoxicity according to this classification

17 relative to the meropenem and levofloxacin arms,

18 and a little bit less in the 007 study relative to

19 the colistin arm.

20   Now, the one thing I will say is it's a

21 little bit tricky to interpret the 007 data when

22 you're comparing plazomicin to colistin in terms of

1   nephrotoxicity. Because of the small sample size,

2   there is a little bit of difference in terms of the

3   concomitant medications that were taken. So in the

4   colistin arm, there was a little bit of higher use

5   of diuretics and other nephrotoxic medications. So

6   again, you have to view this trend of less

7   nephrotoxicity with plazomicin with a little bit of

8   caution

9   Ototoxicity I think has already been

10   discussed, again, pretty significantly by the

11   sponsor. In terms of the phase 1 studies, there

12   were 5 reports of transient tinnitus following a

13   single dose of plazomicin. In the phase 2 and 3

14   complicated UTI trials, there were 3 reports of

15   adverse events associated with cochlear vestibular

16   function. There was a report of hypoacusis,

17   tinnitus, and vertigo, but they were all somewhat

18   atypical for aminoglycoside related ototoxicity in

19   that they either were unilateral or that they fully

20   resolved.

21   Again, as was mentioned, pure tone

22   audiometry and electronystagmography were performed

1   on the phase 1 and phase 2 trials, and they were

2   evaluated by independent experts. The bottom line

3   from those results was that essentially there was

4   no widespread ototoxicity that could be found in

5   those studies. However, ototoxicity could not be

6   fully ruled out.

7   The summary of the safety findings was as

8   follows. The data from the plazomicin and clinical

9   trials, they present a safety profile that's

10   generally consistent with an amino lycoside class

11   drug. The main safety signal that was observed was

12   nephrotoxicity typical of an aminoglycoside,

13   generally associated with reversibility. There's

14   no clear comparison of plazomicin nephrotoxic

15   potential relative to colistin's nephrotoxic

16   potential. However, there's a trend suggesting

17   less nephrotoxicity for plazomicin.

18   Overt ototoxicity due to plazomicin was not

19   identified given the limited duration of treatment.

20   There's no definitive evidence, however, that

21   plazomicin does not have the potential for the

22   aminoglycoside associated ototoxicity.

1   Now I'll hand it off to our firm colleague,

2   Ada, here who will discuss some of the sero

3   monitoring issues.

4   **FDA Presentation - Luning Zhuang**

5   DR. ZHUANG: My name is Luning Zhuang. I'm

6   the pharmacometrics reviewer for plazomicin. My

7   presentation will focus on the therapeutic drug

8   monitoring for plazomicin in cUTI patients.

9   Plazomicin is mainly distributed in

10 extracellular space. Protein binding is around 20

11 percent. Plazomicin has minimal metabolism and is

12 predominantly eliminated by the kidney. The half-

13 life is around 4 hours. TDM using Cmin equal to or

14 higher than 2 microgram per milliliter during first

15 48 hours is proposed by applicant to mitigate the

16 potential nephrotoxicity. Cmin based TDM was not

17 conducted in cUTI patients in either phase 2 or

18 phase 3 studies. However, Cmin is considered to be

19 correlated with nephrotoxicity based on clinical

20 experience for other approved aminoglycosides.

21   In the phase 3 study, plazomicin dose was

22 adjusted daily based on creatinine clearance.

1   Nephrotoxicity was defined as serum creatinine

2   increase equal to or higher than 0.5 milligram per

3   dL from baseline. A total of 22 patients

4   experienced nephrotoxicity in the phase 2 and phase

5   3 studies. Among them, 9 patients had

6   nephrotoxicity occur after 10 days, indicating that

7   nephrotoxicity occurred more than 3 days after

8   plazomicin treatment had stopped.

9   Most of the nephrotoxicity occurred in cUTI

10   patients with renal impairment from the phase 2 and

11   phase 3 study. The nephrotoxicity incidence was

12   lower in plazomicin arm than that in comparator arm

13   in patients with creatinine clearance higher than

14   90 milliliters per minute. Only one patient with

15   creatinine clearance higher than 90 milliliters per

16   minute had nephrotoxicity. Therefore, no exposure

17   response analysis was conducted in patients with

18   normal renal function.

19   On the other hand, a significant

20   exposure-response relationship was identified

21   between estimated first Cmin, which is a Cmin prior

22   to second dose and nephrotoxicity in patients with

1   creatinine clearance between 30 to 90 milliliter

2   per minute. The Cmin was estimated based on

3   population PK model, and the first Cmin was used as

4   a PK measure in the exposure-response analysis

5   since Cmin didn't change substantially during the

6   treatment.

7   To evaluate the cutoff values for first Cmin

8   based on TDM, classification and regression tree

9   analysis was conducted in cUTI patients with

10   creatinine clearance between 30 to 90 milliliter

11   per minute. The first Cmin of three microgram per

12   milliliter was predicted to be the critical

13   threshold associated with high nephrotoxicity

14   incidence. A total of the 244 patients were

15   included in this analysis with 8.6 percent

16   nephrotoxicity. Among them, 216 patients had first

17   Cmin lower than 3 micrograms per milliliter and

18   have nephrotoxicity around 5.1 percent.

19   Twenty-eight patients have first Cmin higher

20   than 3 micrograms per milliliter, and their

21   nephrotoxicity incidence was 35.7 percent. The

22   table shows the relationship between the first Cmin

1   range and percentage of patients with

2   nephrotoxicity. The nephrotoxicity for the

3   patients with first Cmin higher than 3 micrograms

4   per milliliter -- the nephrotoxicity was

5   dramatically increased to 30 percent and above.

6   The first Cmin between 2 to 3 micrograms per

7   milliliter was associated with around 10 percent

8   nephrotoxicity.

9   The two first Cmin cutoffs, 2 and 3

10   micrograms per milliliter was compared from

11   different angles. A reasonable TDM cutoff should

12   be sensitive to a lot more patients with

13   nephrotoxicity to have dose adjustment in order to

14   maximize the nephrotoxicity mitigation. Original

15   TDM cutoff should also be specific to reduce

16   unnecessary dose adjustment for patients without

17   nephrotoxicity in order to minimize the potential

18   efficacy loss.

19   Based on the current data, the incidence of

20   nephrotoxicity was higher in patients with first

21   Cmin equal to or higher than 3 micrograms per

22   milliliter as compared with those with first Cmin

equal to or higher than 2 micrograms per

milliliter, and the dose adjustment would be needed

in fewer patients using first Cmin equal to or

higher than 3 micrograms per milliliter than

2 micrograms per milliliter.

In terms of weighting 2 TDM cutoffs, the

following considerations should be highlighted.

First, nephrotoxicity is reversible and treatment

duration of plazomicin is short for cUTI patients.

Second, no dose reduction based on first Cmin was

conducted in the phase 3 trial, and there was a

signal that efficacy may be compromised with lower

exposure based on the phase 2 dose-ranging study.

The cutoff of 3 micrograms per milliliter

provides a higher specificity, while the cutoff of

2 micrograms per milliliter shows a better

sensitivity. The specificity here is defined as

out of patients without nephrotoxicity. The

percentage of patients can be correctly classified

as no dose adjustment is needed. The sensitivity

here is defined as out of patients with

nephrotoxicity. The percentage of patients can be

1   correctly classified as dose adjustment is needed.

2   The first Cmin equal to higher than

3   3 micrograms per milliliter is helpful to minimize

4   the potential efficacy loss, but less patients with

5   nephrotoxicity may have dose adjustment. Well, the

6   first Cmin equal to higher than 2 micrograms per

7   milliliter is helpful to mitigate nephrotoxicity to

8   a greater extent with a higher risk of advocacy

9   loss. In brief, the cutoff 3 micrograms per

10   milliliter is an option if efficacy loss is a major

11   concern for TDM. The cutoff of 2 micrograms per

12   milliliter is an option if the safety is a major

13   concern for TDM.

14   Dose adjustments in cUTI patients was

15   further evaluated using both TDM cutoffs, 2 and 3

16   micrograms per milliliter. Because the treatment

17   is short and the PK samples take 24 to 36 hours to

18   be available for TDM, more than one dose adjustment

19   may not be clinically feasible. One dose

20   adjustment was considered by increasing dosing

21   interval to 1.5-fold in cUTI patients with

22   creatinine clearance between 30 to 90 milliliter

1   per minute. Based on simulation, around 92 percent

2   of patients may have seemingly lower than

3   2 micrograms per milliliter after one dose

4   adjustment using 2 micrograms per milliliter as a

5   TDM cutoff. Well, 97 percent of patients may have

6   Cmin lower than 3 micrograms per milliliter after

7   one dose adjustment using 3 micrograms per

8   milliliter as a TDM cutoff.

9   Dosing strategy was also evaluated in

10   patients with creatinine clearance between 15 to 30

11   milliliter per minute. Limited safety and efficacy

12   data are available in patients with severe renal

13   impairment. However, a higher risk of

14   nephrotoxicity compared to that in patients with

15   mild and moderate renal impairment is expected.

16   Since the treatment option is limited in

17   patients with severe renal impairments, the

18   following approaches can be considered to evaluate

19   the dosing strategy. Leveraging the findings and

20   knowledge from patients with creatinine clearance

21   higher than 30 milliliters per minute, and

22   considering the dose is given every 48 hours, TDM

1   should be carefully evaluated.

2   To summarize, it may not be necessary to

3   perform TDM for patients with creatinine clearance

4   higher than 90 milliliter per minute due to the

5   lower nephrotoxicity incidence as compared to the

6   active control. Cmin based TDM could be beneficial

7   to mitigate nephrotoxicity in cUTI patients with

8   creatinine clearance between 30 to 90 milliliters

9   per minute.

10   Different threshold concentrations for TDM

11   may be selected based on different benefit-risk

12   preferences. TDM shall be further evaluated in

13   cUTI patients with creatinine clearance between 15

14   to 30 milliliters per minute, although limited

15   efficacy on the safety data are available.

16   Next, my clin pharm colleague, Dr. Kunyi Wu,

17   will continue to discuss the TDM for plazomicin in

18   BSI patients.

19   **FDA Presentation - Kunyi Wu**

20   DR. WU: Good morning. I'm going to talk

21   about the therapeutic drug monitoring for

22   plazomicin in patients with blood stream infection.

1   TDM was conducted in study 007. It was an AUC

2   based TDM. The TDM range was 210 to 315.

3   According to the applicant, the decision to use TDM

4   was based on observed high variability of

5   aminoglycosides PK in critically ill patients. The

6   intent of the TDM is to avoid the risk of extremely

7   high or low exposures that could be associated with

8   unacceptable toxicity or poor efficacy.

9   The TDM range was predetermined based on

10 plazomicin, 28 percent of the mean AUC, which is

11 262 in phase 2 cUTI patients with normal renal

12 function who received the 15 milligrams per

13 kilogram per day plazomicin. TDM strategy was

14 modified after initiation of study 007. Based on

15 the final protocol, doses were adjusted on day 3,

16 day 6, and day 10 based on the estimated AUC on day

17 1, day 4, and day 8, respectively, in order to

18 maintain the AUC into the target range.

19   The difference between the sampling time and

20 the dose adjustment time was due to the assay

21 turnaround time, which was 28 [indiscernible] to 36

22 hours. In addition to the TDM, doses were also

adjusted based on renal function and the

physician's clinical judgment during the treatment.

This slide shows the overall plazomicin AUC

in BSI patients in the course of 7- to 14-day

treatment based on population PK and post hoc

analysis. The 10th percentile of overall AUC is

165 and the 90th percentile is 361. This range is

wider than the predetermined TDM orange, which is

210 to 315. The figure shows the daily AUC in BSI

patients from day 1 to day 14 based on post hoc

analysis. Only about 40 percent ranging from 30 to

60 percent of the patients' daily AUC fell in the

range of 210 to 315 during the treatment,

indicating that the TDM was not able to maintain

all patients' AUC within the target range.

This figure shows the individual patients;

AUC. Each line in the figure represents one BSI

patient in the study. Most of those patients

received more than one dose adjustment during the

treatment. The figure shows those patients' AUC

fluctuated over the course of treatment. So

despite the TDM and the renal function based dose

1   adjustment, a large variability in exposure was

2   still observed in BSI patients.

3   Thus far, I only discussed the overall

4   plazomicin exposure in BSI patients in the course

5   of the treatment. Now, let us discuss the

6   relationship between exposure and the clinical

7   outcome.

8   In trying to relate the TDM range to

9   efficacy and safety, some difficulties were

10   encountered. First, only a very limited number of

11   patients were enrolled in study 007. Specifically,

12   a total of 29 BSI patients received the plazomicin

13   and 4 of them were on CRRT at baseline. Therefore,

14   only 25 patients were in the PK data set, including

15   cohort 1 and cohort 2.

16   Due to the limited number of patients, no

17   exposure-response analysis can be performed for

18   either efficacy or safety. Secondly, all BSI

19   patients in study 007 received the plazomicin

20   treatment with TDM. In other words, nobody

21   received the treatment without TDM. In addition,

22   as discussed in the previous slide, only about 40

percent of the BSI patients' AUC fell into the TDM

range daily. Due to the AUC fluctuation for each

individual patient, AUC may stay in the target

range for one day and fall out of the range the

next day. Therefore, it is not possible to

evaluate the benefit of TDM range in this patient

population.

Because of the difficulties discussed in the

previous slide, we used alternative approaches to

evaluate TDM range. We evaluated the lower bound

of the range based on the PKPD target from animal

studies. The PKPD index, AUC over MIC, is closely

related to plazomicin antibacterial activity. PKPD

targets of plazomicin for bacterial stasis from

baseline was determined based on 17

enterobacteriaceae strains using a neutropenic

murine thigh model.

The table shows for the median of the PKPD

target values, the AUC required to attain the

target for MIC equals 4 is 96. For the 75th

percentile of the PKPD target values, the AUC

required to attain a target for MIC equals 4 is

156. So the lower bound of target AUC range, which is 210, is considered to be sufficient to attain the PKPD target for bacterial stasis from the baseline against the enterobacteriaceae for MIC up to 4 micrograms per mL.

We evaluated the upper bound of the TDM range based on observed nephrotoxicity in studies 007. Nephrotoxicity here is defined as a serum creatinine concentration increase of 0.5 milligrams per deciliter or greater from baseline. In cUTI patients, it was observed that an increased incidence of nephrotoxicity was related to increase the exposure, so a high AUC is expected to result in higher incidence of nephrotoxicity. As a consequence upper bound AUC may be helpful to limit the incidence of nephrotoxicity.

In study 007, about 30 percent of patients in plazomicin arm experienced nephrotoxicity. In contrast, about 50 percent of patients in the colistin arm experienced the same thing. The incidence of nephrotoxicity in both plazomicin and colistin arms may be due to multiple causes and may

1   not all be due to treatment medications.

2   To summarize my talk, for AUC based TDM

3   range in BSI patients, the proposed lower bound,

4   which is 210, is sufficient to attain the PKPD

5   target for bacterial stasis against the

6   enterobacteriaceae for MIC up to 4 micrograms per

7   mL. However, the proposed upper bound, which is

8   315, is questionable due to 30 percent incidence of

9   nephrotoxicity.

10   Consideration should be given to the

11   tolerability of the risk of nephrotoxicity in

12   patients who have limited or no alternative

13   treatment option. Up until now, the TDM range, low

14   and high bound, has been evaluated. However, the

15   clinical utility of TDM, in other words, the

16   benefit for BSI patients' AUC to stay in the range,

17   has not been demonstrated.

18   This concludes my presentation. Thank you.

19   **Clarifying Questions to the FDA**

20   DR. BADEN: I would like to thank the agency

21   for also thoroughly presenting a lot of data and

22   analyses of this compound and its development. To

1   the committee members, please get myself or

2   Dr. Chee's attention so we can start a list for

3   clarification questions for the agency. While we

4   are creating that list, I will start with the first

5   question to Dr Mishra.

6   In the 007 study, how do we understand

7   source control? Which is what I think you were

8   getting at with the lines being removed or not.

9   What assessments are there of adequacy of source

10   control at the time of initiation of treatment with

11   the study medications?

12   DR. MISHRA: Well, obviously these patients

13   are very sick. They're in the ICU. Many of them

14   have multiple lines.   It's probably maybe an

15   impossible task to have a completely comprehensive

16   source workup. However, I think the question is,

17   in a case like this, we would have liked to have

18   seen at least a limited workup, particularly as

19   related to line associated infections. And I think

20   in a lot of these patients, we didn't actually find

21   that information. We really just had limited blood

22   culture data and really nothing beyond that.

1   DR. BADEN: So the information wasn't

2   clearly available.

3   DR. MISHRA: Yes.

4   DR. BADEN: Okay. Thank you.

5   Dr Rubin, if we were to think that colistin

6   were no better than placebo, how does that affect

7   your analyses of efficacy or noninferiority?

8   DR. RUBIN: If there was a thinking that

9   colistin was no better than placebo in this setting

10   of the study due to the issues that have been

11   discussed, then it would become very difficult to

12   conclude that plazomicin was effective based on a

13   statistical comparison showing that it was not too

14   much worse than colistin.

15   DR. BADEN: Dr. Lo Re?

16   DR. LO RE: Vincent Lo Re. A question for

17   Dr. Mishra. How do we understand the uncertainty

18   regarding the primary bacteremias? I was struck

19   just by the fact that you noted that 57 percent of

20   the plazomicin treated patients had either negative

21   or no blood cultures at the time of starting

22   treatment and remained culture negative for CREs, I

1   believe it was throughout the rest of the study.

2   So can you clarify how the review of those

3   case report forms proceeded. And given that the

4   inclusion criteria for study 007 allowed for

5   presumed CRE infections, were there any concerns

6   expressed over the potential for misclassification

7   of bloodstream infections? It just seems unusual

8   to conduct a study for CRE bloodstream infections

9   without documentation of bloodstream infection from

10   CRE. So I just wanted to get more perspective from

11   your standpoint on the uncertainty behind this.

12   DR. MISHRA: Well, to the second point that

13   you talked about in terms of not having confirmed

14   CRE infection prior as opposed to suspected

15   infection, I think the sponsor did try to enrich

16   the population in terms of going to sites where

17   they had high rates of CRE infections. And also,

18   there were some other diagnostic tests that they

19   could use in order to presume that it was a CRE

20   infection. And I think for the most part, we did

21   see that there were CRE infections, at least at

22   baseline.

1   I think to answer the initial question about

2   the uncertainty around the primary bacteremia, it's

3   a tricky question. Again, we really

4   comprehensively did look through the entire CRF and

5   look through their entire hospital visit. I think

6   the interpretation of them can essentially go one

7   of two ways. You could essentially say that they

8   were adequately treated because of lines replaced,

9   and prior therapy, and really these patients really

10   weren't terribly infected to begin with. The

11   other, you could also possibly say that there are

12   low levels of intermittent bacteremia that you

13   didn't really pick up at baseline and that that was

14   actually kept at bay, or kept under control, or

15   eventually treated by plazomicin.

16   So that's the way that I approached the data

17   in terms of how I'm looking at it. I don't think

18   we're going to get a full answer to that question,

19   but I think the main point to be made is that you

20   can't ignore the uncertainty. The uncertainty is

21   there, and there's this large population of this

22   very small sample size that we don't really know

1   what to say about their infection status at

2   baseline.

3   Does that help answer?

4   DR. LO RE: Can I have a second question?

5   DR. BADEN: I realize the applicant may have

6   clarifying information on these points. At this

7   time, we're going to focus on questions to the

8   agency, but please keep track of comments that will

9   clarify issues raised, and we will certainly want

10   to discuss them and hear them.

11   DR. LO RE: I have a second question for Dr.

12   Nambiar. In your introductory comments, one of the

13   challenges that I'm having is related to the

14   definition of substantial evidence in this setting.

15   And on slide 7 of your introductory comments, you

16   noted that substantial evidence of efficacy under

17   the LPAD pathway requires evidence consisting of

18   adequate and well-controlled investigation,

19   specifically data from one adequate investigation,

20   and confirmatory evidence to constitute substantial

21   evidence.

22   I'm just curious, can you clarify further

1 and expound upon what does the agency consider as

2 adequate investigation, and clarify what do you

3 think is required for confirmatory? Especially

4 since the therapy here is limited for patients with

5 limited or no treatment options.

6   Particularly for study 007, what I'm

7 struggling with is we have one small study with no

8 formal hypothesis testing, one uncontrolled cohort

9 study, and mouse septicemia data. So I'm just

10 trying to get a sense of, in terms of adequacy and

11 confirmatory, what is the agency's thinking.

12   DR. NAMBIAR: The requirement is that we

13 have adequate and well-controlled investigations.

14 It's typically in plural, but we are also allowed

15 to rely on one adequate and well-controlled trial

16 if we have other supportive information. And the

17 other supportive information can come from -- it

18 could be another body site of infection. It could

19 be information from, say, animal models of

20 infection.

21   So there are other sources of information

22 that we can use to support the single adequate and

1   well-controlled trial, but for any particular

2   indications, whether ones considering cUTI or

3   whether ones considering BSI, each one at least you

4   need to have one adequate and well-controlled trial

5   that provide the substantial evidence of

6   effectiveness.

7   As we noted, the cUTI trial was an adequate

8   and well-controlled trial. There was hypothesis

9   testing. There was a prespecified analysis plan.

10   The bloodstream infection study, though originally

11   designed as a superiority study, a design of what

12   could have been an adequate and well-controlled

13   trial, because of the difficulties in enrollment

14   and the study having been stopped early, at the

15   time it was stopped, the analysis plan said that

16   there was no intent for any kind of formal

17   hypothesis testing. It was only meant to be a

18   descriptive study.

19   DR. BADEN: Dr. Follmann?

20   DR. FOLLMANN: Part of what I'm struggling

21   is similar to what Dr. Lo Re just mentioned. It

22   has to do with the rules of the game with LPAD

1   pathway, and should I sort of unquestionably follow

2   what's been given to me in terms of guidance or

3   question those.

4   One thing that I thought of has to do with

5   the unmet need. I was wrestling with the idea of

6   you have the cUTI trial, which is noninferiority.

7   So if it's noninferiority, we have a comparator

8   which is viewed to be adequate and inadequate

9   therapy. So how can there be unmet need in the

10   cUTI population is one question.

11   Then related for the 007 study, I think when

12   it was designed, there weren't the novel BL and

13   BLIs, which we now have. So again, what's the

14   unmet need? And the landscape that you're

15   suggesting to us is we should have one study and

16   sort of change the trade-off between type 1 and

17   type 2 errors for this setting.

18   So explain more about the unmet need and the

19   thinking behind the LPAD designation.

20   DR. NAMBIAR: So in terms of unmet need

21   development programs, as we've outlined in our

22   guidance, there are different avenues or approaches

1   that one can take. Ideally, if it were possible,

2   one could just do a study in patients who have

3   infections due to organisms of a particular

4   phenotype, the phenotype that you're interested in,

5   much like the study 007. And we've seen that from

6   a practical standpoint that doing such a study and

7   demonstrating superiority is very challenging.

8   The potential for a product to address unmet

9   need, I think that's a determination that we base

10   on what evidence we have that the drug can target

11   infections of a certain type or can target

12   organisms of a certain type. So that information

13   will in fact come external to the trials. So it

14   would come from animal models with infection from

15   in vitro studies.

16   The UTI study is primarily to show us that

17   the test drug does work in that particular body

18   site of infection, and it an allcomer population

19   study. So that study is really not designed only

20   to address an unmet need. I think that gives you

21   evidence that it works in a body site of infection,

22   and all the other information external to the trial

1   that could potentially treat infections due to

2   organisms that are resistant to other currently

3   available therapies, those are the kinds of things

4   we take into consideration, determining an unmet

5   need.

6   Now, that's a little different from LPAD.

7   So you would have to keep the two a little

8   separate. There's an unmet need and there's LPAD.

9   Every unmet need development program is not

10   necessarily under the LPAD pathway.

11   DR. FOLLMANN: But both of these drugs are

12   addressed for an unmet need that's part of what

13   we're judging them on.

14   DR. NAMBIAR: Correct. Right. The

15   differences for LPAD, as I had said, it's something

16   that the sponsor has to request for an LPAD

17   designation. It certainly has to be for the

18   treatment of a serious infection, and then there

19   are some other additional requirements. But the

20   bottom line is whether you seek approval under the

21   LPAD pathway or not, you still have to meet the

22   statutory standards or requirement for

1   effectiveness.

2   DR. FOLLMANN: I have a couple of other

3   questions.

4   DR. BADEN: Dr. Weina has a follow-on, and

5   then we'll come back.

6   DR. NAMBIAR: Dr. Baden, can I just finish?

7   There is one more thing I wanted to let you know.

8   DR. BADEN: Please.

9   DR. NAMBIAR: So I think for these programs,

10   what we've generally done is we've taken a greater

11   degree of uncertainty. And that's why we agreed to

12   a wide -- a noninferiority margin. The alpha was

13   0.10 two-sided. So that's where the uncertainty

14   is, but at the end of the day, even within that

15   framework of uncertainty, we have to be able to

16   make an assessment if the product was safe and

17   effective.

18   DR. FOLLMANN: So another way you might see

19   uncertainty, the way I might put it there's a

20   different trade off with type 1 and type 2

21   errors --

22   DR. NAMBIAR: Correct.

1   DR. FOLLMANN: -- or we're more likely to

2   take a chance on accepting a drug that might not

3   work in this situation. So we changed sort of our

4   calculus for evidence.

5   DR. BADEN: Dr. Weina, a follow-on question?

6   DR. WEINA: So just help me in my own head

7   understand the struggle I'm having with the idea of

8   an unmet need and noninferiority, which by

9   definition, noninferiority means you're comparing

10   it to something that you have something, so it's

11   not an unmet need. Yes? No?

12   DR. NAMBIAR: I'll start, and maybe Ed can

13   chime in as well. So that's the struggle, right?

14   So even if there is an unmet need and you want to

15   design a study, and you only want to study it in

16   patients who have no treatment options, then you

17   will need to do a study like study 007, because you

18   weren't able to demonstrate superiority because

19   here are patients who have no other treatment

20   options.

21   The difficulty in doing a study just in

22   infections due to a particular kind of organism or

1   a particular phenotype of interest is very

2   difficult and challenging as we've seen from this

3   example. So as an alternative, what we have found

4   acceptable is if you do a noninferiority trial, at

5   least you know that it works in whatever body site

6   of infection you've picked. But all the other

7   information to support the unmet need comes from

8   what can the drug potentially treat. Can it target

9   certain kinds of organisms for which you right now

10   do not have too many options?

11   DR. WEINA: So again, we're not talking

12   then -- we're starting to kind of skirt around the

13   issue of, again, limited population, this is the

14   population we're proving it in, but now we got

15   noninferiority. I understand the trial that was

16   designed for superiority because then you can argue

17   unmet need difficulty with that trial, so let's

18   make it noninferiority. But now we're talking

19   again about off-label use, which we struggle with

20   in a lot of our discussions with drugs that come

21   here.

22   DR. COX: So let's just step back. So we

1   think about noninferiority. You have to have an

2   active comparator because you're comparing yourself

3   to something else that you know to be active, that

4   you have a reliable treatment effect. So that's

5   going to limit who can get in your trial.

6   You want to compare the investigational

7   agent to an active comparator in the NI trial, and

8   the limitation is going to be around resistance

9   phenotypes because wouldn't have a valid comparison

10 if the patients are resistant to the comparator,

11 and you would certainly have ethical concerns about

12 giving somebody a drug that you didn't think was

13 going to be effective for a serious infection.

14   So the noninferiority trial when done can be

15 a very good way to assess efficacy in a certain

16 setting. It gives you a trial that you can enroll.

17 It allows you to enroll patients with the usual

18 types of drug resistance that you encounter. And

19 then if you think about it, you may have a drug

20 that operates via new mechanism of action. So all

21 the attributes of that drug and something that

22 differentiates that drug may not actually

demonstrate it from the results of the clinical

trial that is a noninferiority trial.

But you know based on the mechanism of action of

that drug, you know, that it may retain its

activity when there's resistance to other classes

of agents.

If you think about this, this isn't too

different than what we've been through over the

last several decades. Drugs that have been

approved versus the usual prevailing types of

resistance phenotypes that were out there 30 years

ago have shown themselves to work well in serious

infections caused by certain types of bacteria.

New resistance mechanisms may pop up over time to

other drugs that don't impact activity of that

drug.

So the NI trial can be a good way to

evaluate efficacy. It may not show all the

attributes of a molecule, if it's a different

class, if it is chemically modified in a way that

is not impacted upon existing resistance

mechanisms.

1   The other thing, too, is it can be a more

2   feasible trial. You've seen some of the issues

3   with regards to trying to enroll a trial when

4   you're targeting a particular resistance phenotype.

5   That resistance phenotype may not occur to

6   frequency where enrolling that trial can be done in

7   a timely fashion. You can balance the trade-offs

8   of trying to study a particular resistance

9   phenotype or studying patients with serious

10   infections caused by this similar type of bacteria

11   even though they may not have a particular

12   resistance phenotype, such a study could be more

13   easily enrolled.

14   So there's a whole bunch of trade-offs here

15   as you think about it. And then you can start to

16   ask the question, too, about generalizability and

17   relevance. A CRE patient population, you may want

18   to study patients who have CRE because of

19   particular patient characteristics. It may not

20   necessarily be solely resistance phenotype that's

21   driving you to want to see how the drug performs

22   there. It may also be because these patients have

1   comorbidities, renal problems, diabetes, heart

2   disease, other factors that make them different

3   than the general population.

4   So you can start to ask other questions,

5   too, like can you match those patient

6   characteristics that would allow for a broader

7   patient population and go beyond a particular

8   resistance phenotype, particularly if the

9   resistance phenotype of interest is not against the

10   class of drug that you're trying to investigate, if

11   that all makes sense.

12   So it's a complicated issue. We've sort of

13   been through this in a variety of different

14   settings, but just trying to summarize it sort of

15   in a nutshell as sort of the different ways that

16   you can think about this.

17   DR. WEINA: And I understand. Again, the

18   point that I think I was trying to make is trying

19   to fit it within this regulatory pathway of the

20   LPAD, which really kind of argues against some of

21   the examples that you gave, things that we've

22   approved in the past in noninferiority and stuff.

1   DR. COX: So say a little bit more, if you

2   will, just so I can understand.

3   DR. WEINA: I was just trying to -- again, I

4   think all of your arguments are absolutely on the

5   mark using our normal regulatory pathway for

6   approval. But right now, we're considering this

7   under the LPAD regulatory pathway for approval,

8   which changes the math in some ways because of the

9   fact that we have substantial evidence of

10   effectiveness with an unmet medical need, a number

11   of things that are all brought into the equation

12   that we don't normally have in approving a drug

13   because of the different regulatory pathway that's

14   quote/unquote "recently" been approved.

15   DR. COX: We do take unmet need into

16   consideration in some of the previous advisory

17   committee meetings. That has been part of what

18   we've talked about as we've talked about wider

19   noninferiority margins and such. So it is part of

20   the overall structure.

21   DR. BADEN: Dr. Follmann, continue.

22   DR. FOLLMANN: Well, just to add onto that,

1 would you say that the unmet need is more for the

2 resistant pathogens that you think we'll be

3 developing, and then we'll have this drug in the

4 armamentarium to address its future? Because for

5 the people in the study, they have a comparator

6 that works with them or is thought to work for

7 them.

8 DR. COX: Right, yes. I think the unmet

9 need is present. I mean, we do have patients out

10 there for whom there are very few treatment

11 options. The study may not enroll those patients,

12 but it still I think provides a good way to assess

13 the efficacy of the drug. And then you get to the

14 generalizability question, is that result

15 generalizable to the broader population?

16 I think in many ways, yes. I mean, there

17 are going to be some limitations, but it is a good

18 test of efficacy and it allows you to understand

19 how the drug works. And that's why I was thinking

20 back 20 years ago, a drug approved, resistance

21 phenotypes that are present today may not have been

22 present then. But if it's a resistance mechanism

1   that doesn't impact upon the mechanism of the drug

2   that you're choosing to use, most people would have

3   a fair degree of confidence that that drug should

4   retain its activity.

5   So I think we think about the unmet need

6   currently and a good test of efficacy to see

7   whether a drug works, and then we can use that

8   information, I think, as to how the drug would be

9   used today and certainly in the future, too,

10 because we would expect that new resistance

11 mechanisms will pop up. So a drug with a new

12 mechanism of action may have utility now and also

13 continuing to have utility in the future as new

14 resistance mechanisms pop up.

15   DR. BADEN: But, Dr. Cox, that begs the

16 question that the older drug that had activity

17 still has activity if it's the comparator, and how

18 one has a yard stick to compare to if the new

19 mechanism obviates the activity of the older drug.

20   DR. COX: So I didn't quite follow. Try me

21 one more time.

22   DR. BADEN: So if you use penicillin,

1   penicillin works well. Resistance emerges.

2   Penicillin is now your noninferior comparator, but

3   it has no activity against the organisms in

4   question. And then your new agent is being

5   compared to an antibiotic that has limited

6   activity, but it's noninferiority, not superiority.

7   DR. COX: Right. So in the noninferiority

8   trial, we would insist that the active comparator

9   drug be one that's active. And we do look at the

10 resistance phenotype as being a baseline

11 characteristic. We have encountered situations

12 where it wasn't anticipated, but there was a higher

13 rate of resistance in the comparator arm in the

14 study. So there it's very important for us to look

15 at the patient populations who on their baseline

16 characteristics are susceptible to the comparator

17 in order for us to have a valid test of the

18 efficacy of the drug in a noninferiority trial.

19   DR. NAMBIAR: And if I can just add, I think

20 the primary analysis population for the cUTI trial

21 patients, the organism had to be susceptible to the

22 test drug and the comparator drug, so it was as a

1   valid comparison.

2   DR. BADEN: Dr. Follmann?

3   DR. FOLLMANN: So 007 is a very difficult

4   study for us to evaluate. It's very underpowered N

5   of 37 when the plan was to be 286, and yet it's

6   sort of dancing around superiority with some

7   analyses. And maybe there's some evidence for

8   noninferiority, but it's also very fragile because

9   of the study being so small.

10   So what I sometimes like to do is think,

11 okay, this was sort of a study that couldn't be

12 executed for exogenous reasons we could say because

13 they couldn't accrue. So you sort of threw out the

14 analysis plan from the window, out the window. And

15 now we're trying to use our best judgment, I guess,

16 as to how to interpret the evidence. And there's

17 no plan, so different people can have different

18 perspectives on how to interpret those best

19 evidence. I think the FDA had a clever and sort of

20 different way of approaching this to try and look

21 at noninferiority for 007, recognizing its

22 limitations and so on, but sort of a different

1   maneuver.

2   I have two minds about this. One is that,

3   oh, it's just way underpowered; forget about it; or

4   the other is that when you have an underpowered

5   study, you try and use statistical methods or

6   thinking that's more efficient and kind of glean

7   more information from the study.

8   So I might be interested in the secondary

9   endpoint of time to death, up to day 28, and so on,

10   which was one of the analyses that you did. I was

11   wondering if Dan had done an analysis of time to

12   death, up to day 60, another way maybe to get more

13   information with more endpoints. But there are

14   different ways I guess to try and deal with a study

15   that's super underpowered and looking at maybe more

16   efficient endpoints or different analyses is one

17   way that one could approach it.

18   So the question is have you done a

19   time-to-event analysis using up to day 60, which I

20   think the sponsor had done something like that.

21   DR. RUBIN: Your points are well taken. The

22   time to death through day 28 was one of the key

1   secondary endpoints and is on my slide 15, and was

2   favorable to plazomicin. I think there were

3   Kaplan-Meier curves in the briefing book showing

4   survival data out to longer times. I'm not sure if

5   we have a p-value or hazard ratio in front of us

6   for that.

7   Another kind of more efficient analysis,

8   which was listed as an additional analysis of the

9   primary endpoint but was not in our briefing book

10   was a Cochran-Mantel-Haenszel test that tried to

11   adjust for the stratification factors and also had

12   a p-value that was more favorable for plazomicin.

13   So your points are well taken that there are

14   different ways to approach them. Our thinking was

15   that sticking with what had been specified in the

16   final protocol was the best way to preserve the

17   integrity of randomization and the benefits of

18   a prespecification, but that's what we have in

19   terms of the more efficient time.

20   DR. BADEN: Follow-on?

21   DR. FOLLMANN: Just to mention, if the

22   sponsor could present their results. I know it's a

1   bit different because you were careful to say your

2   analysis population is both HABP/VABP and

3   bloodstream infections versus sponsor is just

4   looking at bloodstream infections and excising the

5   HABP/VABP group, which didn't -- maybe have

6   increased the evidence in favor of the drug.

7   Anyway, if the sponsor could present their

8   analysis like that, and it's not exactly what I

9   want, but it's something to look at.

10   DR. RUBIN: Okay. I think figure 8 in the

11   briefing book has some time-to-event data out to

12   day 60.

13   Is that the sponsor's briefing book or our

14   briefing book?

15   DR. PALEVSKY: No, it's the FDA's.

16   DR. RUBIN: Okay.

17   DR. FOLLMANN: Okay. Thank you.

18   DR. BADEN: Dr. Kartsonis, you had a

19   follow-on question?

20   DR. KARTSONIS: I just wanted to make a

21   comment to remind the committee about these kinds

22   of studies we're doing here in carbapenem resistant

1   infections. This is now I think the third study

2   that is out there that are looking at carbapenem

3   resistant infections. All of them have struggled

4   to recruit. All of them have enrolled about 50 to

5   60 patients, including one that Merck has done as

6   well, so I can speak a little bit to that.

7   I think the expectation that we will have a

8   fully powered study of hundreds of patients in

9   carbapenem resistant infections is wishful

10   thinking, and I do think we have to take the data

11   we currently have and try to analyze it I think in

12   the best way like the FDA has been trying to do as

13   well as the sponsor has been doing. So I do want

14   to remind folks that this is a study that went on

15   for over a few years. The ones that Allergan did

16   and also Merck have done have also taken three-plus

17   years and have all recruited about 50 to 70

18   patients. So I do think there is a lot of value

19   that can still be generated from these studies that

20   we shouldn't at least lose a perspective on.

21   I guess the question I have is, in the face

22   of all the data and all these uncertainties that

1   we've had, irrespective of how you look at the

2   data, it does appear that there's a consistent

3   effect for plazomicin versus the comparator. And

4   even in the analyses, Shrimant, you mentioned the

5   ones where on day 1, they were negative. It still

6   appears that the mortality in the colistin arm is

7   still ranging around 30 to 50 percent, irrespective

8   of whether or not you knew they were positive on

9   day 1, irrespective of whether they were negative

10   on day 1, or whether or not they were positive on

11   day 1.

12   So I do think we just have to remind

13   ourselves that the totality of the data is an

14   important factor here.

15   DR. BADEN: Thank you. There are still many

16   more questions on our list from the committee,

17   however, we have reached the lunch hour. So we

18   will now break for lunch. We'll reconvene again in

19   this room at 1:30. I will remind the committee not

20   to discuss it amongst ourselves or with anyone else

21   and that we will continue questions to the agency

22   as well as to the applicant after lunch. See you

1 all at 1:30.

2   (Whereupon, at 12:41 p.m., a lunch recess

3 was taken.)

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1   A F T E R N O O N   S E S S I O N

2   (1:35 p.m.)

3   **Open Public Hearing**

4   DR. BADEN: It is now 1:35. We shall resume

5   the meeting.

6   Both the FDA and public believe in a

7   transparent process for information-gathering and

8   decision-making. To ensure such transparency at

9   the open public hearing session of the advisory

10   committee meeting, FDA believes it is important to

11   understand the context of an individual's

12   presentation. For this reason, FDA encourages you,

13   the open public hearing speaker, at the beginning

14   of your written or oral statement to advise the

15   committee on any financial relationship that you

16   may have with the sponsor, its product, and if

17   known, its direct competitors. For example, this

18   financial information may include the sponsor's

19   payment of your travel, lodging, or other expenses

20   in connection with your attendance at the meeting.

21   Likewise, FDA encourages you at the

22   beginning of your statement to advise the committee

1   if you do not have any such relationships. If you

2   choose not to address this issue of financial

3   relationships at the beginning of your statement,

4   it will not preclude you from speaking.

5   The FDA and this committee place great

6   importance in the open public hearing process. The

7   insights and comments provided can help the agency

8   and this committee in their consideration of issues

9   before them. That said, in many instances and for

10   many topics, there will be a variety of opinions.

11   One of our goals today is for this open public

12   hearing to be conducted in a fair and open way

13   where every participant is listened to carefully

14   and treated with dignity, courtesy, and respect.

15   Therefore, please speak only when recognized by the

16   chairperson. Thank you for your cooperation.

17   Will speaker number 1 step up to the podium

18   and introduce yourself? Please state your name and

19   organization you're representing for the record.

20   MR. THORNHILL: Hi. My name is Barrett

21   Thornhill. I'm the executive director of the

22   Antimicrobial Innovation Alliance, of which

1   Achaogen is a member. Our coalition is a coalition

2   of pharmaceutical innovators focused on working

3   with Congress and the administration to help spur

4   the development of critical need products that

5   respond to one of our most pressing public health

6   challenges, antimicrobial resistance.

7   Multidrug resistance pathogens know no

8   boundaries. Every state is experiencing outbreaks

9   and increased deaths. If you listen to our

10   domestic and global experts, this crisis is going

11   to get a lot worse. The assistant director general

12   of the WHO has said, quote, "We are fast running

13   out of treatment options." The UK government has

14   released a report predicting deaths from AMR will

15   exceed cancer in 30 years and that CMO added that

16   without action now, quote, "We are really facing a

17   dreadful post-antibiotic apocalypse." The agency's

18   own Dr. Janet Woodcock has testified many times

19   before Congress about the, quote, "fragility of the

20   antimicrobial pipeline" and the need for a, quote,

21   "broad continuing platform of antibiotics for a

22   wide variety of diseases."

1   CRE infections are especially deadly and are

2   occurring among our most vulnerable patients,

3   including those in ICUs and those with prolonged

4   hospital stays. There are at least 70,000 cases of

5   CRE annually in the U.S. alone, and that number is

6   expected to double within four years. More

7   frightening is the CDC reports that CRE infections

8   are associated with mortality rates above 50

9   percent.

10   A serious consequence, these organisms are

11   becoming resistant to our last line of antibiotic

12   defenses. That was the case last year when a woman

13   in Nevada died from an infection that was resistant

14   to 26 antibiotics. Former CDC director, Tom

15   Frieden said, quote, "Without urgent action now,

16   more patients will be thrust back to a time before

17   we had effective drugs."

18   We talk about a pre-antibiotic era and an

19   antibiotic era. If we're not careful, we will soon

20   be in a post-antibiotic era; and in fact for some

21   patients and some microbes, we are already there.

22   Even with growing resistance and an increase in

1 infections, it remains an enormous economic

2 challenge to bring a new antibiotic to market. The

3 Presidential Advisory Council on Combatting AMR

4 determined that the ROI for antibiotics is poor and

5 unpredictable. A 2014 AEGIS report followed up and

6 said the net present value of antibiotics for six

7 leading infections has now topped $50 million, and

8 for two types of infections, the return is actually

9 negative.

10   What we need are new antibiotics that

11 target priority pathogens. This is why plazomicin

12 is so important. At the end of 2016, legislation

13 which my group worked on for four years with the

14 FDA and the IDSA, became law. The 21st Century

15 Cures Act was passed to accelerate the discovery,

16 development, and delivery of new treatments.

17 Included in this bill was Section 3042 that

18 established the LPAD pathway intended to treat

19 patients with unmet medical needs.

20   Dr. Woodcock testified that, quote, "Drugs

21 approved using an LPAD pathway will be based on a

22 more streamlined development program that

1   established that the drug is safe and effective in

2   a limited population of patients with serious or

3   life-threatening infections and unmet medical

4   needs." Plazomicin is precisely the type of drug

5   Congress was thinking about when developing LPAD,

6   and now with the opportunity to be the first drug

7   approved for this pathway.

8   Bloodstream infections have flipped over 1

9   million patients per year, making it the single

10   most expensive disease that U.S. treats in

11   Medicare. This treatment under review can save

12   lives. I urge this committee to support the

13   licensure of plazomicin to help patients and

14   address this growing public health crisis. Thank

15   you for your time.

16   DR. BADEN: Thank you for your comments.

17   Will speaker number 2 step up to the podium

18   and introduce yourself? Please state your name and

19   any organization you're representing for the

20   record.

21   DR. SHENDELMAN: Hi. My name is Shoshana

22   Shendelman. I'm representing myself, and I have

1   nothing to disclose. First, I'd like to thank the

2   FDA for allowing me to share our family's

3   experience on plazomicin, and I hope that

4   understanding our situation will help to provide

5   some context for approval of new options for

6   complicated infections.

7   My dear cousin, Dr. Fred Noband, or "Fari"

8   as he was known to our family, was the head of

9   neurosurgery at Lenox Hill Hospital, and he was

10   devoted to saving the lives of others. He became a

11   surgeon because he believed in our ability to

12   change the world through improvements in medicine

13   and science, and he did go on to save countless

14   lives as a neurosurgeon. He was also a beloved

15   son, brother, husband, and father of two young

16   daughters.

17   Fari was treated for AML in 2013 and

18   underwent several bone marrow transplants,

19   chemotherapy, and surgical procedures. He was in

20   remission from the cancer and scheduled to be

21   released from the hospital within a few days. His

22   fight with this often deadly form of cancer had

been successful, and we were ecstatic. But like

many other immunosuppressed patients with a long

hospital stay, he developed a multidrug resistant

infection. In his case, the primary infection was

an antibiotic resistant enterobacter, and he soon

became septic.

As he quickly declined, an additional

secondary infection developed, Stenotrophomonas

maltophilia, and the hospital's head of infectious

disease informed us that the bacterial strains were

not susceptible to any antibiotics, including

colistin and that we had no options. They

recommended palliative care and told us to say our

final goodbyes.

As a scientist, although in a different

field, I'm a neurobiologist, I had heard that there

were new antibiotics in development to treat

multidrug resistant infections, and I knew that the

FDA and CDC had programs ongoing that might give us

access to these new drugs. After some quick

research and help from several New York area

infectious disease specialists, we determined that

1   the enterobacter strain was sensitive to

2   plazomicin, and we immediately reached out to

3   Achaogen to access this drug.

4   This was on a Friday afternoon, and I still

5   recall the late Friday night calls with the FDA,

6   the hospital board, and the company to access this

7   drug. It was locked in a warehouse in

8   Pennsylvania, and we were told that if we didn't

9   initiate the drug within 24 hours, our cousin was

10   not going to make it.

11   Somehow they were able to find someone to

12   open the warehouse and get us this drug, and we

13   started to see an effect almost immediately after

14   implementing plazomicin. Within a few hours, his

15   vital signs started to improve and he began on the

16   road to recovery. Within a few days, he awoke and

17   soon was joking around with us as though he had not

18   been on death's doorstep a few days prior. The

19   ability of new antibiotics such as plazomicin to

20   treat previously fatal infections is

21   groundbreaking. Plazomicin can literally mean the

22   difference between life and death to a patient with

a complicated resistant infection.

I'll shift gears for a minute and talk about our experience with the other strains, the stenotrophomonas and our experience trying to gain access to a different medication. In contrast to our experience gaining swift access to plazomicin, the process to receive the second antibiotic was long and drawn out, requiring extensive administrative red tape and lengthy reviews by multiple committees.

The drug had to be shipped from a central facility in Europe. Altogether, access took several weeks, and over the course of those weeks, as the enterobacter infection cleared, the stenotrophomonas infection took over, and we watched a newly healthy patient begin to decline again. And that drug that we had so desperately been waiting for arrived at the hospital the morning after our cousin passed away.

I'd like to highlight a few things that we learned from this personal experience that I think are relevant to this committee. First, the

1   incidence of multidrug resistant infections is on

2   the rise as everyone in this room is well aware.

3   It's important to have as many tools in our arsenal

4   as possible when treating complicated infections.

5   Secondly, these infections are often fast moving,

6   and it's important that clinicians have ready

7   access to these drugs so that they can be

8   implemented immediately when needed.

9   I work on drug development in other areas,

10   and I've sat in this room and listened to public

11   statements and been on the other side of that

12   table. As a scientist, I intellectually knew about

13   rising multidrug resistant infection numbers and

14   lack of treatment options, but until I faced this

15   issue up close, I hadn't recognized the urgency of

16   the situation. And when a patient is a loved one,

17   you start to think about drug development

18   differently. The number of patients and incidence

19   of disease take on a different meaning. In my

20   opinion, plazomicin is an important new tool that

21   should be made available to clinicians as broadly

22   as needed. Thank you.

1   DR. BADEN: Thank you for your comments.

2   Will speaker number 3 step up to the podium

3   and introduce yourself? Please state your name in

4   any organization you're representing for the

5   record.

6   MR. NAHUM: Good afternoon. My name is

7   Armando Nahum, representing Achaogen. I have no

8   financial disclosures.

9   Someone once said that in life, even more

10 than education, experience is sometimes the best

11 teacher. Well, if that is true, I can tell you

12 with all certainty that there's no one I know that

13 has been taught more or has been more profoundly

14 affected by the personal devastation and particular

15 loss caused by hospital-associated infections than

16 my own family.

17   In 2006, three members of my family were

18 impacted with hospital-associated infections in

19 three different hospitals, in three different

20 states, in 10 months time, culminating with the

21 death of my son Josh. He was 27. Josh acquired a

22 multidrug resistant organism in his cerebral spinal

1   fluid during his six weeks in ICU. And since 2013,

2   the CDC has classified CRE as a serious threat to

3   public health and one of three greatest threats to

4   human health by the World Health Organization. And

5   despite the global emergence of CRE, no clear

6   consensus has emerged in regard to the method of

7   detection, and the prevalence of CRE infection is

8   rapidly increasing in hospitals and community

9   settings, and my son is a testament of that.

10   It is important to understand that there is

11   increasing evidence that bloodstream infections due

12   to CRE are associated with high morbidity and

13   mortality. So for this reason, it is imperative

14   that we allow new antibacterial drugs to provide

15   treatment options, especially in cases where

16   resistance has eroded the effectiveness of existing

17   drugs. Thank you very much.

18   DR. BADEN: Thank you for your comments.

19   Will speaker number 4 step up to the podium

20   and introduce yourself? Please state your name and

21   any organization you're representing for the

22   record.

DR. LODISE: Thank you. I'm Tom Lodise.
I'm representing myself. I'm a consultant for
Achaogen. They provided support to travel here
today. I am not being compensated for my time.

Again, I'm here today to support the
approval of plazomicin for the treatment of
patients with CRE bloodstream infections and
complicated urinary tract infections. I'm a
professor at a college of pharmacy and clinical
specialist where I participate in an antibiotic
stewardship program. My reason for adducing
approval is threefold and really stems from my role
as a clinical practitioner and researcher,
antibiotics steward, and clinical pharmacist.

As a practitioner, I strive to practice
evidence-based medicine whenever possible. As
highlighted today, it's very difficult to conduct
trials and generate comparative data in patients
with serious gram-negative infections, including
those calls by CRE. Because of this, we often rely
on microbiologic susceptibility results to guide
therapy.

1   As we observed in recent trials,

2 susceptibility does not always equate to success.

3 As examples, doripenem, ceftibiprole, Tygacil, all

4 agents with favorable microbiologic profile against

5 key gram negatives, were unsuccessful in several

6 other registrational trials and did not meet their

7 primary endpoints.

8   As we have discussed today, we have seen a

9 growing number of studies that have shown

10 suboptimal outcomes with colistin when it's

11 employed as the comparator. I believe the positive

12 findings from the CRE bloodstream trials supports

13 approval plazomicin, although a limited number

14 demonstrates a mortality benefit. When I think

15 about outcomes, you look at our patients, and that

16 is the most difficult one to show a difference, yet

17 across important subgroups, we were able to show a

18 difference in mortality.

19   As an antibiotic steward, there's a true

20 need for non-beta-lactam antibiotics for patients

21 with serious gram-negative infections.

22 Beta-lactams are highly effective and safe

1 antibiotics, and this is reflected in their

2 clinical use. Their use, however, is not without

3 consequence.

4   As we have discussed today, we have seen

5 emergence in ESBL CRE and other highly resistant

6 gram-negative bacteria. This is due in part to use

7 of many of our broad spectrum beta-lactams,

8 including the carbapenems and beta-lactam

9 beta-lactamase inhibitors. Because of their broad

10 spectrum use, we're also concerned about

11 C. difficile colitis, which is a major concern in

12 the healthcare environment.

13   In addition, we cannot use beta-lactams in

14 all of our patients. Many patients are beta-lactam

15 allergic and have other contraindications for their

16 use. Therefore, there's a true unmet need as an

17 alternative beta-lactam for patients with CRE

18 bloodstream infections as well as complicated

19 urinary tract infections.

20   I understand today's approval for a drug

21 will be also to think about practical concerns, so

22 we think about a lot of our drugs we use to treat

1   CRE dosed multiple times a day by prolonged

2   infusions. Within the healthcare industry, there's

3   an increased emphasis on quality and efficiency of

4   care, so when we think about a single, once-daily

5   drug, this has the potential to facilitate early

6   discharge and treatment in other environments other

7   than hospitals. So again, there's practical

8   benefits to having other CRE drugs particularly for

9   our non-beta-lactam patients.

10   Finally, I'd like to speak as a clinical

11   pharmacist. We would welcome the addition of a new

12   aminoglycoside. TDM is very favorable to us. Most

13   hospitals now have a PK dosing, so I anticipate

14   plazomicin will be readily incorporated in the

15   practice.

16   Why there's some hesitancy on approving a

17   drug with TDM. I actually see it as an advantage.

18   As we're well aware, patients with serious

19   gram-negative infections, there's substantial

20   interpatient variability and pharmacokinetics. As

21   we know, serum creatinine and GFR estimating

22   equations on the way we dose most of these

1   antibiotics do not accurately reflect renal

2   function and drug clearance of many renally

3   eliminated drugs.

4   As we know, serum creatinine often lags

5   behind true renal function in patients with rapid

6   change of renal function and cannot be used to

7   estimate renal function in patients with augmented

8   renal function. A good example of this is the

9   findings with Avycaz and its complicated

10   intra-abdominal trial. As we saw there in patients

11   with moderate renal impairment, we saw lower

12   response rates, and this was due in part to rapidly

13   improving renal function and underdosing those

14   patients.

15   So there was a lot of discussion today about

16   AUC dosing. I see this as an opportunity. I am

17   also on the vancomycin consensus guidelines. We

18   are moving towards AUC dosing for vancomycin. I

19   view this as a innovative approach and the future.

20   So again, while there may be some hesitancy with

21   the AUC dosing, this is going to be readily

22   incorporated into practice with vancomycin and also

1   plazomicin. Thank you.

2   DR. BADEN: Thank you for your comments.

3   Will speaker number 5 please step up to the

4   podium and introduce yourself? Please state your

5   name and any organization you're representing for

6   the record.

7   DR. GELFAND: Good afternoon. My name is

8   Michael Gelfand. I'm a practicing infectious

9   disease physician in Memphis, Tennessee. I'm also

10   a professor at the University of Tennessee and

11   chief of OID at Methodist University Hospital in

12   Memphis. I was paid to travel here, but received

13   no other compensation, just the airfare. I have no

14   relationship with Achaogen otherwise. My remarks

15   will be personal and will not represent an opinion

16   of the University of Tennessee or of the Methodist

17   healthcare system.

18   I'm routinely involved in the care of

19   infectious disease patients with immunocompromised

20   states, organ transplantation, stem cell

21   transplantation, as well as HIV patients. When

22   caring for these patients, we of course are all

1 aware of the current state of hospital infectious

2 practice.

3   It is characterized by the rising resistance

4 of gram-negative rods to multiple classes of

5 antibiotics, including carbapenems, older

6 aminoglycosides and polymyxins and their increasing

7 number in elderly and immunocompromised patients.

8 Many of these patients come to us with

9 comorbidities. They come to us from the places

10 such as long-term care facilities and nursing homes

11 where resistance, including carbapenem resistance,

12 is rising. And patients like that are then

13 confronted with a relative paucity of therapeutic

14 alternatives.

15   While a number of new beta-lactam agents

16 have recently been approved for the treatment on

17 label and are intended for the management of

18 resistant gram-negative infections, the data that

19 supported their approval did not include

20 substantial information on carbapenem resistant

21 bacteria of a clinical type. I think it would be

22 highly desirable to have additional alternatives

1   for the treatment of carbapenem resistant

2   gram-negative bacteria. And the reasons as a

3   clinician to have these alternatives would include

4   emergent resistance against older agents, including

5   new beta-lactam agents recently introduced,

6   especially in severe infections such as bacteremia,

7   but also noticing recent data suggesting that this

8   resistance is rising in the presence of pneumonia,

9   immunocompromised state, and hemodialysism, and a

10 desirability of being able to use combination

11 therapy possibly to impede the emergence of

12 resistance.

13   We are aware of an editorial accompanying a

14 paper in Clinical Infectious Diseases suggesting

15 that we'll need a bigger boat and a better boat to

16 float our patients from an ocean of resistance.

17 And I'm hopeful that plazomicin will be an agent

18 that will allow as combination therapy to construct

19 this Noah's ark of therapeutic efficacy to avoid

20 the emergence of resistance.

21   We need non-beta-lactam agents for patients

22 who are allergic to penicillin, cephalosporins, and

1   carbapenems. We need a convenient agent that can

2   be given once a day. And we certainly need less

3   toxic agents as compared to older aminoglycosides

4   and colistin. So in my opinion, plazomicin

5   represents these desirable characteristics that

6   would allow us to perhaps improve the care of

7   patients with carbapenem resistant bacteria.

8   Finally, I wanted to, in the period of

9   openness, report to the committee that while I'm an

10   American citizen, I was born in Moscow, Russia, and

11   I don't want my remarks to be construed as an

12   attempt at collusion --

13   (Laughter.)

14   DR. GELFAND: -- or influencing their vote

15   on plazomicin. I also wanted to mention that while

16   I'm relatively young, I was a personal participant

17   in pre-antibiotic as well as antibiotic era when I

18   was infected as a child with at that time emerging

19   beta-lactamase positive Staph aureus and was one of

20   the first recipients of new drug methicillin for

21   the treatment of staphylococcal sepsis, benefiting

22   from emergence of new antibiotics.

So thank you very much for your time and for listening to my remarks, and thank you.

DR. BADEN: Thank you for sharing your thoughts, and we accept your affirmation of no collusion.

(Laughter.)

DR. BADEN: Will speaker number 6 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

DR. GOLAN: My name is Yoav Golan. I'm from Tufts Medical Center. I'm an infectious disease physician whose research interest is antibiotic resistance and hospital-acquired infections. My disclosures are my travel here, flight and Uber, was paid by Achaogen. And I also served as a consultant to Achaogen and have some stock.

I'm speaking for myself, and I'm kind of speaking as an ID doctor as well as someone who's doing research, and I have two basic comments. One has to do with the unmet need, and the other one has to do with the evaluation of effectiveness when

1   the unmet need is great.

2   When it comes to the unmet need -- and I

3   think that there were quite a few presentations

4   here. And I don't really have to add to that. The

5   mortality that we see from gram-negative pathogens

6   nowadays is much higher than we used to see in the

7   past. There are multiple studies that show that

8   resistance is a factor, and the more resistant a

9   pathogen is, whether it's an ESBL producer or a

10   CRE, the higher is the mortality. I think part of

11   that is not that we don't have treatment options,

12   but that the treatment options that we have a

13   really not very -- are suboptimal.

14   I think it is important to remember that the

15   pathogens that actually cause those urosepsis or

16   intra-abdominal infections, or even gram-negative,

17   catheter-related bacteremia have not changed. And

18   there haven't been many reports about the change in

19   their virulence, suggesting that a lot of the

20   mortality really has to do with inappropriate

21   therapy. And I think that when we evaluate new

22   treatment options, we have to remember that we have

1 a relatively wide margin for improvement here just

2 by improvement in treatment.

3   Now, my second comment has to do with

4 effectiveness and evaluation of effectiveness, and

5 I think there were a few comments that were similar

6 to mine. I just want to mention that what we have

7 been seeing and probably will continue to see our

8 suboptimal studies. Particularly when you start to

9 dissect them from a an independent immunology

10 perspective, from a statistics perspective, it's

11 really easy to kind of distance yourself in seeing

12 the big picture and kind of dividing it into

13 fragments, and each of the fragments doesn't really

14 tell you a lot.

15   I think that we should really take a

16 Bayesian approach when we do that, particularly

17 when we're evaluating an antibiotic that belongs to

18 a class for which we have a lot of experience, and

19 actually look at in what way this antibiotic

20 differs from other antibiotics in this class for

21 which we have a lot of information; to what extent

22 this difference in design has resulted in

1   difference in in vitro activity; and look at the

2   safety data very carefully. But at the end of the

3   day, I think that when you get to the clinical

4   trial, you really have to take this Bayesian

5   approach and ask given the change in design, given

6   the decrease in resistance to this agent, given the

7   mechanism of action, how should we interpret the

8   clinical data that's available to us? And I think

9   that you may reach somewhat different conclusions.

10   I think that this is particularly critical

11   when what's considered to be best available therapy

12   or frequently used antibiotics are suboptimal. I

13   think many people talked about the fact that

14   colistin or tigecycline that are so commonly used

15   for those types of resistant pathogens in very

16   severe infections would never have been approved by

17   the FDA. Based on the available clinical data,

18   there was a question of whether it's actually

19   different from placebo. And I think that this

20   question was very relevant because we've seen the

21   very high mortality rate in studies when colistin

22   has been used.

1   My last comment has to do with the fact that

2   although we've seen the CRE study completed, I

3   think that there may be better uses in clinical

4   practice to plazomicin because if you look at many

5   of the CRE patients in the clinical trial, they

6   were either treated with an antibiotic for which

7   they were resistant like a carbapenem as part of

8   the regimen or a tigecycline type of antibiotic

9   that doesn't really have good plasma levels and, as

10   you know, is a static antibiotic and so forth.

11   While I think that in the real world, the

12   combination of plazomicin with more active agents

13   may actually result in better activity, I would

14   argue that in many of the patients in the CRE

15   study, plazomicin was actually used as an

16   aminoglycoside monotherapy that many of us would

17   think maybe should not be the case and should have

18   a better combination than those studies.

19   So with that in mind, I think that

20   plazomicin would be an important agent for us as

21   infectious disease doctors. People already

22   mentioned the fact that we have several

1   beta-lactams being approved, have been approved, in

2   the pipeline, but we don't really have many of the

3   other classes. And I think it will be particularly

4   important to have something that we can use in

5   synergism, particularly early in the state of

6   infection to reduce the inoculum and improve the

7   effectiveness of therapy. Thank you.

8   DR. BADEN: Thank you for your comments.

9   Will speaker number 7 step up to the podium

10   and introduce yourself? Please state your name and

11   any organization you're representing for the

12   record.

13   DR. BURDETTE: I'm Dr Steve Burdette. I'm

14   an infectious disease provider in Dayton, Ohio. My

15   travel has been supported by Achaogen but not my

16   time. I'm here representing myself. I'm a

17   professor of medicine and the program director for

18   infectious diseases at Wright State University,

19   Boonshoft School of Medicine. In my 13 years in

20   practice, I have been spending time as the medical

21   director of both antimicrobial stewardship for the

22   hospital as well as for the system, and I also run

1   infection prevention for an 800-bed level one

2   trauma center, which is a tertiary referral place.

3   I oversee the antibiotic administration of

4   dozens of patients every day, and after I leave

5   here, I will go back to the hospital and make more

6   rounds tonight. In my professional time, I've had

7   the ability to serve on the Infectious Disease

8   Society of America's guidelines committee as well

9   as on their clinical affairs committee, and I have

10   been on one of IDSAs task force for into microbial

11   stewardship.

12   I want to start off on why we need more

13   options for gram-negative infections. I am greatly

14   appreciative of the FDA approving

15   ceftolozane-tazobactam, ceftaz-avi, mero-vabor, but

16   already we have resistance to those antibiotics.

17   We need more options.

18   A lot of discussion today of colistin, a lot

19   of discussion of the renal issues with colistin.

20   When I use colistin, my patients don't feel well,

21   and sometimes they don't feel well for a long time.

22   They have various neurologic, other complications

1   that may or may not be pulled out in the studies.

2   They don't like the way they feel on either

3   colistin or polymyxin B; a lot of electrolyte

4   issues as well that leads to more and more

5   medications. We need more options.

6   We have a significant number of patients

7   with beta-lactam allergies. The literature is very

8   clear. Patients with beta-lactam allergies have

9   worse outcomes because you have to go to more

10   difficult antibiotics or antibiotic combinations.

11   We need better options for the beta-lactam allergic

12   patients.

13   There's also been some discussion of

14   tigecycline. Tigecycline, I don't like to use it

15   for bacteremia. I don't like to use it for urinary

16   tract infections. I don't like to use it for

17   sepsis. I think the literature is very clear, but

18   sometimes with these multidrug resistant pathogens,

19   we have to use an antibiotic like that. We need

20   more options.

21   So where would plazomicin fit into this in

22   terms of treating multidrug resistant

gram-negatives? It gives us another non-beta-

lactam allergy always beneficial to us. As

previous speakers have said, that idea of

combination therapy, if I had a very sick person

with a multidrug resistant gram-negative

bloodstream infection, I'm probably going to use

combination antibiotic therapy. As an infectious

disease provider, I'm very comfortable using an

aminoglycoside as the second agent. If you don't

have aminoglycoside, then it becomes a little bit

more challenging what combination do you use.

In my facility right now, I already have

about a 2 percent amikacin resistance when it comes

to our resistant gram negatives. When you throw in

the CREs that's been discussed, the rate of

amikacin resistance goes up much greater. So when

you need options to treat folks who cannot get

amikacin, you're really running out of options, so

we need more things for those folks.

Lastly, the literature is pretty clear that

if you don't get the antibiotics right empirically,

the patients have worse outcomes. Studies have

1   shown increased mortality, increased morbidity, and

2   over half of the time, the empiric antibiotics are

3   not correct. So as we get into more and more

4   resistant gram negatives, we need to have more

5   options to deal with those.

6   Lastly in closure, I have a patient I've

7   been treating now for two weeks, spina bifida

8   patient, has had heavy antibiotic exposure, has a

9   couple of different very resistant gram-negative

10 infections; just recently had a reaction to one of

11 the options that was approved a couple of years ago

12 through the FDA, and I'm running out of options.

13 And his mother just asked me to pass along to you,

14 if he pulls through this, he's going to need more

15 options when he gets his next infection. With his

16 spina bifida, with his chronic respiratory failure,

17 it's not if he gets another infection, it's when.

18 He needs future options. Thank you.

19   DR. BADEN: Thank you for your comments.

20   Will speaker number 8 step up to the podium

21 and introduce yourself? Please state your name and

22 any organization you're representing for the

1   record.

2   MR. NAHUM: Good afternoon. My name is

3   Armando Nahum, once again, representing Dr. Juan

4   Diaz, infectious disease physician, chairman of

5   infection prevention Florida Hospital, Orlando.

6   Dr. Diaz has no financial disclosures.

7   "I am an infectious disease physician in

8   Orlando, Florida. Unfortunately, I treat patients

9   with multidrug resistant organisms frequent enough

10   that it is common threat in my practice. I

11   encounter extended spectrum beta-lactamase isolates

12   on a nearly daily basis. However, there are other

13   organisms that are becoming much more prevalent in

14   clinical practice, specifically organisms such as

15   CRE that have higher mortality, and scarce

16   treatment options are a real and urgent threat for

17   the Center of

18   Disease Control.

19   "The infectious disease community oftentimes

20   is faced with limited options on treatment choices,

21   both because of resistance and patient factors, but

22   also because of adverse effects. In current care,

1   there's a lack of antimicrobials with significant

2   activity towards these isolates or relatively few

3   alternative agents have significant difficulties

4   with standardized dosing, increasing MICs and sides

5   effects including nephrotoxicity.

6   "Restricting utilization of carbapenems may

7   also have a role in decreasing its resistance. I

8   have reviewed some of the preliminary information

9   on plazomicin, including their phase 3 trials for

10   complicated urinary tract infections. It appears

11   that plazomicin demonstrates a significantly higher

12   composite cure than meropenem at the test of cure.

13   Moreover, there was no reversible ototoxicity noted

14   in a trial.

15   "In addition, expanding our armamentarium

16   for treating bloodstream infection is extremely

17   important at this time in our current healthcare

18   arena. As you well know, patients with serious CRE

19   infections have significant mortality and disease

20   related complications. The phase 3 trials

21   demonstrate a survival benefit with plazomicin

22   treated patients, which was sustained through

day 60. There was higher microbiological response

rates, therefore supporting the findings of a

mortality benefit observed. Most importantly,

plazomicin was associated with an improved safety

profile compared with Colistin when used as part of

a combination regimen for the treatment of

life-threatening infections due to CRE.

"At this time, I urge you to please review

this new agent to explore new ways of treating our

patients in a safer fashion and expanding our

current antimicrobial choices towards treatment of

multidrug resistant infections. Thank you very

much."

DR. BADEN: Thank you.

Will speaker number 9 step up to the podium

and introduce yourself? Please state your name and

any organization you're representing for the

record.

DR. SHAPIRO: Thank you for the opportunity

to speak today. I am Dr Danielle Shapiro. I'm a

physician and senior fellow at the National Center

for Health Research. Our Center scrutinizes

1   scientific and medical data and provides objective

2   health information to patients, providers, and

3   policymakers. Our statement today reflects our

4   views and also that of the National Physicians

5   Alliance. We do not accept funding from

6   pharmaceutical companies, so we have no conflicts

7   of interest.

8   Antibiotic resistant bacteria are a major

9   public health concern. We must address this

10   through enforced antibiotic stewardship, infection

11   control, and development of effective and safe

12   antibiotics that save people from deadly

13   infections.   Unfortunately, the sponsor has not

14   proven the safety or efficacy of plazomicin for

15   patients who have limited or no treatment options.

16   Although there is a compelling unmet need to treat

17   these deadly infections, we cannot lower the

18   standards to approve this drug or any other drug

19   that fails to demonstrate safety or efficacy

20   through appropriate clinical research and

21   appropriate statistical methods. That is what the

22   law requires.

1   We will focus on the following questions.

2 Number 1, do the studies show that this will work

3 when other options are limited? In the UTI trial,

4 plazomicin was noninferior. In other words, the

5 older control drug was similarly effective. Since

6 the study population could have been treated with a

7 control drug, the study population cannot be

8 characterized as having limited or no options.

9 Therefore, the results provide no evidence that

10 this newer drug will work for the intended

11 population.

12   Worse, we do see a safety signal in terms of

13 a toxic effect on the kidney for plazomicin

14 compared to the older drug. We should not accept a

15 more toxic drug when the older drug works as well

16 and is less toxic. Keep in mind that the goal of

17 noninferiority is to provide added benefits for

18 patients such as fewer adverse events. Since a

19 noninferior drug is no more efficacious, it should

20 have some other proven benefit like a less serious

21 side effect.

22   In the bloodstream infection trial, we also

1   did not demonstrate that plazomicin was safe or

2   effective. Testing the effect of plazomicin with

3   noninferiority or with exploratory analysis does

4   not demonstrate that it is effective in patients

5   with no other options. We cannot draw conclusions

6   about the benefit or harms based on what the

7   sponsor admits is descriptive rather than

8   inferential data. The results are not

9   statistically significant, meaning that these

10 results did not rule out harm for patients and

11 could have been due to chance alone.

12   Number 2, are the results valid?

13 Interpreting these results, particularly BSI, is

14 difficult because there was not a standard

15 collection of data, most randomized patients had

16 negative or no blood cultures, and the source of

17 infection was uncertain, especially in those who

18 had an IV catheter. Furthermore, intending

19 population who would use this drug was not studied

20 in these trials, so what will this drug look like

21 in the real world? We need to clearly define the

22 population that would be treated with this drug

1   based on the evidence provided. We cannot

2   extrapolate this data from the study population who

3   were well treated with an existing drug to the

4   intended population.

5   Number 3, what evidence do we need for

6   approval? We cannot approve this drug based on a

7   single noninferiority study and a failed

8   superiority study. Studies testing these drugs for

9   unmet medical need of patients who have no other

10   options cannot be noninferiority because by

11   definition there is another option being tested and

12   the new drug could even be slightly worse. It is

13   not scientifically valid or ethical to base the

14   claim of noninferiority on a failed superiority

15   trial.

16   We urge the panel to recommend that FDA

17   require additional well-designed superiority

18   studies that use appropriate statistical methods to

19   determine whether plazomicin cures infections and

20   saves lives for patients who have no other options.

21   With reliable methods, even small studies can show

22   a clinically meaningful and significant benefit.

1   Since there is no evidence that plazomicin

2   works or is safe for patients who have limited or

3   no options, approval will do more harm than good.

4   As you all know, once approved, these new drugs are

5   often promoted and prescribed for much wider

6   patient population. This can expose tens of

7   thousands of patients to drugs that don't work and

8   cause harm. Simply labeling this drug as limited

9   population would not be sufficient to limit the

10   drug's use to an appropriate patient population.

11   Thank you so much for the opportunity to

12   share our perspective.

13   **Clarifying Questions (continued)**

14   DR. BADEN: Thank you. I'd like to thank

15   all of the open public hearing speakers for sharing

16   their thoughts, and especially those who shared

17   their personal stories. This helps round out our

18   perspective on why we're here. The open public

19   hearing portion of the meeting is now concluded,

20   and we will no longer take comments from the

21   audience. The committee will now turn its

22   attention to address the task at hand, the careful

1   consideration of the data before the committee as

2   well as the public comments.

3   Given that we were not able to complete the

4   clarification elements with both presenting groups,

5   there are a few more questions for the agency that

6   we'll complete, and then we will return to the

7   questions we have for the applicant. So where we

8   left the agency questions, Dr. Le, I think you were

9   next.

10   DR. LE: Yes. I really enjoyed the FDA's

11   exploration of the data, particularly as it relates

12   to the TDM, both for toxicity and efficacy. In

13   particular for the toxicity, the threshold that you

14   used during CART, identifying Cmin, resulted in

15   improved specificity, did you by any chance

16   evaluate it from -- because it's obvious that it's

17   exposure-response related, right, and increasing

18   dose or exposure relate -- did you by any chance to

19   do a CART for the AUC as well?

20   DR. LIU: It's Chao Liu, the pharmacometric

21   team leader for this review. So we did assess the

22   correlation between the AUC and the nephrotoxicity

1   that also show the cause associations. So in terms

2   of finding out one classifier to predict the

3   nephrotoxicity, we're still operating the

4   characteristic analysis, and it shows that trough

5   concentration in 24 hours to have a better

6   predictive power as compared with AUC. So we

7   choose the trough concentration as a predictor to

8   correlate with the nephrotoxicity.

9   DR. LE: The reason why I ask that is

10   because what's proposed here is two different TDM

11   processes, one that's more Cmin based and the other

12   one is AUC based. Whereas the Cmin clearly

13   identifies a threshold for nephrotoxicity, what is

14   that for AUC? Because if I'm going by AUC for

15   efficacy, well, I have the AUC unless I extrapolate

16   it to the Cmin to make that correlation to

17   nephrotoxicity. Because most patients with this

18   BSI will likely be on higher dose or a higher

19   exposure by AUC. So that's why it's nice to have

20   that information in there for some correlation.

21   DR. LIU: Right. We did some exploratory

22   analysis that quantitatively correlates the trough

1 concentration with the AUC, and we see that there

2 is some correlation between the trough

3 concentration and AUC. Though, in terms of using

4 an explorer matrix to predict the nephrotoxicity,

5 we do see a better predictive power using trough

6 concentration as compared with the AUC. So

7 although these two explore matrices were

8 correlated, trough concentration correlates better

9 with the nephrotoxicity risk as compared with say

10 AUC.

11   DR. LE: Thank you for that. Now related to

12 the effectiveness side, I know that you were trying

13 to select the lower end by using the static rather

14 than the one log kill, and you were comparing this

15 for bloodstream infection. I'm not sure in

16 clinical practice if we would target stasis when

17 we're treating a patient with bloodstream infection

18 rather than a one log kill.

19   Can you comment on that?

20   DR. WU: Sure. My name us Kunyi Wu. I'm a

21 clinical pharmacology reviewer for plazomicin. As

22 Achaogen talked about, they already talked about

1   the great uncertainty in animal PKPD targets,

2   regarding the animal PKPD target to the

3   gram-negative BSI. And to my knowledge, the

4   relationship between the animal PKPD target to the

5   clinical PKPD target, especially regarding the

6   gram-negative BSI has not been established.

7   So to answer your question, because of the

8   severity of the infection, as you mentioned,

9   especially in BSI patients, we did think about not

10   only the medium for the PKPD target values for

11   bacterial stasis. We thought about the 75th

12   percentile of the PKPD targets for stasis, and also

13   we take the one log kill into consideration.

14   Could I have the backup slide number 6?

15   Maybe it's 5. I can't remember exactly what

16   number; 7, try. Sorry.

17   (Laughter.)

18   DR. WU: Yes, this one. The up table shows

19   the median value for PKPD targets, stasis and also

20   1 log kill. You can tell the 1 log kill number is

21   89.   The median value for PKPD stasis for 1 log

22   kill is 89. The lower table shows the target AUC

1   value to achieve the attainment for 1 log kill,

2   where MIC equals 2 is 178. And that the lower

3   bound for TDM range is 210. 210 is higher than

4   178, so the lower bound is high enough to achieve

5   the value for PKPD targets where MIC equals 2.

6   DR. BADEN: Thank you. Dr Daskalakis?

7   DR. DASKALAKIS: I think this is a fairly

8   simple question -- Demetre Daskalakis -- for the

9   FDA. Is there any concern that in the bloodstream

10   infection, the only bacteria other than one is a

11   klebsiella?

12   DR. MISHRA: I guess the short answer to

13   that question is no. I mean, in general, that's

14   sort of what we expected in terms of what they were

15   able to recruit, so, no, it's not surprising.

16   DR. DASKALAKIS: Thanks.

17   DR. BADEN: Thank you. Dr. Honnegger?

18   DR. HONNEGGER: Sorry. I have a couple of

19   questions. I'll try to be brief. One brief for

20   Dr. Nambiar. As far as the LPAD or LPAD mechanism,

21   because of the known uncertainty going into these

22   approvals, is there additional built-in mechanism

1   for post-approval monitoring for drugs that go

2   through this pathway?

3   DR. NAMBIAR: Just under the LPAD pathway,

4   there is no requirement for postmarket studies,

5   unlike accelerated approval where's there

6   requirement for a confirmatory postmarket study.

7   But certainly in any instance when we have

8   concerns, especially from a safety standpoint or

9   any other unanswered questions, postmarket studies

10   could be done, but there isn't a requirement under

11   LPAD, if that's your question.

12   DR. HONNEGGER: Thank you.

13   The next question is about, because they

14   allow -- because it's been made clear that it's

15   difficult to study CRE bacteremia in treatment,

16   it's hard to get big numbers, and then you want to

17   know what are other supportive studies you'd want

18   to see, would it be considered -- right now,

19   normally, we wouldn't use an aminoglycoside first

20   line for bacteremia. It usually is a beta-lactam,

21   if you can. Would a noninferiority study comparing

22   this drug with a beta-lactam in known bacteremia

1   that's not necessarily highly resistant, that's

2   susceptible to beta-lactams, be permitted?

3   DR. NAMBIAR: Let me make sure I understand

4   the question. So you're saying can someone design

5   a noninferiority trial in sort of an allcomer

6   population in gram-negative bacteremia, and not

7   necessarily just the CRE studies? Is that your

8   question?

9   DR. HONNEGGER: Yes. This isn't my

10   expertise on gram-negative bacteremia, but going

11   into a study where we use upfront aminoglycoside I

12   don't think is commonly practiced now. It was in

13   the past, and sometimes it's used after

14   identification of the organism now, but it's not

15   common.

16   DR. COX: Just in general, yes, you can

17   design studies that don't target a particular

18   resistance phenotype. People oftentimes refer to

19   that as usual drug resistance because the organisms

20   that we encounter on a daily basis usually have

21   some type of resistance to something along the way.

22   It may not be the particular problematic or

1   concerning resistance mechanisms that are sort of

2   on the forefront today.

3   So in a variety of different indications,

4   yes, you could design a study. And one of the

5   things that you might think about when designing

6   such a study to look at the usual or prevailing

7   resistance phenotypes, not necessarily the ones

8   that occur infrequently, might be you try and

9   enrich the study for patients that had

10   comorbidities, that had greater underlying

11   conditions, that had greater severity of illness.

12   So you might not get the particular

13   resistance phenotype you're looking for, but you

14   might make a study that would be more enrollable

15   because there'd be a larger pool of patients out

16   there to try and get information that would help

17   you to understand how the drug works against

18   particular pathogens and in inpatients who have

19   particular acuity of illness. If the drug's

20   mechanism of action is orthogonal, unrelated to the

21   mechanism of resistance that's a particular

22   problem, that could be a way to do a feasible trial

1   to get some very good quality data to understand

2   how the drug works.

3   DR. HONNEGGER: Thank you. And then just

4   lastly for Dr. Mishra, in terms of your

5   analysis -- I appreciate you going into the cases

6   in detail since they're small numbers for the

7   bloodstream infections. Your analysis in terms of

8   there being differences in the number of patients

9   who had no documented bacteremia at day 1 or

10   thereafter, but that was different than what we saw

11   from the company about what was their

12   baseline -- it could be, like you said, that they

13   could have no subsequent bacteremia because the

14   drug was actually having an effect. But to have

15   baseline, is it true that the proportion of

16   patients with ongoing bacteremia was similar

17   between colistin and plazomicin?

18   DR. MISHRA: Let me make sure I --

19   DR. HONNEGGER: Or when the drug was

20   started, the proportion of patients that still had

21   ongoing bacteremia documented was similar between

22   the groups.

1   DR. MISHRA: Right. There were 4 patients

2   in each arm that had positive bacteremia at 24

3   hours prior to starting. I guess that's one way to

4   sort of look at that question.

5   DR. HONNEGGER: Okay. And then you talked

6   about differences in the diagnosis of line

7   infections in the group and that there were maybe

8   some discrepancies. But as far as the proportion

9   of patients who had central lines -- maybe they all

10   did -- and the proportion of patients that actually

11   got their lines pulled, was that similar regardless

12   of whether they were called a primary- or a

13   line-associated infection?

14   DR. MISHRA: That I'd probably have to look

15   into more detail. I don't want just tell you

16   straight off. There were patients who had lines

17   replaced. I can't tell you the proportion between

18   the two in terms of whether that happened on day

19   1e. When I was more looking at that calculation, I

20   was looking more specifically about when that

21   happened around the time of starting drug to see if

22   potentially it could have affected the rest of

1   their course. But there were patients who had

2   lines that were changed during the course of their

3   drug, after starting it as well.

4   DR. HONNEGGER: Thank you.

5   DR. BADEN: Dr Gripshover?

6   DR. GRIPSHOVER: I'm not sure if mine is for

7   the agency.

8   DR. BADEN: Well, I have you on the agency

9   list. If not, then we'll come back to the

10   applicant.

11   DR. GRIPSHOVER: Okay. It can sort of go

12   either way I think because it's about the

13   pharmacology. In terms of the bacteremias that

14   were in the UTI study -- and that's why it might be

15   the agency -- do we have data on the

16   pharmacokinetics in there? If we approve this for

17   a urinary tract, people are going to probably use

18   it for bacteremias. And I'm thinking did we have

19   any data to be able to help how we're going to

20   monitor it if we are using AUC.

21   Do we have any data in terms of efficacy and

22   drugs on in particular the bacteremias? But I

1   don't know if the pharmacology was even collected

2   on them.

3   DR. ZHUANG: Hi. This is pharmacometrics

4   reviewer from FDA. Can you clarify your questions?

5   You're asking the relationship between exposure and

6   efficacy in cUTI patients? Is that your question?

7   DR. GRIPSHOVER: Yes, actually in the

8   bacteremic ones.

9   DR. BADEN: No, no, the bacteremic UTI.

10   DR. GRIPSHOVER: UTI. So in study 009 in

11   the UTI study, there were I believe 24 --

12   DR. BADEN: There were 46 bacteremias

13   divided between the two groups.

14   DR. GRIPSHOVER: -- yes, between the two

15   groups.

16   DR. BADEN: How did they behave?

17   DR. ZHUANG: Actually, we didn't conduct a

18   subgroup analysis for exposure -- to identify the

19   relationship between exposure and efficacy. But

20   for the general cUTI patients, we conducted

21   exposure-response analysis for efficacy. So for

22   that part, we didn't see any trend. There's a

1   slight relationship, but because these are only

2   under one dose, it's only one dose available for

3   all the patients. But for the subpopulation, we

4   didn't conduct any analysis yet, so we don't know.

5   DR. BADEN: Thank you. Dr. Schaenman for the

6   agency side.

7   DR. SCHAENMAN: Yes. This is a question for

8   Dr. Nambiar, I believe. I think as clinicians who

9   have faced MDR infections, we all appreciate the

10   importance on a systems basis for the LPAD; we all

11   support that idea. But I think as some of my

12   colleagues have raised, we're kind of struggling

13   with how to actually apply that framework in

14   practice.

15   So I'm interested to know if this is the

16   first drug that's come up under LPAD as opposed to

17   the QIDP or if there are other precedents that you

18   could tell us about that might give us some

19   guidance in how we go through answering the two

20   questions before us.

21   DR. NAMBIAR: So you're right. This is the

22   first application we have received specifically

1   asking for approval under LPAD. QIDP is a little

2   different. QIDP is a designation that is granted

3   for certain products. For indications, it is not

4   related necessarily to an approval process. What

5   QIDP gives you in this context was a priority

6   review, which is why the application received a

7   priority review.

8   Does that help?

9   DR. SCHAENMAN: So I guess any other words

10 of advice or guidance, since this we'll be setting

11 a precedent then for other LPAD applicants.

12   DR. NAMBIAR: Yes. Would you like me to go

13 through what LPAD does provide and doesn't provide?

14 Would that help to just go through it again?

15   DR. BADEN: Maybe we can save that for when

16 we get to the question, when we actually look at

17 the formal question.

18   DR. NAMBIAR: Okay.

19   DR. BADEN: Thank you. Dr. Green, did you

20 have a last question for the agency before we can

21 go back to the applicant?

22   DR. GREEN: I do, and I don't know if

1   Dr. Mishra can do this or not. When he was doing

2   his presentation on a case-by-case basis, we

3   started off with a total of 29 bloodstream

4   infections in 007. But after he got through kind

5   of walking through it, I was left with the sense

6   that if you were to look at your evaluable patient

7   population, it was less than 29.

8   I don't know whether you're willing to or

9   not, but can you tell us the number of patients you

10   actually thought were evaluable after you sort of

11   went through all your concerns and contingencies

12   about these patients?

13   DR. MISHRA: Well, I don't think that I

14   would say that I thought that absolutely none of

15   the patients were not evaluable. I think I still

16   would look at the whole set of 29 as being an

17   evaluable population. I think the bigger question

18   was, yes, I did feel that there was a strong or a

19   large percentage of that population where the

20   uncertainty was higher.

21   Is that a way to answer that question? I

22   mean, I won't fully discount these patients that

1   had completely negative cultures and say that they

2   were not evaluable.

3   DR. GREEN: Thank you. I think you answered

4   the question, at least for me.

5   DR. BADEN: We have completed the list of

6   remaining questions from the agency's presentation

7   and we can turn back to the questions we have for

8   the applicant. I know the applicant have a series

9   of clarifications from issues raised since they

10 were sharing their thoughts, so please,

11 Dr. Connolly.

12   DR. CONNOLLY: Thanks for the opportunity to

13 provide some clarifications. I would first like to

14 provide you with some additional information about

15 this catheter and primary BSI issue. We also did

16 do a case-by-case analysis of these patients, and I

17 want to start with the plazomicin treated patients

18 who are characterized as either primary bacteremias

19 or potential catheter related bacteremias.

20   So the first was considered to have a

21 primary BSI because their catheter was pulled and

22 the culture was negative. We have two patients who

meet those criteria. We had a primary BSI whose

blood culture remained positive after removal of

the catheter and eventually cleared with a new

catheter in place; another primary BSI where the

culture remained positive after removal of the

first catheter and cleared with a new catheter in

place; a primary BSI where the blood culture

remained positive after removal of the catheter and

the catheter tip was negative for CRE; and then a

primary BSI, but the blood culture cleared with the

catheter in place.

        So one thing I did want to clarify is that

we collected data on every single catheter when it

was placed and when it was removed. So we can look

at those timings in relation to positive blood

cultures. And to mention, for these patients, none

of these had a negative outcome.

        Let's also take a look at the colistin

treated patients, and here I've included their

outcomes. These are all the ones labeled as

primary BSI. We had bacteremia that persists

beyond the catheter removal. This patient was

1   neutropenic with a potential gut translocation

2   source. A second patient considered primary by the

3   investigator had persistent bacteremia despite

4   removal of the catheter with another potential GI

5   source and a complicated course after hiatal hernia

6   surgery with peritonitis requiring small bowel

7   resection, so another possible gut source.

8   Another primary BSI with bacteremia

9   persisting after removal of the initial catheter,

10   another one persisting with bacteremia at the time

11   of line removal who had a colonic perforation and

12   polymicrobial blood cultures that included

13   bacteroides, so suggesting this was a gut source;

14   two more who had primary BSIs because the culture

15   from the catheter tip that was removed was

16   negative, and then a culture that cleared without

17   removal of the catheter.

18   As you can see for several of these

19   patients, consequences were severe. Four of these

20   patients actually went on to die by day 28 despite

21   the uncertainty around the source of their

22   bacteremia.

DR. BADEN: Dr. Connolly, I know you have five areas to clarify. So for this first area -- and I'll commend to the committee we can ask for further clarification on each topic -- the implication here is these are the patients who had catheters in. So there were 7 colistin treated patients who have catheters in, and the remainder did not.

DR. CONNOLLY: No. Actually, the implication -- nearly all patients had a catheter at the initial time of that positive culture, and I also wanted to provide a clarification, every single patient included in the analysis population did have at least one blood culture that was confirmed to have CRE on the basis of central laboratory confirmation. Most of them had a catheter. Most of those catheters were removed to the point of source control. What I've just shown you here were the patients who had primary bacteremias and also had catheters and what our analysis was of those.

DR. BADEN: And these are the patients who

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1   the catheters remained in beyond day 1, so to

2   speak, while the others had them removed, or these

3   are just primary bacteremias?

4   DR. CONNOLLY: No, these are primary

5   bacteremias, and I wanted to share how the

6   catheters were handled.

7   DR. BADEN: I see. And on the colistin

8   group, if I understand correctly from the agency's

9   presentation, 8 of the 21 colistin treated

10   patients, the colistin MIC was greater than 2.

11   DR. CONNOLLY: Yes, that's correct. So

12   patients were enrolled in the study based on local

13   laboratory data. So the local laboratories were

14   using several different colistin susceptibility

15   testing methodologies, and we only discovered after

16   when we ran these in the central laboratory that

17   they were resistant to colistin.

18   We have looked at the impact of this on the

19   primary outcome, so I can show you here. If we

20   remove those and look at patients who had colistin

21   susceptible baseline pathogens, we still see a high

22   rate of mortality, so 56 percent for colistin

1   treated patients despite Colistin susceptibility,

2   so to look at the impact of that.

3   DR. BADEN: Dr. Clark, you had a follow-on

4   question?

5   DR. CLARK: Yes. On the primary BSIs,

6   despite what you presented there, those criteria

7   don't seem to meet what the definitions of catheter

8   related or primary bacteremia were in the studies.

9   Is that correct?

10   DR. CONNOLLY: So correct. Ultimately, the

11   investigators needed to provide an assessment, and

12   when they couldn't determine the source, they

13   called it primary.

14   DR. CLARK: And one other question on

15   susceptibilities. Is it true that all the patients

16   who got meropenem in both groups had MICs less than

17   8?

18   DR. CONNOLLY: No, that is not the case.

19   Although that was the recommendation provided to

20   the investigators, some of those patients had

21   meropenem MICs above 8; in fact, I believe all of

22   them did who got meropenem.

1   DR. CLARK: Can you tell us what the MICFs

2   were between the two groups, colistin and

3   plazomicin?

4   DR. CONNOLLY: For meropenem, who received

5   meropenem, in general, they were greater than 32.

6   DR. CLARK: For all patients? There was no

7   difference I'm saying between the colistin

8   group --

9   DR. CONNOLLY: No, there was no difference.

10   So meropenem MIC greater than equal to 8 was 71

11   percent and 81 percent for the plazomicin and

12   colistin treatment group.

13   DR. CLARK: Okay. Thank you.

14   DR. BADEN: Please continue with the

15   clarifications.

16   DR. CONNOLLY: Sure. I did want to clarify

17   also about the culture status at baseline just to

18   be sure we are clear what that looked like. One

19   important thing to remember about this study, the

20   way it was designed was to test plazomicin against

21   colistin as definitive therapy for CRE infections

22   not as empiric therapy. So we should expect that

these patients received empiric therapy and that

that empiric therapy may have an impact on their

blood culture status. Even if these patients

aren't considered cured, that therapy is likely to

render these cultures negative.

The important point here is that when we

look at the proportion of patients who had positive

cultures at the time of enrollment, no cultures

obtained at the time of enrollment, and negative

cultures at the time of enrollment, that is well

balanced between the treatment arms. So these

patients are entering into the randomized portion

of this study on a level playing ground.

I also wanted to take a second look at what

was the impact of having a negative culture. Did

this mean that these patients were cured? I think

we can acknowledge that 72 hours of empiric therapy

is unlikely to cure a patient with a CRE BSI, and

we see in these patients who have negative cultures

at the time of initiation of study drug,

consequences, even in the plazomicin arm, we have a

death even though they had a negative culture. And

1   then in the colistin arm, we see that 3 of the 6

2   patients, despite negative cultures at the time of

3   enrollment, go on to meet the primary endpoint in

4   the study.

5   DR. BADEN: Any questions on these data?

6   Dr. Lo Re?

7   DR. LO RE: Vincent Lo Re. So given that

8   the inclusion criteria for this study was presumed

9   or confirmed carbapenem resistant

10   enterobacteriaceae, in the subgroup of individuals

11   where there was no blood cultures, what were the

12   triggers that the clinicians made to indicate that

13   these were presumed carbapenem resistant isolates?

14   DR. CONNOLLY: So let me clarify, every one

15   of these patients did have a positive culture for

16   CRE. The issue is that those cultures were often

17   taken. So what would happen in the study is the

18   patient would present with signs and symptoms of

19   illness.   These are hospitalized patients.

20   Cultures would be drawn. They would be started on

21   empiric therapy. And only when that initial blood

22   culture turned positive for CRE or there was some

1   microbiological confirmation that it was likely

2   CRE, were they then considered for randomization in

3   this study. At the time of randomization, a second

4   culture was drawn to determine whether that patient

5   was still bacteremic.

6   So the cultures that qualify them for

7   enrollment in the study were taken up to 96 hours

8   prior to actual randomization, but then we took a

9   second culture at the time of randomization to

10   determine what proportion of patients would still

11   have positive cultures, and that's what we're

12   looking at here.

13   DR. LO RE: So when Dr. Mishra was noting

14   that 57 percent of the plazomicin group did not

15   have a evidence of either active CRE bacteremia at

16   the time of enrollment or during the drug

17   treatment, that neglected that there was prior

18   culture results for CRE available.

19   DR. CONNOLLY: Exactly. He was referring to

20   the cultures taken at the time of randomization and

21   then post-baseline. He was not referring to the

22   cultures that were taken that actually qualified

1   the patient for enrollment into the study.

2   DR. LO RE: That's helpful. Thank you.

3   DR. BADEN: Dr. Kartsonis, you had a comment

4   on this?

5   DR. KARTSONIS: Yes. I just wanted to make

6   one comment about this, about studies like this for

7   bacteremia or candidemia that historically have

8   been done. If you actually look at the data, if

9   you take most of the candidemia studies, or you

10   look at the one bacteremia in the study that was

11   done with daptomycin in the past, not everybody's

12   going to have culture on the day they get

13   randomized into the study.

14   The candidemia studies did allow for 4 days

15   of prior therapy, and the prior daptomycin study

16   allowed for up to 48 hours. So indeed, in both of

17   those studies, you do have a number of patients at

18   the time of randomization who already have negative

19   cultures. This is completely common and very

20   consistent with what have been done with other

21   studies in the past. And if you actually look at

22   the efficacy on all of those studies, it didn't

1   matter on day 1 whether or not they still had

2   positive cultures or not. So it's an important

3   factor to keep in mind as well.

4   DR. LO RE: Just one other follow-up

5   question.

6   DR. BADEN: Yes, Dr. Lo Re?

7   DR. LO RE: Can you just give us a sense of

8   what the median time prior to enrollment of the

9   people who did not have either CRE bacteremia

10 isolated at the time of enrollment or during

11 treatment was? How far prior to enrollment was

12 that? Was it relatively recent or was it 7 days,

13 14 days before? I'm just wanted to get a sense.

14   DR. CONNOLLY: Oh, no. The farthest out it

15 could be was 96 hours, that culture. And some of

16 them were certainly closer, and I don't have it up

17 at the top of mind. But we also did stratify

18 patients based on whether they received less than

19 36 hours of empiric therapy, so new therapy for

20 this new infection or greater than 36 hours. We do

21 have data around that.

22   DR. BADEN: Dr. Clark, you had a follow-on?

1   DR. CLARK: I just had a question for Dr.

2   Kartsonis. When you talk about the studies for

3   daptomycin or a treatment of candidemia, those were

4   much larger studies, and probably the numbers of

5   patients who had negative cultures are a much

6   smaller percentage.

7   DR. KARTSONIS: Yes. And if you actually

8   look at the candidemia studies, including the one I

9   ran for caspofungin, up to 30 percent of the

10   patients on day 1 had a negative culture. So it's

11   completely common that you have to account for

12   those factors, and it's consistent with the prior

13   studies that have been done for fluconazol,

14   micafungin, anidulafungin, and what have you. Yes,

15   they are much larger studies. Obviously, they are

16   not inferiority based.

17   DR. BADEN: Dr. Connolly, along the issue of

18   prior treatment in positive culture, how much

19   colistin -- could these patients have received

20   colistin previously, not just in the 24 to 96 hours

21   before enrollment?

22   DR. CONNOLLY: So yes, these patients could

1 have received colistin previously for an unrelated

2 infection.

3   DR. BADEN: How many of them had?

4   DR. CONNOLLY: There were I believe 3 in the

5 colistin arm who had previously received colistin

6 in the time period around enrollment for another

7 infection.

8   DR. BADEN: Thank you. Please go on with

9 your clarifications.

10   DR. CONNOLLY: Sure. I would also like to

11 share with you a Kaplan-Meier curve. I think this

12 was requested looking at -- so this is in that

13 primary analysis population. This includes all

14 patients, so both the BSI and HABP/VABP. So this

15 is preserving that original intent.

16   Looking at death through day 28 and through

17 day 60, what we've included here are hazard ratios

18 through day 20 and through day 60, as well as

19 p-values from one-sided log rank tests.

20   DR. BADEN: Dr. Follmann?

21   DR. FOLLMANN: So a clarifying question.

22 This is the bloodstream infection group?

1   DR. CONNOLLY: No, this is the entire

2   primary analysis population. This includes both

3   the bloodstream and HABP/VABP patients.

4   DR. FOLLMANN: Thank you.

5   DR. CONNOLLY: I'd also like to ask Dr.

6   Satlin to come to the podium. There's been a lot

7   of discussion here around unmet need and how do

8   these data sets potentially address that, and how

9   to think about them. So I'd like to ask him to

10   make some comments.

11   DR. SATLIN: Hi, everyone. I'm Michael

12   Satlin. I'm an infectious disease physician at

13   Weill Cornell Medicine in New York City, and I am a

14   paid consultant by Achaogen. I think where I

15   practice here actually matters because New York

16   City has been the epicenter for CRE. In fact,

17   we've been facing patients infected with these

18   organisms for over a decade.

19   I think a lot of great points were made

20   about the

21   unmet need in the public speaking session. One

22   additional point I would like to add is that even

1   with the new beta-lactam beta-lactamase inhibitors,

2   those are primarily only active against the KPCC

3   CRE, and we certainly have patients who are

4   infected with non-KPCC CRE for which currently

5   colistin is our primary treatment option.

6   I'd like to also share with you a

7   perspective about some struggling with the

8   uncertainty of whether plazomicin is superior to

9   colistin or less toxic than colistin. We have been

10 managing patients with CRE infection for over a

11 decade. We have nearly 100 patients a year with

12 CRE infection in our hospital, and we published a

13 study last year.

14   It was a multicenter study in New York City,

15 published in AAC, where we found that despite a

16 decade of experience in managing patients with CRE

17 infection, by relying on colistin based therapies,

18 we are still seeing a 50 percent mortality rate,

19 and that's despite all the things we've been trying

20 to learn about the polymyxins. And it made us

21 start to wonder, are these patients just so sick

22 and they have so many comorbid illnesses that no

matter what drug we have, we're going to see this

high mortality rate?

I really think this study 007 was critical

not only for this drug but for the field, that the

answer to that question is no. If you actually

have a drug that's much more effective, such as

plazomicin, you can substantially lower the

mortality rates. And whether the actual mortality

rate is 10 percent or 15 percent or 20 percent, we

have thousands of patients in observational data

sets that consistently show this 40 to 50 percent

mortality rate with colistin. Similarly for

toxicity, we also have thousands of patients who've

received colistin, and we consistently see that

almost half of them develop nephrotoxicity.

So again, whether the nephrotoxicity with

plazomicin is 5, 10, 15 percent, I think there's

strong data, not just from the data that have been

presented here, but by what we know about colistin,

that it is much, much less than it would be with

colistin. So I think there are a number of

considerations, both for cUTI and BSI, where

1   clearly we need additional drugs. We need

2   plazomicin, and I think being able to offer our

3   patients plazomicin instead of colistin is a major

4   benefit to obviously the patients and also the

5   clinicians that take care of them.

6   DR. BADEN: Thank you. Other points you

7   wanted to clarify, Dr. Connolly? Because we have

8   more questions.

9   DR. CONNOLLY: Of course. I had one last

10   point of clarification. I did want to clarify our

11   intentions around the AUC based TDM for BSI

12   patients, as well as provide some information that

13   may help with how do we think about clinical

14   utility for this type of a TDM for these patients.

15   So as mentioned, we are targeting an AUC

16   range that's around at 210 to 315, and that is

17   based on the TDM algorithms that have been

18   developed and the AUC range roughly observed in the

19   study. I think our original intent for this type

20   of TDM was to try and reduce the variability and

21   exposures that these patients see due to their

22   dynamic changing physiology from their critical

1   illness. So because we can do a randomized

2   controlled trial now of TDM without TDM with these

3   patients, what we can do is take all of the PK data

4   and our population PK model and run simulations,

5   and ask ourselves what would have happened if we

6   didn't do TDM in these patients.

7   So what I'm showing you here are AUC values

8   on the Y-axis over time, so with the initial dose,

9   the first TDM, the second, and the third. In the

10 blue boxes, we're showing without TDM, and in the

11 red with TDM. So just to orient you to this, this

12 is based on the data collected from BSI patients

13 and run through that pop PK model.

14   So what we see happening in the absence of

15 TDM over time is we see increasing AUCs, increasing

16 exposures for these patients, including extreme

17 high AUCs that may place them at increased risk of

18 nephrotoxicity. With the application of TDM, we

19 reduce that variability and those extremes.

20   I'm not trying to imply that this is

21 actually a therapeutic window. I know that's

22 something that you're very interested in getting

1   to, so two of the main purposes of TDM here is

2   reducing that variability and avoiding those

3   extreme high exposures.

4   DR. BADEN: Dr. Gripshover?

5   DR. GRIPSHOVER: Just a quick clarifying

6   question. It looks like most of them were actually

7   too high. Is that if we didn't change? So did you

8   look at Cmin also?

9   DR. CONNOLLY: Yes. You're correct. The

10   tendency is if we don't change, we see increases in

11   exposures over time. There is some variability on

12   the low end as well. It's a little bit hard to see

13   what the gray dots, but we see as we go over time,

14   there are more extremes on the low end as well. But

15   you're right. The bias is towards the high end.

16   DR. BADEN: Dr. Rej?

17   DR. REJ: This is Robert Rej. A question

18   about the assay that you used for the TDM studies,

19   is that bout equivalent to the microsphere assay

20   that you're contemplating as a companion device

21   under 510(k)?

22   DR. CONNOLLY: Right. So in the context of

the clinical trial, we used an immunoassay that is

not the same as the QMS assay that we're proposing

to commercialize in concert with Thermo Fisher.

The bridge between those or the link between those

two assays is our reference standard, which is an

LC-MS/MS assay.

So the initial immunoassay, we had to do

methods comparison study with that to show that

that would meet the criteria for equivalence, if

you will, to LC-MS/MS. The same is required for

QMS. And then planned as part of that submission

for the IBD is method comparison across all three.

other clarification.

DR. REJ: Thank you.

DR. BADEN: Other clarifications,

Dr. Connolly, from the morning session?

DR. CONNOLLY: One clarification. You did

ask about AUC, is there a relationship between AUC

and nephrotoxicity? One thing to clarify is that

all of these relationships were run in cUTI patient

population because that's where we have the most

data, and now we're having to extrapolate the BSI

1 patient population because that population was too

2 small, as we have all acknowledged, to run a robust

3 exposure-response relationship. But I can share

4 with you the relationship to AUC that we

5 characterize with cUTI patients, just to clarify.

6   Shown here, this is looking at pooled cUTI

7 studies and the incidence of nephrotoxicity with

8 increasing the AUC. So if we recall the background

9 rate in the meropenem and levofloxacin arms was

10 around 4 percent of patients experiencing serum

11 creatinine elevations. And here where we start to

12 see a real jump up is around that 400 range to 10

13 percent, and then above that at 540 percent. So

14 it's a sort of shallow relationship, but you can

15 see it really does jump up when you hit 500 and

16 above.

17   DR. BADEN: Thank you.

18   DR. CONNOLLY: Thank you.

19   DR. BADEN: Then we will resume where there

20 were more clarifying questions from panel members.

21 Dr. Honnegger?

22   DR. HONNEGGER: [Inaudible - off

1   mic] -- applicant?

2   DR. BADEN: Applicant, yes, the applicant

3   questions.

4   DR. HONNEGGER: Regarding bloodstream

5   infections in the 009 study, we have time to

6   clearance -- just looking for more data on

7   bloodstream infections. Do you have the time to

8   clearance plotted for these patients and any other

9   measures of their outcome? I think they all

10   survived.

11   DR. CONNOLLY: In the 009 patient study,

12   none of these bacteremias led to death. And the

13   blood cultures were not drawn as frequently, so

14   what we have around the outcomes for these patients

15   is we were able to show clearance of bacteremia at

16   those two time points, day 5 and test of cure. We

17   can also look at their outcomes in terms of their

18   primary infection, so I'll show you that here.

19   This is the composite cure rate in cUTI

20   patients with concurrent bacteremia at the test of

21   cure visit showing 72 percent, uh, in the

22   plazomicin arm as opposed to 56 percent in the

1   meropenem arm, keeping in mind this is a small

2   subset.

3   DR. BADEN: Do you have a comparable for the

4   day 5, comparable graphic?

5   DR. CONNOLLY: Yes. Here's what I can show

6   you actually, so this is interesting. I can show

7   you over time --

8   DR. BADEN: Thank you.

9   DR. CONNOLLY: -- what competent cure looks

10   like in patients with concurrent bacteremia. And

11   interestingly, these curves overlap substantially

12   others then at day 5, where meropenem, there's a

13   higher rate of response in the meropenem arm, but

14   then we see that flip as we move out over time with

15   a higher response rate for plazomicin at test of

16   cure and long-term follow-up.

17   DR. BADEN: Thank you. Dr Follmann?

18   DR. FOLLMANN: Yes. I was curious about the

19   choice of the endpoint for the cUTI study where you

20   used a composite of clinical cure plus

21   microbiological eradication, which is a biomarker,

22   not a direct reflection of a patient's clinical

1   course. To me, it would have been more natural to

2   look at the clinical outcome by itself without

3   imposing traditional microbiology on it.

4   Was it thought that was a harbinger of the

5   future, that they would be more likely not to

6   relapse? If so, why wouldn't you just look at a

7   later clinical endpoint?

8   Those are my questions about the choice of

9   that composite endpoint. I would have just used

10   clinical cure, and maybe the FDA would comment on

11   this as well.

12   DR. CONNOLLY: Sure. What I would say was

13   this was consistent with the guidance document from

14   FDA.

15   DR. FOLLMANN: So why did the guidance

16   suggest that kind of endpoint as opposed to just a

17   straight cure endpoint?

18   DR. COX: I'll give it a shot, Joe, but you

19   help me out. So most of the data that we used to

20   develop the noninferiority margin, a lot of the

21   trials look at microbiological cure. We actually

22   struggled to find ones that also included on a

1   level where we could make sense out of combined

2   clinical and microbiological cure together.

3   So we do feel that we do have a clinical

4   endpoint here and that there is a clinical

5   component to this. And if we think about the drug,

6   its mechanism of action is actually to treat the

7   bacteria that's causing the infection, so it's a

8   pretty reasonable thing to also look at are we

9   eradicating the bacteria in the setting of a

10   urinary tract infection.

11   The other thing we learned as we started to

12   look at this, and some folks have pointed this out

13   to us, is that you can actually look at some

14   non-antibacterial treatments that make people

15   clinically feel better. You can give NSAIDs or

16   whatever, and people will feel better, but that

17   doesn't necessarily treat the urinary tract

18   infection.

19   So we actually think it's a pretty good

20   endpoint to be looking at the microbiologic

21   outcome, is the antibacterial drug essentially

22   treating the bacteria, and then also is the patient

1　feeling better, and are the symptoms urinary tract

2　infection essentially going away. So we think it's

3　a pretty good endpoint to include both components,

4　the microbiological and the clinical. I

5　　　　DR. FOLLMANN: I had one other question for

6　the sponsor. By arm, do you have who ended up on

7　dialysis in 007 for the colistin arm and your drug,

8　plazomicin?

9　　　　DR. CONNOLLY: At baseline, we had 4

10　patients on the plazomicin receiving CRRT, and I

11　believe there were two patients in the colistin arm

12　receiving CRRT at baseline.

13　　　　DR. FOLLMANN: I didn't mean at baseline. I

14　meant after the end of the study or at the end of

15　follow-up, how many were on dialysis?

16　　　　DR. CONNOLLY: Post-baseline use of CRRT.

17　　　　DR. FOLLMANN: Yes.

18　　　　DR. CONNOLLY: I do believe we have the data

19　for post-baseline. And there certainly were

20　patients who required CRRT after enrollment in both

21　treatment groups. I do know sometimes the

22　indication provided for receipt of CRRT was sepsis;

1   at other times, it was for renal adverse events.

2   Here we go. Let me bring that up. So any

3   CRRT -- and I believe this is post-baseline -- we

4   have one patient in the plazomicin group in cohort

5   1 and 3 and the colistin group, and the subset for

6   which CRRT was indicated for a renal adverse event

7   were 2 out of the 3 in the colistin group. And

8   then we also have the data here for cohort 2

9   plazomicin treated patients, 3 requiring CRRT

10   post-baseline; 2 of those were for a renal adverse

11   event.

12   DR. FOLLMANN: Thank you.

13   DR. BADEN: Dr. Palevsky?

14   DR. PALEVSKY: So a clarifying question

15   regarding the use of CRRT for, quote, "sepsis,"

16   because the data does not support that there is a

17   role for sepsis. Do you know anything about dosing

18   of the CRRT? Because if it's being done as CBBH at

19   a high dose for cytokine manipulation, that could

20   be having a very major effect on your clearances of

21   the drug and an effect on efficacy.

22   DR. CONNOLLY: Yes. The dosing

recommendations for CRRT were developed based on PK

for other aminoglycosides; our PK, but also knowing

how those drugs are handled in the context of CRRT.

So they were developed for both high rates of ultra

filtrate and dialysate, as well as low rates. And

all of the patients who received CRRT in this study

were on low rates.

DR. PAVLESKY: Even the ones being treated

supposedly for sepsis?

DR. CONNOLLY: Yes.

DR. PAVLESKY: Okay.

DR. BADEN: Dr. Schaenman?

DR. SCHAENMAN: I had a few questions that

would help with potential labeling recommendations.

I'd like to start with taking a look at slide 99

from the sponsor's original presentation, and I

have a clarifying question for you, Dr Connolly.

I'm a little unclear from your presentation and

from the information provided to us prior to this

day as to what exactly is the TDM recommendation

for the cUTI patients? Is it for everybody or just

for the patients who are at risk for

1   nephrotoxicity, and where are we drawing the line?

2   DR. CONNOLLY: Sure. So in terms of

3   labeling, that's certainly an ongoing discussion

4   with FDA. Our position would be that TDM would be

5   recommended for patients with renal impairment at

6   baseline. So those patients who experienced an

7   increased risk of nephrotoxicity. And based on the

8   data we're showing here, that would include severe,

9   moderate, and potentially mild renal impairment.

10   DR. SCHAENMAN: So meaning less than 90.

11   DR. CONNOLLY: Yes.

12   DR. SCHAENMAN: I just wanted to point out

13   that there is some renal impairment, even if

14   patients are starting with normal renal function.

15   And of course these patients are often a moving

16   target. They might have come concomitant

17   nephrotoxic medications. They might be older.

18   Especially in the setting of transplantation, where

19   people are often on calcineurin inhibitors, we

20   often see a lot of nephrotoxicity that comes out in

21   the setting of treatment.

22   Could I also see slide 100? It's just the

1 next slide right after this. In addition to some

2 nephrotoxicity in the mild or zero renal

3 insufficiency patients, you can also see that

4 there's a real heterogeneity of Cmin in the

5 patients initially. So this is just raising

6 concern for me in terms of TDM and also the

7 question of applicability because this is, again,

8 primarily this white population.

9   Although I think you did show safety from

10 your phase 2 study, I'm just wondering, can we

11 extrapolate from this in a non-Caucasian

12 population, especially African Americans, in terms

13 of how can we safely dose this drug?

14   DR. CONNOLLY: Sure. So in terms of African

15 Americans in particular, 9 percent of the patients

16 included in the population PK analysis were African

17 American or black, and we did look at race as a

18 covariate for exposures. So that's the data we

19 have to rely on currently to say that exposures are

20 not impacted by race.

21   Also, one thing around TDM is this is really

22 a tool that we would like to provide a to

physicians in order to manage these patients in the

context of all of those other challenges that you

mentioned. So the proposed labeling reflects the

patients we studied clearly, and you absolutely

have to take into consideration the clinical

context for any patient that you're managing and

think of this as a tool to help manage that

patient.

DR. SCHAENMAN: And one final follow-up

question. I was gratified to see that at the ToC

visit, that there was significant, better impact

in plazomicin compared with meropenem. That's

really reassuring since we often see a cycle of

recurrent infection even when patients are treated

appropriately. It seems like from your previous

data that that cause of failure in the meropenem

arm was not due to meropenem resistance. Again,

this is in 009, the cUTI study.

My question was, did you look at cure at ToC

to see whether it was associated with Cmin or

increase in creatinine? In other words, I had this

slight concern when I saw that good impact that

1 perhaps the patients who had that persistent cure

2 were slightly overdosed during the initial

3 treatment period.

4 　　　　DR. CONNOLLY: Oh, sure. We didn't do that

5 exact correlation asking if the patients who were

6 cures at Test of

Cure were those who had elevated Cmins, although

8 the numbers there probably don't add up when we see

9 that the proportion of patients who had elevated

10 Cmins early compared to the high rates of response

11 at test of cure that are sustained to the long-term

12 follow-up.

13 　　　　We do have some hypotheses around why an

14 aminoglycoside or even any concentration

15 dependent-killing agent might have a persistent

16 effect. One is due to the differences in the way

17 these antibiotics kill bacteria. So with a

18 concentration-dependent agent, the higher the

19 concentration you get, the more bacteria killing

20 you see, whereas with a drug like meropenem, once

21 you are above that MIC, as long as you're there,

22 you don't increase with more drug killing. So it

1   may be that initial killing, and killing of the

2   potential reservoirs is greater with a

3   concentration-dependent drug such plazomicin.

4   In addition, we know from our human ADME

5   studies that plazomicin persists in the urine for a

6   prolonged period of time after dosing, whereas

7   meropenem, a less stable drug, that's not likely

8   the case. And this observation is very consistent

9   actually with what we see for beta-lactams in this

10   indication. We see very similar response rates for

11   doripenem, avi-caz [ph] out at that

12   test of cure visit where you lose that efficacy

13   from end of therapy or the day 5 visit down to test

14   of cure. And where we've seen maintenance is with

15   those concentration-dependent killing agents.

16   DR. BADEN: Dr. Palevsky, you have follow-

17   on?

18   DR. PAVLESKY: Yes, thank you. All of your

19   assessments of kidney function relevant for dosing

20   guidelines were based on a Cockcroft-Gault

21   creatinine clearance estimates. Yet in clinical

22   practice, what's generally reported are eGFR, which

1   don't necessarily correlate with the

2   Cockcroft-Gault creatinine clearance.

3   Do you have a plan for how you're going to

4   address that in terms of labeling and guidance

5   should this come to market?

6   DR. CONNOLLY: Sure. What we have currently

7   proposed in the labeling, and certainly because we

8   did use Cockcroft-Gault, and particularly for obese

9   patients, we used ideal body weight in that

10   equation, currently the proposal is to stick with

11   what we did in the clinical trial to ensure that

12   those exposures are consistent with what were

13   achieved in that context.

14   DR. BADEN: Dr. Clark, do you have a follow-

15   on?

16   DR. CLARK: I had a question about the

17   converse [indiscernible] situation. Were there any

18   patients who had undetectable levels, trough

19   levels, well below 1, and were there correlates

20   with outcome in those patients?

21   DR. CONNOLLY: Oh, in the cUTI study? Oh,

22   yes. Certainly there were patients who had very

low Cmin or completely would clear. We didn't do

correlations between Ctrough and efficacy. We only

looked at AUC at correlation since AUC is the

driver for efficacy.

DR. BADEN: Dr Rej, a follow-on?

DR. REJ: Following up on measurement of

creatinine, some aminoglycosides have been shown to

interfere with at least a certain class of

creatinine measurements. Have you looked into that

with a plazomicin?

DR. CONNOLLY: So to answer that question, I

would ask Julie Seroogy, one of our clinical

pharmacology experts, who also knows the most about

our assay.

DR. SEROOGY: Julie Seroogy, clinical

pharmacology. What I can speak to is in the

context of the plazomicin assay and the

interference studies we've done with that. So

we've looked at other aminoglycosides and their

interference with the plazomicin assay and a lot of

the selectivity experiments that were done. But we

haven't gone the other way to see specifically

1   whether the renal assays of plazomicin had an

2   effect on that, so that's something we'd have to

3   consider.

4   DR. CONNOLLY: Yes. I could potentially

5   pull that up for you. We did look at a series of

6   endogenous -- with the selectivity of other drugs

7   as well as endogenous, and I believe it had no

8   effect on plazomicin. I think your question was

9   for the other way around, right?

10   DR. REJ: Yes. My question is that someone

11   aminoglycosides affect the creatinine measurement,

12   and I was wondering whether the effects of this

13   drug as an interference have been looked at.

14   DR. CONNOLLY: Let me see if I can clarify.

15   So if you're asking whether the presence of the

16   aminoglycoside in the sample interferes with the

17   creatinine test, yes, we have not addressed that

18   yet. That is not something that we're aware of.

19   DR. REJ: [Inaudible - off mic] -- you

20   haven't?

21   DR. CONNOLLY: We have not.

22   DR. REJ: You have not.

1   DR. CONNOLLY: Yes.

2   DR. BADEN: We are short on time, however, I

3   do want to push through and clarify everything we

4   can. Dr. Kartsonis, did you have a question from

5   earlier?

6   DR. KARTSONIS: Yes. My question was with

7   regard to the microbiology. In protocol 7, do We

8   know if the isolates that were recruited were

9   mostly KP2's or KP3's? And also do we have any

10   efficacy regarding metallo-beta-lactamase producing

11   organisms from protocol 7 maybe in the other

12   cohort?

13   DR. CONNOLLY: So yes. We did have a small

14   proportion of patients who had infections due to

15   non-KPC-producing organisms. Just looking at what

16   we have here. I'll start with this.

17   So certainly, KPC was -- so what I'm showing

18   you here is actually the isolates from study 007,

19   and then the isolates from surveillance. In 007,

20   they were largely KPC. We did have some MBLs,

21   VIMs, and MDMs often in combination with the KPC.

22   And then we had a couple of OXA-48 in that study.

1   DR. BADEN: Presumably given the numbers,

2   this is a couple per group.

3   DR. CONNOLLY: Oh, absolutely, yes.

4   DR. REJ: Any word on the efficacy?

5   DR. CONNOLLY: Yes, that's what we're

6   looking at here, yes.

7   DR. REJ: Okay. Sorry.

8   DR. CONNOLLY: Okay. Here we go. So this

9   is microbiological response at test of cure in BSI

10   patients with carbapenemase-positive pathogens. So

11   we can look in cohort 1. You can see KPC

12   predominantly an 89 percent rate for plazomicin

13   versus 36 for colistin. And then we can go down

14   the line.

15   So as I mentioned, when we see the VIM or

16   MDM, it's in combination with another

17   carbapenemase. So KPC plus VIM, we had 3 patients

18   in the plazomicin group who had good outcomes, and

19   we had one NDM plus VIM in the plazomicin group and

20   one in the colistin group.

21   DR. REJ: Thank you.

22   DR. BADEN: One more question about the

1   microbiology. You had mentioned earlier that the

2   resistance was largely due to RMTs to the

3   plazomicin plasma. In the in vitro data, it looked

4   like some percent of isolates were or became

5   resistant. In the in vitro data, the isolates that

6   became resistant, was it also the RMT mechanism or

7   were there other mechanisms at play?

8   DR. CONNOLLY: No. So what we do in vitro

9   selection, in vitro selection for resistance, what

10 we generally see are isolates that have plazomicin

11 MICs in the 8 to 16 to 32 range, and those are

12 being characterized molecularly to try and ferret

13 out the mechanisms, but it is not the presence of

14 an RMT. And then interestingly, when we look in

15 surveillance, we very rarely see isolates at that

16 MIC range. It's really in surveillance when we see

17 resistance, a vast majority of those have an RMT.

18   DR. BADEN: RMT. But in the in vitro, you

19 were able to select for a resistant organism

20 through a different mechanism.

21   DR. CONNOLLY: Yes, absolutely, like most

22 gram-negative agents, that's relatively

1   straightforward.

2   DR. BADEN: Great. Dr. Rej, did you have a

3   follow-on question from this morning?

4   DR. REJ: [Inaudible - off mic].

5   DR. BADEN: Great. Dr Lo Re?

6   DR. LO RE: Just a question. So given the

7   challenges of enrollment in study 7, I know that an

8   amendment was made to include an additional

9   uncontrolled cohort. Could you just take me

10   through the thinking on the decision of why the

11   decision was made to include that uncontrolled

12   cohort versus, for example, changing inclusion

13   criteria? I just was trying to get a sense of how

14   you thought these data would be or should be

15   interpreted in the context of the very different

16   cohort 1.

17   DR. CONNOLLY: Sure. So cohort 2 was

18   actually added at the request of multiple

19   investigators who felt they had patients who could

20   potentially benefit from plazomicin therapy because

21   they had no options, but who were not eligible for

22   enrollment in cohort 1. So in some ways, cohort 2

1   is almost like an expanded access cohort.

2   Two of the groups of patients in there,

3   patients with known colistin resistant pathogens

4   would not be appropriate to put them in the

5   randomized controlled arm. In addition, patients

6   who had polymicrobial infections that involved

7   acinetobacter or pseudomonas, which are not target

8   pathogens for plazomicin, were allowed in cohort 2

9   but not in cohort 1.

10   The other types of patients who were allowed

11   in are a very distinct population, so cUTI

12   patients. The reason we didn't include cUTI

13   patients in cohort 1 is because they have a very

14   low rate of mortality compared to BSI and

15   HABP/VABP. So we were challenged to figure out an

16   endpoint that could be applied across all of those

17   infection types. So that's how the cUTI patients

18   were included in cohort 2.

19   Then finally the low APACHE II scores less

20   than 15, again, because we had a mortality based

21   end point in cohort 1, we had to ensure a

22   sufficient severity of disease so that we could

1   potentially demonstrate difference on a

2   mortality-based endpoint.

3   DR. BADEN: Great. Any more questions from

4   committee members? Dr. Palevsky?

5   DR. PAVLESKY: So a couple hopefully quick

6   questions. In the materials that were provided

7   ahead of the meeting, there is discussion of

8   plazomicin inhibition of the MATE2-K transporter.

9   Inhibition of that transporter can actually alter

10 creatinine secretion, which then draws into

11 question the use of a creatinine based

12 determination of AKI.

13   Do you have any information on how much of

14 an interference with creatinine secretion there is,

15 how it varies based on level of kidney function,

16 and do you have any data using another marker of

17 kidney function such as cystatin C that's not

18 affected by the transporter?

19   DR. CONNOLLY: Sure. I'll start with the

20 really simple one, your second one, do we have data

21 using cystatin C or other markers? No, we do not

22 have. So to get back to the potential impact of

MATE2-K inhibition by plazomicin on serum

creatinine elevations, first of all, when we look

at the IC50 of plazomicin for that transporter

compared to drugs like cobicistat, which are known

to inhibit it and bump serum study 007, the IC50 is

nowhere -- is much, much higher for plazomicin than

something like cobicistat. And even in that

situation with cobicistat, we see moderate bumps in

the range of 0.3 milligrams per deciliter.

So we don't think the plazomicin

concentrations achieved clinically would

sufficiently inhibit that transporter to actually

bump serum creatinine. We have also conducted a

dedicated DDI study, so clinical study using

metformin as a substrate for MATE2-K, and we see no

impact on metformin PK With co-administration of

plazomicin, so as a surrogate. And also we see no

impact on metformin PK in urine either.

DR. PAVLESKY: The second question related

to recovery of kidney function, the

definition -- what was the precise definition, and

do you account for the fact that patients,

1 particularly patients who have a severe acute

2 illness, may after their illness have a decrease in

3 creatinine production? So even if you recover to

4 the same serum creatinine, you haven't recovered

5 kidney function.

6   DR. CONNOLLY: Sure. I'd actually like to

7 ask Dr. Dwyer to address the question specifically

8 around the definition we used.

9   DR. DWYER: Jamie Dwyer, Vanderbilt. I'm a

10 nephrologist.

11   So you're correct. There are various

12 definitions for the recovery of nephrotoxicity. We

13 used a 0.5 milligram per deciliter increase from

14 baseline at any time across the study. We

15 categorized the subjects into three groups: full

16 recovery, partial recovery, and then a persistent

17 elevation.

18   Full recovery was that the last

19 post-baseline serum creatinine value had to be less

20 than 0.5 milligrams per deciliter above the

21 baseline value. Partial recovery, getting to a

22 point you made earlier, was that the last

1   post-baseline serum creatinine value had to be

2   greater than or equal to 0.3 less than the peak,

3   but that did not meet the definition for full

4   recovery. And then persistent elevation was

5   criteria that met neither the definition of the

6   other two.

7   DR. PAVLESKY: But you have no data on

8   creatinine production and whether recovery is

9   affected particularly in the more severely ill

10   patients because of the underlying critical illness

11   decreasing creatinine production.

12   DR. CONNOLLY: Right now. You're correct.

13   DR. PAVLESKY: Then just one other question.

14   You used the 0.5 definition rather than using the

15   current consensus AKIN/KDIGO definitions. Is there

16   reason for that, recognizing that there's a dispute

17   about the best definition to use?

18   DR. CONNOLLY: So we also did apply RIFLE

19   criteria. I mean, these are not --

20   DR. PAVLESKY: The RIFLE being surpassed

21   more than a decade ago by AKIN, and then

22   subsequently KDIGO.

1   DR. CONNOLLY: Yes. So essentially we chose

2   the 0.5 five milligram per deciliter and also the

3   RIFLE because these were values we had seen used in

4   similar drug labels, even recent ones such as the

5   new tenofovir label, for these types of drugs. So

6   we tried to look at precedents in this space, and

7   we applied similar definitions.

8   DR. BADEN: Dr. Le?

9   DR. LE: I have a question regarding what

10   you mentioned earlier for the use of weight for the

11   cUTI studies. For those greater than 125 percent,

12   you still use ideal body weight, correct, in

13   your --

14   DR. CONNOLLY: We used the ideal body weight

15   in the creatinine clearance calculation, and we

16   used an adjusted body weight for calculation of the

17   dose.

18   DR. LE: Okay. Did you use at all the ideal

19   body weight plus the 40 percent? Is that to adjust

20   the body weight for the dose --

21   DR. CONNOLLY: That's the adjusted body

22   weight.

1   DR. LE: -- but not the creatinine

2   clearance?

3   DR. CONNOLLY: Correct. And in doing so,

4   what we found ultimately is that the AUC

5   distribution for patients with high BMI versus low,

6   we were able to achieve very similar AUCs across

7   those patients using this type of correction for

8   obesity.

9   DR. LE: And you can certainly apply this

10 for the UTI. Would you be considering the same for

11 the BSI patients, where a higher exposure may be

12 needed?

13 DR. CONNOLLY: No. For calculation of the

14 initial dose, this is recommended for all patients

15 for that initial dose.

16 **Questions to the Committee and Discussion**

17 DR. BADEN: I think we have answered all

18 clarification questions, and we can move forward

19 now with consideration of the questions.

20 We'll now proceed to the questions to the

21 committee. We will be using an electronic voting

22 system for this meeting. Once we begin the vote,

1   the buttons will start flashing and will continue

2   to flash even after you've entered your vote.

3   Please press the button -- we're not going to vote

4   quite yet because we need to look at the question,

5   and then we will vote.

6   We see the question here. Yes?

7   DR. FOLLMANN: I thought we were going to

8   get a little clarification.

9   DR. BADEN: Correct. That's where I'm

10   going. I'm just looking at the guidance.

11   (Laughter.)

12   DR. BADEN: So I wanted to present the

13   question, and then we will ask Dr. Nambiar to

14   discuss a little bit about the LPAD rules and

15   guidance as to how we should weigh the evidence in

16   light of this pathway and the precedent we're

17   setting.

18   DR. NAMBIAR: Thank you, Dr. Baden. So what

19   I think I can do is just review the information I

20   presented this morning about LPAD.

21   There are the three key requirements and

22   then some additional requirements that regard

1 labeling and promotional materials. The three

2 requirements for LPAD are that the drug is intended

3 to treat a serious or life-threatening infection in

4 a limited population of patients with unmet needs.

5 The standards for approval under the 505(c) and (d)

6 standards for licensure under 351 the Public Health

7 Service Act are met. So there's no change in our

8 standards for approval. There needs to be a

9 written request from the sponsor that the drug be

10 approved as a limited-population drug.

11   Just to review with you what the standards

12 for approval are, the sponsor must provide

13 substantial evidence of effectiveness for the drugs

14 intended use and sufficient information to conclude

15 that it is safe for use under conditions

16 prescribed, recommended, or suggested in the

17 proposed labeling. For us to consider a product, a

18 drug to be safe and effective, we look for

19 substantial evidence of effectiveness for treatment

20 of the proposed indication, and the benefits for

21 the proposed population should outweigh the risks.

22   In terms of the additional requirements,

1   labeling will indicate the safety and effectiveness

2   has only been demonstrated with respect to a

3   limited population. And as I said, promotional

4   materials need to be submitted 30 days prior to

5   dissemination of such materials.

6   Are there any questions I can clarify?

7   DR. BADEN: Dr. Schaenman, Dr. Follmann,

8   questions about this pathway, or any other member

9   of the committee?

10   (No response.)

11   DR. BADEN: Okay. A question I have is

12   there is also in the background a device question

13   related to the TDM. Presumably, that is not

14   relevant to this consideration. That's a separate

15   discussion, but a companion ID, I assume.

16   DR. NAMBIAR: For today's discussion, we

17   were not planning to touch upon aspects of the

18   device.

19   DR. BADEN: Okay. So if no other

20   questions -- and I do want to note that Dr. Venitz

21   had to leave and that we will now proceed to the

22   voting.

1   The lights will flash. Please press the

2 button firmly that corresponds to your vote. If

3 you're unsure of your vote or wish to change your

4 vote, you may press the corresponding button until

5 the vote is closed. After everyone has completed

6 their vote, the vote will be locked. The vote will

7 then be displayed on the screen. The DFO will read

8 the vote from the screen record. Next, we'll go

9 around the room and each individual who voted will

10 state their name and vote into the record. You can

11 also state the reason you voted as you did if you

12 want to. We'll continue in the same manner until

13 all questions have been answered.

14   The first question is before us. I assume

15 there are no questions about the wording, so we

16 will move forward with voting.

17   (Voting.)

18   DR. CHEE: We have question 1, 15 yeses,

19 zero nos, zero or abstain of course, and 1 no vote.

20   DR. BADEN: We will start with Dr. Palevsky,

21 and with the next vote, we'll start from the other

22 side.

1   DR. PAVLESKY: So obviously it's clear I

2   must have voted yes, with some concerns that we

3   need more information, speaking as a nephrologist,

4   on pharmacokinetics, how best to monitor the drug

5   for preventing nephrotoxicity. I'm uncomfortable

6   with remaining tied to Cockcroft-Gault creatinine

7   clearance, and I think that the company needs to

8   look at dosing recommendations based on circa 2018,

9   means of assessing kidney function, and potentially

10   look at other markers for nephrotoxicity and

11   markers of kidney function such as the statin C.

12   DR. BADEN: Dr. Le?

13   DR. LE: I voted yes primarily because it

14   does appear qualified for the definition of LPAD

15   with one well-controlled control trial with other

16   information that's available there. I like the

17   fact that there is somewhat of a TDM incorporated

18   into this that kind of provides a safeguard in

19   terms of monitoring for nephrotoxicity in patients

20   with cUTI.

21   DR. BADEN: Thank you. Dr. Schaenman?

22   DR. SCHAENMAN: I also voted yes. I did

1   feel that evidence was provided supporting safety

2   and effectiveness for this particular indication.

3   Although there was only a single noninferiority

4   trial presented, I thought that the in vitro

5   studies using clinical isolates, the animal studies

6   as well as the limited bloodstream infection data

7   all supported the idea that the drug was effective,

8   and especially in the framework of the LPAD

9   labeling plan and the clear unmet need of having

10   additional treatments for MDR gram-negative

11   infections.

12   May we talk about labeling suggestions?

13   Okay. I would suggest that the packaging mention

14   limitations of the clinical trial, including

15   generalizability to nonwhite population. As was

16   mentioned previously, I do think that TDM should be

17   suggested given the interpatient variability

18   observed even in patients with relatively minor or

19   even normal renal function, but especially for

20   those with renal insufficiency to ensure efficacy

21   and avoiding nephrotoxicity in patients with

22   urinary tract infection. And I would also like to

1 add that postmarketing studies would be very

2 beneficial.

3   DR. BADEN: Dr. Lo Re?

4   DR. LO RE: Vincent Lo Re. I voted yes. I

5 thought that the phase 3 study 009 sufficiently

6 demonstrated noninferiority to meropenem and higher

7 composite cure rates and microbiological

8 eradication rates at test of cure, especially for

9 key resistant subgroups. I thought there appeared

10 to be few SAEs, which generally appeared to reflect

11 the aminoglycoside class. And I thought that just

12 given the continued emergence of resistance to both

13 old and new antimicrobial agents, limited existing

14 treatment options and a continued need for

15 additional antibiotic options for persons with

16 complicated UTIs, that this new antibiotic will

17 fill that important unmet need. And I would agree

18 with Dr. Schaenman that additional postmarketing

19 studies on safety would be valuable.

20   DR. BADEN: Dr. Daskalakis?

21   DR. DAKSKALAKIS: Demetre Daskalakis. I

22 also voted yes on the grounds that study 009 did

1 demonstrate noninferiority, and I think it

2 represented an adequately powered study to make

3 that assertion. I think that from the perspective

4 of complicated urinary tract infection, this drug

5 is important and adds to the limited armamentarium

6 that we have for resistant organisms.

7   From the perspective of labeling, I think

8 that there needs to be clear guidance about

9 therapeutic drug monitoring, and I think that there

10 are still some discussions happening. So I think

11 if there is ambiguity, it's best to implement

12 therapeutic drug monitoring across the board rather

13 than base it on creatinine clearance if that

14 becomes an area of a lot of conversation. It's

15 easier for clinicians to understand that they

16 create a subgroup of individuals who may or may not

17 qualify for that monitoring.

18   I would also recommend clear guidance on

19 bacteremic UTIs just to make it clear from the

20 perspective of duration of therapy. That may be

21 something that the labeling should also include.

22 And I would also comment that it's worth, I think

1   in the setting, to not only advise clinicians about

2   a limited population, but also to comment that it's

3   probably wise to limit the exposure of this agent

4   to whatever is necessary for therapeutic purposes.

5   We don't have a lot of experience nor a lot

6   of long duration therapy in UTIs, so I think it's

7   important to comment to limit the group and also

8   limit the time people are on the drug. And

9   finally, I think it's also important to make a

10   comment about ototoxicity and the fact that we

11   don't really know very much. So I think that a

12   non-statement on this will mean that clinicians may

13   think that this is not a problem. And since we

14   don't know, I think it needs to be clearly stated

15   in the labeling. Thank you.

16   DR. BADEN: Dr. Baden. I also voted yes,

17   and I echo the earlier comments. The comments that

18   I would highlight, the safety data set are quite

19   limited, however, the study offered was reasonable

20   for the question being asked and is clinically

21   relevant.

22   I would presume that this agent has the

1   similar toxicity as this class of drugs

2   aminoglycosides until date are generated otherwise,

3   echoing a Dr. Daskalakis' comment that ototoxicity,

4   vestibular toxicity, those other toxicities should

5   be presumed until data can be generated that they

6   are or not a concern.

7   This also lends itself to the TDM and

8   monitoring analogous to the class, again, until

9   data are generated that can better direct practice.

10   I also think there needs to be better data

11   generated on the microbiologic effect and

12   characterizing organisms and the different

13   resistant mechanisms, as that will be important in

14   better understanding activity going forward.

15   Dr. Weina?

16   DR. WEINA: Peter Weina. I obviously voted

17   yes as well. I still struggle with the issue of

18   the idea of unmet needs, and that's after availing

19   myself of the 2017 guidance for industry issued by

20   the FDA and actually speaking of the noninferiority

21   complex -- no --

22   (Laughter.)

1   DR. WEINA: -- the noninferiority trials and

2   how to utilize them for the unmet medical need.

3   I'm a little bit of a cynic, and regarding the

4   labeling, totally agreeing what has been previously

5   said, the clinicians are the worst when it comes to

6   it. The lawyers are really good at reading the

7   labels; we're not. And we have to make sure that

8   it specifically says exactly what we want it to say

9   because, otherwise, it's going to end up being used

10   in every way but what it's for. So that's all.

11   DR. BADEN: Dr. Honnegger?

12   DR. HONNEGGER: Jonathan Honnegger. I also

13   voted yes, for the same reasons that have been

14   mentioned before. I felt it met the criteria or

15   the LPAD pathway. I welcome a drug that treats the

16   CRE multidrug resistant organisms. I also just

17   want to add, in additional studies, I just want to

18   remind there is obviously no pediatric data yet, so

19   I would encourage that to be done.

20   DR. BADEN: Dr Green?

21   DR. GREEN: Michael Green. I voted yes.

22   Today's meeting brought the committee face to face

1   with the crisis of multidrug resistant bacteria,

2   their terrible impact on patient outcome, the

3   response of our legislator, the FDA, and perhaps

4   most importantly, the pharmaceutical industry to

5   address the crisis. Results of 009 study in my

6   mind clearly showed that plazomicin met the

7   noninferiority endpoints that were built into this

8   protocol.

9   I actually was comfortable with the unmet

10   need standard being met and wasn't bothered by the

11   use of meropenem when one looks at the fact that

12   approximately 80 percent of the isolates were ESBL

13   positive and 75 percent of the isolates were

14   aminoglycoside resistant in both the plazomicin and

15   the comparator group. I think the approval of

16   plazomicin with an indication for complicated UTI

17   provides an important new tool against the epidemic

18   of CRE, and I'm thankful for that.

19   Then to mimic my colleague to my left, I

20   hope and trust that future studies in the pediatric

21   population are being planned because we need them,

22   too. Thanks.

1   DR. BADEN: Dr. Gripshover?

2   DR. GRIPSHOVER: Hi. I voted yes because as

3   everyone else, I felt that study 009 did show

4   efficacy and did [indiscernible] mean that it was

5   noninferior to meropenem. I think it showed

6   reasonable in the UTI, especially if people had

7   normal renal function and over the short duration

8   of treatment because it really was a short duration

9   of treatment, 5 days for most people.

10   So I think that label should highlight that

11 we went to limit it to susceptible organisms and

12 use a special caution with renal insufficiency.

13   DR. BADEN: Dr. Clark?

14   DR. CLARK: Yes. I voted yes. I think

15 approval is appropriate for the limited population

16 suggested in the sponsor's proposed indication for

17 complicated UTI. And while there may be some

18 generalized ability concerns given the

19 demographics, I thought the data were convincing in

20 terms of noninferiority of plazomicin to the

21 comparator. I also thought it was reassuring that

22 bacteremic of patients ultimately cleared their

1   bloodstream infection with plazomicin.

2   I'm interested in seeing future data in

3   immunocompromised patients, especially renal

4   transplant recipients who have very high rates of

5   UTI, especially recurrent UTIs and those due to MDR

6   gram negatives. I disagree with monitoring drug

7   levels probably in all patients and have some

8   concerns about the ototoxicity issue that should be

9   noted in the labeling.

10   DR. BADEN: Dr. Follmann?

11   DR. FOLLMANN: This is Dean Follmann. I

12   voted yes. After some thought about the unmet need

13   and the back and forth on that, I thought it made

14   sense to accept the limited pathways argument that

15   the FDA had for this. So the single trial with the

16   endpoints that they required were met pretty

17   easily. I felt the safety profile was acceptable.

18   I appreciated the explanation of the composite

19   endpoint that Ed gave, and I also was comforted by

20   looking at the clinical endpoint at late follow-up

21   visit, which also showed it easily met the

22   noninferiority margin. So I felt comfortable

1 voting yes.

2   DR. BADEN: Dr. Hawkins?

3   DR. HAWKINS: Yes. I felt comfortable

4 voting the affirmative. And although it may be

5 obvious, I think it's very, very important that in

6 our hospitals, we're also limited by who could

7 write and prescribe these drugs. I think it's

8 very, very important in the labeling, where

9 possible, to indicate that only individuals

10 trained, such as infectious disease or other

11 specialists, be the ones that write this drug.

12   DR. BADEN: Ms. Dunn?

13   MS. DUNN: Yes. Five years ago, I had a

14 very serious blood infection and was on an

15 intravenous antibiotic routine of multiple

16 medications for about 10 weeks. So I did live

17 through some of this, not quite as serious as what

18 we've been talking about today, but it was still

19 pretty serious for me. I am concerned about

20 labeling and dosing for the patients, but I do

21 believe that this is a hopeful drug for patients

22 who are in a very critical state. So it's good to

1   know that there's something out there on the

2   horizon for them and hopefully will be available

3   soon. So   I definitely feel that the benefit

4   outweighs the risk. Thank you.

5   DR. BADEN: Dr. Rej?

6   DR. REJ: I obviously also voted yes for

7   many of the reasons that were expressed around the

8   table. And I think that the evidence presented

9   meets the bar for approval in this category. I

10   think that definitely the criteria for the TDM

11   component needs to be clarified and be much more

12   specific. And again, even though it's a minority

13   of aminoglycosides that interfere with certain

14   creatinine measurements, I think the sponsor should

15   look to be sure that there is no interference with

16   the measurement of creatinine.

17   DR. BADEN: So I'm asked to summarize after

18   each vote. The arguments against, none; the

19   arguments for, unmet need, a well-controlled trial

20   was offered, however much more data are needed,

21   including better safety data, dosing data, renal

22   monitoring data, microbiologic activity data.

1   However, those should be encouraged upon the

2   applicant to help generate those data in the

3   future.

4   We can move to question 2. Has the

5   applicant provided substantial evidence of the

6   safety and effectiveness of plazomicin for the

7   treatment of bloodstream infections in patients

8   with limited or no treatment options? If yes,

9   please provide any recommendations regarding

10   labeling. If no, what additional studies,

11   analyses, are needed?

12   Any questions about the question?

13   (No response.)

14   DR. BADEN: If not, then we can proceed to

15   voting the same process as previously.

16   (Voting.)

17   DR. CHEE: Question 2, you have 4 yeses, 11

18   nos, zero abstain, and 1 no vote.

19   DR. BADEN: One no voting. Okay. So we

20   will start with Dr Rej.

21   DR. REJ: So I did vote yes, but after

22   considerable deliberation, I felt in the end the

1   data met the criteria needed for approval for this

2   category of drug. And again, all my comments about

3   the TDM part for question 1 apply here, too.

4   MS. DUNN: I voted yes.

5   DR. BADEN: Dr. Hawkins?

6   DR. HAWKINS: Dr. Hawkins. I voted no. I

7   had difficulty with patients and substantial

8   benefit. I had trouble with that; need more

9   patients, and I understand the limitations are

10   indicated by our panelists in the industry.

11   DR. BADEN: Dr. Follmann?

12   DR. FOLLMANN: I'm Dean Follmann. I voted

13   no. This is a tough decision for me in that going

14   in this morning, I was leaning towards yes, but

15   ultimately I think it hinged on looking at the word

16   "substantial." I felt ultimately this was a quite

17   underpowered study and sort of danced around

18   superiority, but it wasn't convincing I guess.

19   There were 17 maybe different analyses that you

20   could look at to support or not support this, and

21   I'm a little uncomfortable when you're in that gray

22   area making some definitive statement about

substantial evidence.

I'd like to compliment the FDA statistical team. I thought it was a very sophisticated nuance discussion of the issues, fair and objective, and I compliment them on that and also for trying to imagine how you could justify this as a noninferiority study.

Ultimately, I wasn't comfortable with that argument either, I think largely because it was designed as a superiority study, which sort of have different incentives and so on, including prior antibacterial drug use at baseline and so on, so that might tend to bring the two arms together. So it was a conundrum. There are so many ways to look at it, and I wasn't comfortable saying it works substantially.

About additional analyses, it would have been nice to run 007 for another 20 patients or so. Maybe there would have been a pretty clear signal then. Unfortunately, you didn't know it was happening at the time and that a bit more would have helped, but that would have been nice

1   obviously. In terms of additional analyses, I

2   liked the time-to-event analysis that we talked

3   about. The sponsor presented that. There was

4   slight mention in the FDA documents about an

5   ordinal outcome. That might be another way to take

6   the existing data you have and try and glean a

7   little more information about it.

8   Another thing that was touched on in the FDA

9   comments is to use covariates of regression

10   analysis to try and either increase the power of

11   the study or to -- I thought of this maybe as a way

12   to bring in cohort 1 -- I mean bringing in cohort 2

13   in the analysis, so we have cohort 1 and bring in

14   cohort 2 and sort of use observational study type

15   techniques to look at the blended cohort.

16   I don't know if I strongly advocate that

17   because I just don't know how comparable they are,

18   and I know you can't level the playing field with

19   very many covariates, maybe one or so. So given

20   you have the data, I would probably do that, but I

21   wouldn't accept it uncritically, as I'm sure you

22   wouldn't. So that's about all I have.

1   DR. BADEN: Thank you. Dr Clark?

2   DR. CLARK: I also voted no. My concerns

3   are similar to Dr. Follmann's. It was a very

4   difficult decision given the need for new agents,

5   but I didn't feel that the applicant met the

6   standard of substantial evidence of safety and

7   efficacy with an adequate and well-controlled

8   study.

9   I was influenced by the case details that

10   were provided by the FDA, which I thought were very

11   helpful, the uncertainty about plazomicin treatment

12   effect due to the small sample size and all the

13   potential confounders such as lack of documented

14   positive blood cultures within 24 hours of drug

15   initiation and the prior potentially effective

16   therapies. I also was not convinced that the

17   noninferiority analysis was an adequate basis for

18   approval given the initial study design and

19   confounding factors that might have impacted

20   outcomes with colistin.

21   DR. BADEN: Dr. Gripshover?

22   DR. GRIPSHOVER: Hi. I voted no as well. I

just want to say first, as an ID physician, I do

understand the need for antibiotics for MDR

pathogens and appreciate the applicant's and the

agency's efforts to develop new drugs to address

this pressing problem. But unfortunately, I don't

feel that this met the criteria for having one

adequate trial to show efficacy in bloodstream

infections in particular. So I felt that 007 was

too small and there were many complications,

including people not being bacteremic at time of

entry and questions about source control, so the

same reasons that were said.

In terms of maybe other studies, I was

thinking -- similar to the noninferiority that we

do UTI, that we -- may meet our criteria, that

maybe if we did a noninferiority in those

[indiscernible] bacteremias as a noninferiority

trial, that we would maybe be able to address that

we're comfortable using it in bacteremias, and then

saving it for our MDR drugs rather than just

targeting the trial for MDR drugs. And that would

allow us to get more data regarding the TDM dosing,

1   too, because I think that that was a little bit

2   unclear as well.

3   DR. GREEN: Michael Green. I voted no.

4   Because of the clear need, I was really tempted to

5   vote yes, and actually I came here today thinking

6   that I was going to vote yes. But this study

7   clearly had a number of limitations that impacted

8   the interpretation of results to support the

9   approval for a bloodstream infection indication.

10   The changes in the protocol, the modifications in

11   the original statistical plan clearly created

12   challenges. But I think the limitation that I just

13   could not overcome were the small numbers. At

14   most, we have a study of 29 patients with

15   bloodstream infection, and at worse we have a study

16   of less than that. So while we desperately need

17   new drugs, I just don't think we have enough data

18   to approve for this indication.

19   I also thought that one might be able to

20   apply the model of what was just done for

21   complicated UTI to bloodstream infections. If you

22   wanted to open the door a little wider to both have

1 a little bit more restricted but still have a broad

2 population for which there's no shortage, you could

3 maybe even say go after ESBL positive bloodstream

4 infections. But to get those numbers, I think it

5 would be fine to do noninferiority.

6   As I stated, for the complicated UTI

7 comment, I don't have a problem using meropenem as

8 a comparator. I think if you're down to having to

9 use meropenem, there's a clear need because it's

10 not going to last for very long, so we could bring

11 it on board. We obviously desperately need it.

12 But I just have a hard time saying yes as a labeled

13 indication on a total of 29 patients. Thank you.

14   DR. BADEN: Dr. Honnegger?

15   DR. HONNEGGER: Jonathan Honnegger. I also

16 voted no for the same reasons, and I made my

17 decision last minute. It was very difficult. I

18 wanted to vote yes because this treats CRE. I

19 believe the supportive data are really there

20 obviously in the UTI and the in vitro

21 microbiological data.

22   Also in less ill patient who had bacteremia

1   in the setting of a UTI or those with APACHE score

2   of less than 15, it appeared to do well and

3   supportive data. It was just a lack of an adequate

4   well-controlled trial. I just didn't feel it was

5   adequate in the numbers, 14 versus 15 in the

6   comparator group. And that was hard, too, because

7   this trial had a very impressive numerical effect

8   on a very meaningful endpoint of mortality.

9   As far as that primary trial, they're going

10   to have to figure out some mechanism to do this,

11   and unfortunately doing this now in retrospect,

12   whether it's a slightly larger design trial for CRE

13   or a noninferiority trial in patients who don't

14   necessarily have CRE.

15   DR. BADEN: Pete Weina. I voted no. Unlike

16   the complicated UTI one where we had a really nice,

17   I thought, noninferiority trial and where the

18   concentrations of the unchanged drug in the urine

19   makes complete sense for clearing the bacteria, I

20   believe this particular trial for bloodstream

21   didn't meet FDA's guidance of substantial evidence,

22   where the definition of evidence is adequate and

1   well controlled. As a clinician, I'd love to have

2   more tools, but I'm uncomfortable with the data as

3   presented. I failed to see the sponsor met the

4   standard that is set forward for us.

5   As I said, I'm a cynic, and I believe an

6   approval is an approval, is an approval, and even

7   drugs with black box warnings are used all over the

8   place until the lawyers start dropping lawsuits or

9   denigrated when compared to another drug. So my

10   recommendation for additional studies and analyses

11   are just to keep track of all the bloodstream

12   infections that the drug is going to end up being

13   used for if it gets approved for UTIs. Thank you.

14   DR. BADEN: Dr. Baden. I voted yes, and I

15   seem to routinely find myself in the minority.

16   (Laughter.)

17   DR. BADEN: However, I hope and I think we

18   are a thoughtful minority. So I have many of the

19   same views as the prior statement, prior panel

20   members and their comments, but a slightly

21   different synthesis. I think that there are many

22   issues with the study design, the change in the

1   study design, the smallness of this study, the

2   focus of a single country, single population, small

3   number of organisms, lack of clarity, and the

4   limitations in disentangling source control, line

5   management, underlying condition, an organism

6   susceptibility and resistance to the comparator.

7   However, we are left with the data we have, not the

8   data I want.

9   There were 2100 participants screened. This

10   is not a trivial undertaking and this is not a

11   trivial problem that we are faced with in terms of

12   the unmet need of gram-negative resistance, and as

13   I mentioned in my concerns with the design, those

14   intrinsically increased the complexity to have the

15   perfect study, so we have an imperfect study. But

16   the totality of the data, including the in vitro

17   data, the animal model, the understanding of the

18   mechanism, the understanding of prior agents in the

19   class and activity, the 009 bacteremic data, plus

20   the 007 having a mortality endpoint, to me the

21   totality of those data are compelling that there is

22   meaningful activity of this agent for an unmet

1   need.

2   Having said that, there are many, many

3   questions that need to be further explored and

4   understood as I already alluded to and as others

5   have alluded to. But for those reasons, I voted

6   yes,

7   Dr. Daskalakis?

8   DR. DASKALAKIS: Demetre Daskalakis. I also

9   voted yes, and a lot of the reasons -- many of the

10   same reasons that Dr. Baden just discussed. I

11   think we all acknowledge that the study is very

12   limited as far as CRE, but I read the question very

13   literally, which reads, has the applicant provided

14   substantial evidence of the safety and

15   effectiveness of plazomicin for the treatment of

16   bloodstream infections in patients with limited or

17   no treatment options?

18   The totality of the data to me says yes. It

19   doesn't say CRE. It says for limited options in

20   treatment. So from my perspective, I think that we

21   have a fairly good signal that this agent has

22   activity against CRE and also a very good signal

1   that it is effective in bacteremic ETI. We have

2   animal models and also in vitro models that support

3   it as well.

4   So from my perspective, I voted yes, again,

5   looking at the totality of the data and not just

6   one isolated study. So I think that in my opinion,

7   though there is more work to do, the totality of

8   the evidence does demonstrate substantial proof

9   that this agent does work and that it does have a

10   very good safety profile.

11   I'll continue on that track of following the

12   question literally and say if this does go on to

13   approval, I think definitely, as I said for UTI,

14   there has to be extraordinary clarity on

15   therapeutic drug monitoring for this drug; so

16   whatever ends up happening from this perspective

17   for septicemia, for bacteremia.

18   I also just want to say from the perspective

19   of the future of this pathway for applicants, I

20   hope that our vote here doesn't discourage

21   individuals from pursuing this type of approval for

22   drugs that are so critical. There is clearly a

1   need, and I want to echo the comment that people

2   will be using this for bacteremic infections that

3   are not urinary tract infections, so

4   it will be very important for us to track what this

5   looks like and then potentially reconsider if this

6   does not get labeled to include bacteremia as not

7   related to urinary tract infections. Thank you.

8   DR. BADEN: Thank you. Dr Lo Re?

9   DR. LO RE: So I voted no, and for me it

10 came down to what were the criteria for substantial

11 evidence. For me, I did not feel that study 007

12 provided substantial evidence for the efficacy of

13 plazomicin for the treatment of bloodstream

14 infections. I had concerns regarding study 007's

15 overall very small sample size; the uncertainty of

16 the primary bacteremia diagnoses in the trial that

17 were expressed by the agency; the problem of

18 nonadherence where some people were switching to

19 alternative regimens early on; the limitations in

20 the statistical analyses that were also highlighted

21 by the FDA; and the largely descriptive nature of

22 the study results, all of which to me made

1   interpretability of those results challenging and

2   introduced a high degree of uncertainty.

3   I appreciate that the sample sizes are going

4   to be small for these studies of antimicrobial

5   drugs for these highly resistant organisms, but to

6   me, this study had too many, far too many,

7   limitations to assure the efficacy of plazomicin

8   for bloodstream infections.

9   I also thought that study 007's cohort 2,

10   which was so different from cohort 1 and with no

11   control group, for me made further evaluation of

12   this group for efficacy difficult. I don't think

13   that this should be the bar that we set for the

14   limited population for the antibacterial drugs

15   pathway. And I think the challenge for the agency

16   going forward is to probably more effectively

17   articulate what the bar should be. But I

18   personally thought that additional data evaluating

19   plazomicin's efficacy in a larger sample of

20   patients with bloodstream infections are needed

21   before we can support a positive benefit-risk for

22   this indication.

1   DR. BADEN: Dr. Schaenman?

2   DR. SCHAENMAN: I also voted no for very

3   similar reasons. I also struggled with this vote.

4   Considering the current crisis and the lack of

5   alternatives, it was very difficult. However, I

6   also felt that we had not reached the threshold of

7   substantial evidence in demonstrating

8   effectiveness.

9   We've already talked about the many problems

10   of trial 007. There was a numerical trend towards

11   efficacy, which was quite encouraging, but the

12   trial did not reach the predetermined goals.

13   Everybody has mentioned the small study size.

14   There was heterogeneity in the inclusion, in the

15   length of time that patients received drugs. And

16   although Dr. Kartsonis did caution us that this is

17   common in candidemia or bacteremia drugs, given the

18   small study size, I felt that it really did limit

19   our ability to interpret the results.

20   As was mentioned before, the initial plan as

21   a superiority study followed by two study

22   amendments that were quite impactful leading to

1 ultimately a descriptive study only, all of this

2 undercut the ability of the sponsor to reach that

3 threshold of substantial evidence, but again,

4 further guidance from FDA as to exactly what that

5 looks like would be helpful.

6 I did want to say, however, that I thought

7 that the safety data was quite reasonable, and

8 given the limited number of choices and

9 alternatives including colistin, meropenem,

10 tigecycline, I thought that in terms of safety,

11 substantial evidence was shown that the drug was

12 safe, again, within the context of need to treat

13 CRE. So that all led to my vote of no.

14 In terms of additional studies that would be

15 required, it may be that where we are now compared

16 to where we were in 2011 or even 2014, as this

17 crisis continues to enfold in metropolitan areas

18 including New York City, perhaps it will be easier

19 to enroll a reasonably powered study to test the

20 question of efficacy in bacteremia.

21 DR. BADEN: Dr. Le?

22 DR. LE: I voted no for the reasons that's

been mentioned by the committee members. Going

forward, I wanted to add three comments in terms of

what some of the possibilities we can integrate for

future studies.

First would be, in terms of the TDM process,

right now there's really only a window of when the

second concentration can be taken between 6 to 10

hours after the dose. If we can broaden that more,

since we are looking at minimum concentration as a

marker for nephrotoxicity, there may be some

patients where we're going to get the second level

at 12, 14, or even 23 hours. So what would that

mean in terms of dosing adjustment? So further

studies into that would be prudent.

The other, I do concur with you in terms

that there is some safety guards that we can see

certain trends when compared to colistin, but I'll

be curious also to know in patients with other

factors, like for instance on the use of

furosemide, diuretics in the ICU, which would be

the case for this population with BSI, how would

the incidence of nephrotoxicity change with that?

1   So integrating those variables in to give a more

2   estimate of what the nephrotoxicity would be in

3   this population.

4   Lastly, it may or may not be a signal, but

5   the 8 adverse events of greater than 10 percent was

6   reported in 007 cohort 1 with some of the cardiac

7   effects. So it would be prudent just to monitor

8   that.

9   DR. BADEN: Thank you. Dr. Palevsky?

10   DR. PALEVSKY: So I also voted no with some

11   degree of reluctance because I would really like a

12   drug as an alternative to using colistin. However,

13   I don't think that the threshold for efficacy and

14   safety was met with a 29-patient study. My

15   comments echo those of multiple that have been

16   made. I am absolutely convinced that if the agency

17   provides the approval based on our recommendation

18   for urinary tract infections, I will see this used

19   in my ICU for bacteremic infections. But I think

20   that it has not met the labeling requirement, and

21   we just need, a larger -- not enormous but a larger

22   study.

1   I do have concerns over the approach for

2   therapeutic drug monitoring, and I think you need

3   extensive data on how the AUC over 24 hours plays

4   out at different levels of kidney function or

5   patients who are on renal replacement therapy. I

6   also think you need to have data on the use of this

7   drug in patients on other modalities of renal

8   replacement therapy other than continue with

9   therapy, although that didn't influence my

10   decision.

11   DR. BADEN: Thank you

12   So as you have heard, 4 yes, 11 no. The

13   primary no arguments were the data are not

14   substantial, multiple additional analyses are

15   needed, the small sample size was just too small,

16   and the multiple changes in the design further

17   undercut the interpretability of the data. TDM

18   will be needed in any case.

19   On the yes side, it has to do with the

20   totality of the data, the difficulty of doing the

21   studies, the tremendous unmet need, and activity

22   for bacteremia in the setting of limited other

1   options, and the need to encourage more development

2   in this space given the unmet need.

3   So that concludes the business of the

4   committee. Before we adjourn, any last comments

5   from the agency?

6   DR. NAMBIAR: Thank you, Dr. Baden. We just

7   wanted to thank the committee for all their useful

8   feedback and very thoughtful suggestions. I would

9   also like to thank the applicant for all the work

10   they've done on this NDA and for their

11   presentations today, and also extend our sincere

12   thanks to the presenters at the open public

13   hearing. We wish you all safe travels, and we'll

14   see you in a few months.

15   **Adjournment**

16   DR. BADEN: Thank you, and the meeting is

17   now adjourned.

18   (Whereupon, at 4:09 p.m., the meeting was

19   adjourned.)

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