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

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

Cindy Chee, PharmD

Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Nina M. Clark, MD

Associate Professor

Director, Transplant Infectious Disease Program

Division of Infectious Diseases

Loyola Medical Center

Maywood, Illinois

Demetre C. Daskalakis, MD, MPH

Acting Deputy Commissioner

Division of Disease Control

New York City Department of Health and Mental Hygiene

Long Island City, New York

Dean A. Follmann, PhD

Assistant Director of Biostatistics

Chief Biostatistics Research Branch

National Institute of Allergy and

Infectious Diseases

National Institutes of Health (NIH)

Bethesda, Maryland

Michael D. Green, MD, MPH

Professor of Pediatrics, Surgery and Clinical &

Translational Science

University of Pittsburgh School of Medicine

Division of Infectious Diseases

Director, Antimicrobial Stewardship & Infection

Prevention

Co-Director, Transplant Infectious Diseases

Children's Hospital of Pittsburgh

Pittsburgh, Pennsylvania

Barbara M. Gripshover, MD

Associate Professor of Medicine

University Hospitals Cleveland Medical Center

Case Western Reserve University

Division of Infectious Diseases and HIV Medicine

Cleveland, Ohio

Jonathan R. Honegger, MD

Assistant Professor of Pediatrics

The Ohio State University College of Medicine

Division of Infectious Diseases and Center for Vaccines and Immunity

Nationwide Children's Hospital

Columbus, Ohio

Vincent Lo Re, MD, MSCE
Assistant Professor of Medicine and Epidemiology
Division of Infectious Diseases
Department of Medicine
Center for Clinical Epidemiology and Biostatistics
Perelman School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Joanna M. Schaenman, MD, PhD
Assistant Professor of Medicine
Division of Infectious Diseases
David Geffen School of Medicine at UCLA
Los Angeles, California

Peter Weina, MD, PhD, FACP, FIDSA
Colonel, Medical Corps, USA
Chief, Department of Research Programs
Walter Reed National Military Medical Center
Division of Education, Training and Research
Bethesda, Maryland

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEMBERS

(Non-Voting)

Nicholas A. Kartsonis, MD

(Industry Representative)

Acting Section Head, Antibacterials/CMV

Vice President and Therapeutic Area Head

Infectious Diseases, Clinical Research

Merck Research Laboratories

North Wales, Pennsylvania

TEMPORARY MEMBERS (Voting)

Lindsey R. Baden, MD

(Acting Chairperson)

Director of Clinical Research

Division of Infectious Diseases

Brigham and Women's Hospital

Director, Infectious Disease Service

Dana-Farber Cancer Institute

Associate Professor, Harvard Medical School

Boston, Massachusetts

Debra Dunn

(Patient Representative)

Libertyville, Illinois

Randy Hawkins, MD

(Acting Consumer Representative)

Private Practice

Inglewood, California

Jennifer Le, PharmD, MAS

Professor of Clinical Pharmacy

University of California San Diego

Skaggs School of Pharmacy and Pharmaceutical Sciences

Faculty-in-Residence

Miller Children's and Women's Hospital of Long Beach

Long Beach Memorial Hospital

La Jolla, California

Paul M. Palevsky, MD

Chief, Renal Section

VA Pittsburgh Healthcare System

Professor of Medicine

Renal-Electrolyte Division

University of Pittsburgh

Pittsburgh, Pennsylvania

Robert Rej, PhD

Director, Clinical Chemistry and Hematology

Laboratory of Molecular Diagnostics

Associate Professor

School of Public Health

State University of New York at Albany

Research Scientist, Wadsworth Center

New York State Department of Health

Albany, New York

Jurgen Venitz, MD, PhD

Professor and Vice Chairman

Virginia Commonwealth University

School of Pharmacy

Department of Pharmaceutics

Richmond, Virginia

FDA PARTICIPANTS (Non-Voting)

Edward Cox, MD, MPH

Director

Office of Antimicrobial Products (OAP)

Office of New Drugs (OND), CDER, FDA

Sumathi Nambiar, MD, MPH

Director

Division of Anti-Infective Products (DAIP)

OAP, OND, CDER, FDA

Shrimant Mishra, MD, MPH

Medical Officer

DAIP, OAP, OND, CDER, FDA

Daniel Rubin, PhD

Statistical Reviewer

Division of Biometrics IV (DBIV)

Office of Biostatistics (OB)

Office of Translational Sciences (OTS), CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:30 a.m.)

Call to Order

Introduction of Committee

DR. BADEN: It is 8:30. We shall begin the day's work.

Good morning. I would like to remind everyone to please silence your cell phones, smartphones, and any other devices if you've not already done so. I would also like to identify the FDA press contact, Teresa Eisenman, who is in the back at the left.

My name is Dr Lindsey Baden. I am chairperson of the Antimicrobial Drug Advisory Committee, and I will be chairing this meeting. I will now call this meeting to order. We'll start by going around the table and introduce ourselves. We'll start with the FDA on the left.

DR. COX: Good morning. Ed Cox, director of the Office of Antimicrobial Products at CDER, FDA.

DR. NAMBIAR: Good morning. Sumathi 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.

DR. CHEE: Cindy Chee, acting designated federal officer for AMDAC.

DR. BADEN: Lindsey Baden, infectious diseases physician at Brigham Women's Hospital, Dana Farber Cancer Center, and Harvard Medical School.

DR. WEINA: Peter Weina, infectious disease physician and director of research at the Walter Reed National Military Medical Center.

DR. HONEGGER: Jonathan Honegger, pediatric infectious diseases, Ohio State University.

DR. GREEN: Michael Green, pediatric infectious diseases, Children's Hospital, Pittsburgh and the University of Pittsburgh School of Medicine.

DR. GRIPSHOVER: Barb Gripshover, adult infectious diseases from University Hospitals Cleveland Medical Center at Case Western Reserve University.

DR. CLARK: Nina Clark, infectious diseases, Loyola University Medical Center in Maywood, Illinois.

DR. FOLLMANN: Dean Follmann, head of biostatistics at the National Institute of Allergy and Infectious Diseases.

DR. HAWKINS: Barney Randy Hawkins, internal medicine and pulmonary medicine, Los Angeles, California.

MS. DUNN: Debra Dunn, patient representative.

DR. REJ: Good morning. I'm Bob Rej, clinical chemist and hematologist, New York State Department of Health in Albany in the School of Public Health at the State University of New York at Albany.

DR. KARTSONIS: Good morning. I'm the industry rep. I'm Nick Kartsonis, and I represent Merck Research Company.

DR. BADEN: I would like to thank all the committee members for making the time and joining us both yesterday and today.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held.

Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus as a gentle reminder, individuals be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings, however, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

I'll now pass to Dr Cindy Chee, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

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

government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for special government employees' services outweighs his or her potential financial conflicts of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflict of interest of their own as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 USC, Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAS, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves discussion of new drug application 210303 for plazomicin sponsored by

Achaogen, Inc. for the proposed indications for the treatment of complicated urinary tract infections and blood stream infections in adults. This is a particular matters meeting during which specific matters related to Achaogen's NDA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Nicholas Kartsonis is participating in this meeting as a nonvoting industry representative acting on behalf of regulated industry. Dr. Kartsonis' role at this meeting is to represent industry in general and not any particular company. Dr. Kartsonis is employed by Merck and Co.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interests, the participants need to exclude themselves from such involvement and their exclusion Will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. BADEN: We will now proceed with the FDA's introductory remarks from Dr. Sumathi Nambiar, director of the Office of the Anti-Infective Products.

FDA Opening Remarks - Sumathi Nambiar

DR. NAMBIAR: Thank you, Dr. Baden.

Good morning everybody, and welcome to today's meeting of the Antimicrobial Drugs Advisory Committee convened to discuss NDA 210303, plazomicin sulfate injection. The applicant is Achaogen. The product has qualified infectious

disease product designation for the following indications: complicated urinary tract infections, catheter related bloodstream infections, hospital acquired bacterial pneumonia, ventilator-associated bacterial pneumonia, and complicated intra-abdominal infections.

The product was also granted breakthrough therapy designation for the treatment of blood stream infections caused by certain enterobacteriaceae in patients who have limited or no alternative treatment options. The applicant has requested review of the BSI indication under Section 506(h) of the Federal Food, Drug, and Cosmetic Act, or the LPAD pathway, which I'll touch upon in subsequent slides. The NDA was granted priority review, as the product has QIDP designation.

The applicant is seeking the following two indications, as a single agent in patients 18 years of age or older for the treatment of complicated urinary tract infections, including pyelonephritis caused by the following susceptible organisms. The

second indication is for patients aged 18 years or older for the treatment of BSIs caused by Klebsiella pneumoniae and Escherichia coli.

For both indications, the applicant is proposing including the following language in labeling, "As only limited clinical safety and efficacy data for plazomicin are currently available, plazomicin should be reserved for use in patients who have limited or no alternative treatment options."

The proposed dosing is based on creatinine clearance, and the dosing intervals could be every 24 hours, every 48 hours, and the dose could be 10 or 15 mgs per kg. In addition, the applicant's proposing therapeutic drug monitoring. An AUC-based approach is proposed for bloodstream infections and a Cmin-based approach for patients with a cUTI if they have moderate to severe renal impairment or the anticipated duration of therapy is greater than 5 days.

I'll spend the next couple of minutes talking about the 21st Century Cures Act and LPAD,

signed into law on December 13th of 2016, and Section 3042 is the limited population pathway for antibacterial and antifungal drugs, otherwise known as the LPAD pathway. The requirements for LPAD are as follows. The drug should be intended to treat a serious or life-threatening infection in a limited population of patients with unmet needs. It's important to know that the standards for approval still need to be met under the LPAD pathway, and the sponsor needs to submit a written request that the drug be approved as a limited population drug.

To meet the standards for approval, the sponsor must provide substantial evidence of effectiveness for the drugs intended use and sufficient information to conclude that it is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling. In our determination if a product is safe and effective, we require substantial evidence of effectiveness for treatment of the proposed indication, and the benefits for the proposed population must outweigh the risks.

Substantial evidence requires evidence consisting of adequate and well-controlled investigations, and the criteria for adequate and well-controlled trials are described in 21 CFR 314.126. We might consider data from one adequate and well-controlled trial with other confirmatory evidence to constitute substantial evidence.

Accepting greater uncertainty or higher risk in patients with serious disease and with an unmet need is an appropriate approach to risk-benefit assessment, however, it's important to note that flexibility in regulations do not allow for marketing approval prior to demonstration of substantial evidence of effectiveness.

Additional requirements under LPAD relate to labeling and promotional materials. All advertising and labeling will include a limited population in a prominent manner and the prescribing information will also contain a statement that this drug is indicated for use in a limited and specific population of patients.

Promotional materials need to be submitted at least 30 days prior to dissemination of such materials.

Moving on to the plazomicin development program, the applicant has conducted six phase 1 studies, including a lung penetration study, thorough QT study, and a renal impairment study. There's a phase 2 trial and the phase 3 trial in adults with cUTI/acute pyelonephritis and a phase 3 trial in adults with bloodstream infection or a HABP/VABP.

Briefly, the phase 2 UTI trial, study 002, evaluated two doses of plazomicin 10 milligram per kilogram or 15 milligram per kilogram, and plazomicin was compared to levofloxacin. Plazomicin was administered for 5 days. There was no option to switch to oral therapy. Patients with creatinine clearance less than 60 mL per minute were excluded from this trial. The primary endpoint was microbiologic eradication of the test of cure visit. In general, the group that received 15 mgs per kg were similar in terms of outcomes compared to the levofloxacin arm.

Study 009 is the phase 3 cUTI trial. It's a randomized, double-blind NI trial where plazomicin was compared to meropenem. In general, the trial design was consistent with our cUTI guidance. After a minimum of 4 days of blinded IV therapy, patients in both arms of the study could be switched to open-label, oral levofloxacin for an additional 3 to 6 days. The co-primary endpoint was a composite of clinical cure rate and microbiologic eradication. The primary analysis population was the microbiologic modified intent-to-treat population, and the co-primary assessments were made at day 5 in the test of cure visits.

The prespecified NI margin was 15 percent, which is wider than what we typically accept for development programs, and that was because if the product were to be approved, labeling would include a statement that it be reserved for use in patients who have limited or no alternative treatment options. In this trial, dose adjustment was based on creatinine clearance. Therapeutic drug

monitoring was not performed.

In general, plazomicin was noninferior to meropenem at the day 5 and TOC visits in the primary analysis population, and the prespecified NI margin of 15 percent was met.

The second phase 3 trial, study 007, was in patients with bloodstream infections or HABP/VABP. This was a randomized, open-label superiority trial where plazomicin was compared to colistin and patients had to have carbapenem resistant enterobacteriaceae. In both arms of the trial, patients could receive concomitant tigecycline or meropenem, and this was based on the susceptibility of the baseline organism.

The primary efficacy endpoint when the trial was originally designed was 28-day all-cause mortality. The primary analysis population was the microbiologic modified intent-to-treat population, which included all randomized patients who had received at least one dose of study drug and had CRE isolated from an acceptable study qualifying baseline specimen. The original sample size for

the study was 286 patients with confirmed CRE. The statistical significance level that was agreed to was the one-sided alpha of 0.05, and Dr. Rubin will discuss this further in his presentation.

There were two protocol amendments. The first amendment changed the primary efficacy endpoint from 28-day all-cause mortality to a composite of 28-day all-cause mortality or significant disease related complications such as new or worsening ARDS, a new lung abscess, empyema, onset of septic shock, and persistent CRE bacteremia. In the second amendment, and uncontrolled cohort 2 was created, and this would include patients who were not eligible for cohort 1.

This study was stopped after two years, as the applicant encountered difficulties in enrolling patients in this trial. The final sample size in the randomized cohort to cohort 1 was 37 in the primary analysis population. The statistical analysis plan was finalized after enrollment was completed, but before they were unblinding of the

results, and the SAP stated that no formal hypothesis testing was to be performed.

The initial dose and dosing interval in the study were adjusted based on baseline estimated creatinine clearance or the type of renal replacement therapy, and subsequent doses were adjusted as needed based on therapeutic drug monitoring using measured plazomicin plasma concentrations and dose adjustment equations.

If you look at the clinical outcomes in study 007, using the 28-day all-cause mortality or SDRCs, which was the endpoint following the first amendment, the mortality rates in the plazomicin arm were lower than what was seen in the colistin arm and it provided the 90 percent confidence intervals and the p-value for that. Similarly, for the 28-day all-cause mortality, the mortality rates in the plazomicin treated patients were lower than what was seen in the colistin arm, and similarly, the 90 percent confidence intervals here extend from 1 to 52 percent and provided the p-value.

If you look at the outcomes by subgroups,

the first row has the results I just showed you, which is the overall population, which includes patients with bloodstream infections as well as HABP/VABP, and then specifically of the subgroup of BSI and the subgroup of HABP/VABPs, in the overall population, the treatment difference was 26 percent with the lower mortality seen in plazomicin treated patients. The exact 90 percent CI spread from minus 1 to 51 percent, and the one-sided exact p-value is .09. In the BSI subpopulation, the treatment difference of 39 percent and the confidence intervals from 9 percent to 66 with a p of 0.03.

Looking at it for the other endpoint, which was the 28-day all-cause mortality, the mortality rates in the plazomicin patients were lower than the colistin treated patients and provided the confidence intervals and p-value here as well.

The primary safety assessment in this NDA was based on the phase 3 cUTI trial with some supportive evidence from the phase cUTI trial, where a few patients received the proposed 15 mgs

per kg dose. Safety from study 007, which was the BSI HABP/VABP study, was assessed separately because there were inherent differences between patients in this trial and the other trials; for example, the duration of treatment, the patient population use of concomitant medications. In general, the safety of plazomicin is consistent with what's known about the aminoglycoside class. There is a signal for nephrotoxicity, and the potential for ototoxicity cannot be ruled out.

So we'll have presentations by the applicant followed by presentations by the FDA. The FDA presentations will be as follows. Dr. Sun will discuss the efficacy seen in the cUTI trial. Dr. Rubin and Dr. Mishra will discuss the efficacy findings in study 007, which is the BSI HABP/VABP study. Dr. Mishra will then provide a summary of the safety inflammation for this NDA. And then we have two presentations from clinical pharmacology primarily focused on aspects of therapeutic drug monitoring as it relates to the cUTI indication. Dr. Zhuang and Dr. Wu will each have their

presentations, one for cUTI and one for BSI. We have time for clarifying questions following both the applicant presentation and the FDA presentation. After lunch, we have an open public hearing followed by questions for the committee.

We have two voting questions for the committee today. The first one is, has the applicant provided substantial evidence of the safety and effectiveness of plazomicin for the treatment of complicated urinary tract infections in patients with limited or no treatment options? If yes, please provide any recommendations for labeling. If no, please discuss additional studies or analyses that are needed.

The second question is, has the applicant provided substantial evidence of the safety and effectiveness of plazomicin for the treatment of bloodstream infections in patients with limited or no treatment options? If yes, please provide any recommendations for labeling. If no, please discuss additional studies or analyses that are needed.

With that, thank you and look forward to the discussions today.

DR. BADEN: Thank you, Dr. Nambiar for an overview of the day's data discussions.

We'll now move to the applicant presentations.

Both the FDA and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with the applicant such as consulting fees, travel expenses, honoraria, and interest in a sponsor, including equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial

relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We'll now proceed with Achaogen's presentations.

Applicant Presentation - Anne Keane

MS. KEANE: Thank you.

Good morning. My name is Anne Keane, and I'm head of regulatory affairs and clinical quality assurance at Achaogen. I'd first like to take this opportunity to thank the division. Throughout the plazomicin development program, you have been unfailingly generous and collaborative with your time and expertise, and the plazomicin program has benefited greatly from both. I'd also like to thank BARDA. Without your support, plazomicin development would never have been possible. And finally, I'd like to thank the members of the committee for this opportunity to present the plazomicin data today.

Plazomicin is a new aminoglycoside intended

for systemic use. It was engineered to overcome the common mechanisms of resistance to the approved aminoglycosides. The key target pathogens for plazomicin are the enterobacteriaceae, including drug-resistant strains. The clinical development of plazomicin began in 2008 and is focused on the treatment of serious infections due to multidrug enterobacteriaceae, including CRA, for patients with limited or no alternative treatment options.

Study 007, the first of its kind superiority study of plazomicin in patients with bloodstream infections or HABP/VABP due to CRE, was open in early 2014. Over the next two years, Achaogen met with the division several times to discuss study 007 enrollment challenges and study feasibility, amending the study twice in an attempt to increase enrollment. In spite of those efforts and due to the continued slow enrollment, an alternative pathway to approval based on a single phase 3 cUTI study was agreed upon with the division. And in December of 2015, Achaogen opened study 009.

Enrollment in study 009 proceeded very quickly. In the spring of 2016, as completion of study 009 approached, enrollment projection suggested that study 007 would not be completed in a relevant time frame with earliest possible NDA submission toward the end of 2022. Achaogen then agreed with the division on a stopping rule for study 007 that would allow the data from 007 to be included in an initial plazomicin NDA based on the results of study 009.

In August of 2016, study 009 was completed and study 007 was closed to enrollment. Top-line data from both studies became available in December of 2016. In May of 2017, FDA granted breakthrough therapy designation for the BSI indication because the findings in study 007 demonstrated preliminary evidence of a substantial improvement over existing therapies.

In October of 2017, Achaogen submitted the NDA for plazomicin requesting indications for cUTI and BSI both for patients with limited treatment options. We've requested review of the data

supporting the BSI indication under the new limited population antibacterial drug or LPAD pathway.

Study 009 was designed in accordance with FDA's 2013 unmet need guidance, which lays out a streamlined development program available for antibiotics intended to treat patients with unmet need. Antibiotics approved via this pathway will have a limited treatment option statement in the indication section of the label.

These programs are still required to meet the normal statutory standard for efficacy and safety, but there is some flexibility in the statistical requirements for the study; for example, a wider noninferiority margin or a superiority study with less stringent statistical requirements may be acceptable. Importantly, the study can be conducted in patients who have alternative treatment option significantly increasing enrollment feasibility for these studies. However, all of these options still require a fairly large trial in the hundreds of patients.

In 2016, Congress passed the 21st Century Cures Act, creating a new pathway called the limited population antibacterial drug, or LPAD pathway. This legislation was the result of many years of effort on the part of professional societies, the antibiotic industry, and government agencies, and it was intended to create a feasible pathway to approval to advance and incentivize the development of antibiotics against the most urgent antibacterial needs, including the need for new antibiotics for infection due to MDR pathogens.

Its passage reflects recognition by Congress that large clinical trials are not possible for serious and life-threatening infections, which occur in limited populations and that physicians and patients are generally willing to accept greater uncertainty from drugs that treat life-threatening and severely debilitating illnesses. The plazomicin BSI indication will be the first application reviewed under the LPAD pathway.

The statute permits flexibility to approve

an antibiotic, alone or in combination, if the antibiotic is intended to treat a serious or life-threatening infection in a limited population of patients. While this substantial evidence standard must be met, the statute states that the determination of safety and effectiveness must reflect the benefit-risk profile of the drug in the limited population, and it must take into account the severity and rarity or prevalence of the infection the drug is intended to treat and the availability of alternative treatment options.

Antibiotics approved by this pathway will require prior review of all promotional materials by the FDA and a limited population statement will be placed prominently next to the drug name on all promotional and labeling materials.

My colleagues will describe the totality of the evidence that supports the approval of plazomicin for the BSI indication via the LPAD pathway. This includes data from studies 007 and 009, extensive in vitro and relevant animal data, and PKPD data that supports a high probability of

target attainment, and exposures achieved in our clinical trials. The data package provides substantial evidence of efficacy and safety and describes a positive benefit-risk for plazomicin for the treatment of BSI in patients who have limited or no treatment options in accordance with the LPAD statute.

Our proposed indications for plazomicin will include a limitations-of-use statement, advising prescribers that limited safety and efficacy data are currently available and to reserve plazomicin for use in patients who have limited or no alternative treatment options. The limited-use statement will apply to both the treatment of urinary tract infection, including pyelonephritis due to the pathogens listed here, and the treatment of bloodstream infections caused by Klebsiella pneumoniae and E coli.

Turning to the agenda for the rest of Achaogen's presentation, Dr. Jamie McKinnell, an infectious disease specialist and researcher from the David Geffen School of Medicine at UCLA, will

discuss the current unmet medical need. Kevin Krause, Achaogen's head of microbiology, will presents the microbiology and clinical pharmacology of plazomicin. Dr. Ian Friedland, a clinical consultant, will review the efficacy data, and Dr. Lynn Connolly, clinical consultant, will present the safety data and then conclude with a benefit-risk assessment.

We have several additional experts with us today. All outside experts have been compensated for their time and travel to today's meeting. Thank you. It's my pleasure now to turn the lectern over to Dr. McKinnell.

Applicant Presentation - James McKinnell

DR. McKINNELL: Good morning. My name is James McKinnell. I'm an infectious disease physician based in Los Angeles, California. My research focuses on treatment of CRE infections and the epidemiology of CRE in the United States. I will focus my presentation today on enterobacteriaceae. When I look at this list of organisms and try to remember which organisms fall

into the family of enterobacteriaceae, I tend to think of them as all of the healthcare-associated gram-negative rods that aren't pseudomonas, acinetobacter, and stenotrophomonas.

E. coli is the most common cause of bacterial infection in man and is a driving factor in the epidemiology of extended-spectrum beta-lactamase or ESBL producing infections. Enterobacter and klebsiella are driving forces of carbapenem resistant enterobacteriaceae or CRE. ESBL are considered a serious public health threat by the CDC largely because of the overall burden of disease and the impact of ESBL on carbapenem consumption.

ESBL infections are notoriously difficult to treat. ESBLs degrade many cephalosporins, including ceftriaxone and antipseudomonal cephalosporins like cefepime and ceftazidime. They also frequently carry cross-class resistance to other antibiotics, including fluoroquinolones and aminoglycosides. As a result, delayed appropriate therapy is common, which leads to initial

antibiotic failure, higher infection related mortality, and higher infection related readmissions.

ESBL is becoming common. On the left, you see community acquired prevalence of ESBL E. coli. So on the left is ESBL E. coli from the community, and on the right hospital-associated prevalence. These data are concerning. By the end of 2014, 16 percent of community and 28 percent of hospital E. coli were ESBL producers. A common strategy to mitigate morbidity and mortality is to use carbapenem therapy often including carbapenems during empiric regimens.

I'm again showing you the prevalence of ESBL among hospital-associated UTI due to E. coli. These are the number of UTI in patients treated with a carbapenem between 2004 and 2009. You can see it stays stable at approximately a 100,000 patients per year. After 2009, we see an increase in carbapenem use coincident with the rise in prevalence of ESBL UTIs. The rise in carbapenem use has led to another problem, carbapenem

resistance.

CRE are the worst of the MDR enterobacteriaceae. They are classified by the World Health Organization as a priority pathogen for research and drug development. The CDC calls them an urgent public health threat. The concern with CRE is that first CRE is spreading. Second, we have limited treatment options and high mortality.

CRE first emerged largely in the Mid Atlantic states and began to spread through transfer of patients from one healthcare setting to another. We now document CRE in all 50 states. Not only do we see geographic spread, we also see rising burden of disease with increasing CRE hospitalizations over the last few years. The particular studies shown here use patient level data from nearly 300 hospitals to project national estimates. The results mirror findings from other studies supporting arise in CRE hospitalizations.

CRE infections have consequences. CRE infections have attributable mortality rates of 30

to 40 percent for serious infections such as intra-abdominal infections, pyelonephritis, pneumonia, and worst of all, bacteremia. Among all of the CRE infections, bloodstream infections are clearly the most lethal.

For multiple publications around the world, CRE bloodstream infections are associated with 40 to 50 percent mortality by day 30. CRE BSI frequently occurs in complex, critically ill patients. Source of bacteremia can be difficult to determine either because an individual patient has multiple potential sources, including intravascular catheters, or the patient may be immunosuppressed. When no source is found, these patients are deemed to have primary bacteremia.

In published studies and in clinical experience, primary bacteremia and catheter-associated bacteremia are common and associated with high mortality. In studies that report mortality for primary and catheter-associated bacteremia, we see a range of mortality from 32 to 79 percent.

Optimal treatment strategies for CRE have previously been defined by clinical experience and non-randomized observational data. The current treatment mantra for CRE has been combination therapy or double coverage. The original data comes largely from clinical experience of failures with monotherapy and meta-analyses of observational studies. You can clearly see the observed survival benefit of combination therapy in this reference.

Crafting a combination therapy regimen can be challenging. These are data from a national selection of long-term acute care hospitals. You can see here that fluoroquinolone resistance among CRE is 98 percent, essentially eliminating this class of antibiotics. Gentamicin or tobramycin resistance is again 98 percent; again, little use in treatment. Amikacin is slightly better at 66 percent, but that means it's an option for only about a third of patients.

Antimicrobial susceptibility of colistin and tigecycline are good, but these are considered agents of last resort. The PKPD profile of

tigecycline does not support its use for septicemia, and the FDA has a black box warning that tigecycline has poor efficacy and severe infections.

Colistin is an agent that was abandoned for decades due to known issues of toxicity, particularly nephrotoxicity. Dosing of colistin is challenging oftentimes requiring ID pharmacist help, and automated susceptibility testing for colistin is unreliable. Despite the known limitations of tigecycline and colistin, we see broad use of these agents simply because we've had nothing else for CRE infections.

The new beta-lactam beta-lactamase inhibitor combinations are recently approved CRE active agents that utilize novel beta-lactamase inhibitors to protect traditional beta-lactam antibiotics from inactivation. For example, beta-lactam protects ceftazidime and vaborbactam protects meropenem.

The audience should be aware that CRE can develop carbapenem resistance through one of two mechanisms. CRE can produce a carbapenemase. The

novel beta-lactamase inhibitors primarily target KPC. Carbapenem resistance can also develop through expression of a cephalosporinase in combination with a porin mutation or efflux pump overexpression, but the novel beta-lactamase inhibitors do not help in this second scenario.

While the newer BL/BLI combinations provide an option, particularly for KPC producing organisms, they have variable or no activity for the non-KPC CRE. Even for KPC, we've observed the emergence of resistance on therapy highlighting the need for additional agents. Unfortunately, non-KPC CRE appears to be on the rise. At ID week last year, LA County Department of Public Health presented data that more than 20 percent of their CRE isolates were non-KPC. In another report from Vancouver, greater than 90 percent of the CRE were non-KPC producers.

In summary, we recognize that there is unmet clinical need for ESBL treatment and CRE management. A reliable carbapenem sparing agent for ESPN infections has value from an antibiotic

stewardship and resistance perspective. In terms of CRE, a non-beta-lactam agent is a potential combination option with novel BL/BLI agents to prevent on-treatment emergence of resistance and as an alternative when novel beta-lactamases may not be the best choice, either for resistance reasons, deep salvage scenarios, or tolerability issues. In light of the high mortality and lack of effective treatment options, we need antibiotics for patients with these serious infections.

Thank you very much for your attention. I'll now turn the podium over to Kevin Krause.

Applicant Presentation - Kevin Krause

DR. KRAUSE: Thank you. My name is Kevin Krause, and I will now review some of the key microbiology and clinical pharmacology attributes of plazomicin. Plazomicin is a new aminoglycoside with activity against enterobacteriaceae, including isolates resistant to currently available aminoglycosides as well as ESBL producers and CRE. Plazomicin inhibited greater than 95 percent of enterobacteriaceae collected in global surveillance

studies at an MIC of less than or equal to 4 micrograms per milliliter, which is the tentative breakpoint applied during the plazomicin development program. In addition, plazomicin inhibited greater than 90 percent of enterobacteriaceae nonsusceptible amikacin, gentamicin, and/or tobramycin when applying this interpretive criteria.

Exposures associated with human doses prevent the emergence of plazomicin resistance in both in vitro and in vivo studies, thereby limiting the potential for clinical resistance development. And finally, efficacy has been demonstrated against target pathogens in a variety of animal models of infection.

Aminoglycoside modifying enzymes, or AMEs, which inactivate current aminoglycosides, are the most common form of aminoglycoside resistance. This mechanism is responsible for more than 99 percent of aminoglycoside resistance amongst enterobacteriaceae in the United States. AMEs are often found in combination with other resistance

elements such as ESBL and carbapenemases, making these isolates multidrug resistant.

Plazomicin was designed to overcome AME based resistance and therefore remains active against multidrug resistant enterobacteriaceae. A second less common mechanism of resistance is target-site modification due to 16S rRNA methyltransferases or RMTs. These enzymes result in pan-aminoglycoside resistance, including resistance to plazomicin. However, RMTs are rare and their prevalence is not increasing in the United States despite decades of clinical use of aminoglycosides. Specifically, only 5 RMT producers were found amongst approximately 6500 enterobacteriaceae isolates collected in the United States between 2014 and 2016 in the plazomicin surveillance program.

Here we show the structure of plazomicin with the major AME classes and their associated sites of action on most aminoglycosides. However, plazomicin lacks the 3-prime and 4-prime hydroxyl groups found in many aminoglycosides, which are

targets of several AMEs. In addition, the hydroxyethyl group at 6 prime position blocks the action of AAC 6-prime AMEs, and the HABA group at the N1 position blocks the action of AAC 3 AMEs as well as less common but clinically important AME classes.

As a result, plazomicin is active against multidrug resistant enterobacteriaceae, including aminoglycoside nonsusceptible isolates, ESBL producers, and CRE. In addition, plazomicin maintains inhibition of protein synthesis, the rapid concentration-dependent bactericidal activity, and the prolonged post antibiotic effects that are key features of the amino glycoside class.

We evaluated the activity of plazomicin against 6,459 enterobacteriaceae in prospective U.S. surveillance studies. Plazomicin was broadly active against these isolates within an MIC 90 of 1 microgram per milliliter. Plazomicin retained activity against isolates nonsusceptible to amikacin, gentamicin, and/or tobramycin, and this 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

aminoglycosides through co-expression of AMEs. As a result, only 67 percent of these CRE isolates are susceptible to amikacin, only 53 percent are susceptible to gentamicin, and only 13 percent are susceptible to tobramycin. However, plazomicin retains its potent activity against the CRE isolates because of its stability against AMEs. Overall, 99 percent of these CRE isolates were inhibited by a plazomicin MIC of less than or equal to 4 micrograms per milliliter.

Like other aminoglycosides, in vitro synergy between plazomicin and beta-lactams has been demonstrated against enterobacteriaceae. Here we show a synergy time-kill curve of plazomicin in combination with ceftazidime against a multidrug resistant Klebsiella pneumoniae isolate encoding an AME, a KPC, and an ESBL. As expected, ceftazidime alone was inactive.

When plazomicin was tested at a concentration of one-quarter of the MIC, bactericidal effects were not maintained through 24 hours. However, when plazomicin was tested at this

same concentration in combination with ceftazidime, an approximate 6 to 8 log improvement in bactericidal activity was observed at 24 hours compared to either drug tests at alone.

The potential for the development of plazomicin resistance was assessed in both in vitro and in vivo models. The enterobacteriaceae isolates were examined in an in vitro chemostat model to understand plazomicin exposures in relation to suppression of resistance development. At plazomicin AUCs of less than or equal to 66, which are well below those achieved with the clinical dose of 15 milligrams per kilogram, resistant isolates were selected with phenotypes similar to those observed in the in vitro passage selection studies demonstrating that these results could be recreated in this model. However, no resistant mutants were observed when exposures were increased to an AUC of 132 or more.

Therefore, the mean plazomicin AUC of 236 associated with the clinical dose is above the mutant prevention concentration. These results

correlate with the results of animal models of infection where no resistance was observed out to 96 hours when animals were treated with exposures at or near target exposures in patients.

In the phase 3 program, emergence of resistance to plazomicin was infrequent. No resistance development was observed amongst 44 plazomicin treated patients in study 007. In study 009, resistance development was observed in 7 post-baseline isolates from 6 of 191 plazomicin treated patients. Only 2 of these patients were clinical failures and only 1 required additional antibiotics

The majority of the recovered isolates had an identical genetic background to the baseline isolate with the addition of a plasmid containing multiple resistance elements, including an RMT. These isolates were found in patients from eastern Europe, which is a region known to have a higher prevalence of RMTs than any in the United States. Most of these isolates were recovered at or before the end of IV visit, suggesting that they existed

at baseline and represent outgrowth of a resistance subpopulation after rapid elimination of the susceptible bacterial population.

Now, I'd like to switch to plazomicin PK, PKPD, and nonclinical efficacy. Like other aminoglycosides, plazomicin has predictable and linear PK with low protein binding of approximately 20 percent. The plazomicin half-life is approximately 4 to 5 hours in the patient population studied with more than 97 percent of the dose eliminated via the kidney as unchanged drug. And finally, there is a low potential for drug-drug interactions as determined by a comprehensive preclinical package and data from a phase 1 drug-drug interaction study.

The proposed plazomicin dose is 15 milligrams per kilogram once daily administered as a 30-minute intravenous infusion for patients with normal renal function or mild renal impairment. As shown in this dosing table, dose adjustments are recommended for patients with moderate or severe 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

reduce the potential for toxicity due to overexposure.

Additionally, a plazomicin specific assay has been developed. Overall, these TDM based dose adjustments are intended to maintain exposures within a target range associated with efficacy while avoiding sustained high exposures that may lead to toxicity. As with other amino aminoglycosides, the ratio of the AUC to MIC is the PKPD driver of efficacy.

The probability of target attainment by MIC is shown here by the blue line for patients with cUTI when applying a stasis target. A stasis target is appropriate for use in cUTI because plazomicin concentrates at the effect site, and this infection type is associated with fewer comorbidities and low attributable mortality. These values are overlaid on the MIC distributions of enterobacteriaceae isolates collected from urinary tract infections during U.S. surveillance, shown in dark blue, and the baseline isolates from study 009, shown in light blue.

The substantial overlap in these data suggests that the isolates with the described clinical and microbiological outcomes from study 009 are similar to enterobacteriaceae collected from across the United States. These PKPD analyses show that there is a greater than 90 percent probability of target attainment in patients with cUTI due to enterobacteriaceae with MICs of less than or equal to 4 micrograms per milliliter.

A similar analysis was conducted for patients with bloodstream infections. In red is the probability of target attainment for the 1 log kill target, which is appropriate for patients with bloodstream infection when source control is challenging, when effective combination partner antibiotics aren't available, or in the presence of significant underlying comorbidities.

In blue is the probability of target attainment by MIC for the stasis target, which is appropriate for use in patients when used combination therapy or in the setting of available

source control. Both of these sets of data or overlaid on the MIC distributions of enterobacteriaceae isolates from bloodstream infections collected during U.S. surveillance, again shown in dark blue, and the baseline isolates from study 007 shown in light blue.

As with study 009, the isolates collected in study 007 have a similar MIC distribution with those from U.S. surveillance with the exception of the RMC containing isolates found in this clinical program that had MICs of greater than or equal to 128 micrograms per milliliter.

These PKPD analyses show that like cUTI, there's a greater than 90 percent probability of target attainment for patients with BSI due to enterobacteriaceae across the vast majority of the MIC distribution. These data support the adequacy of the plazomicin dosing regimen for target pathogens in these patient groups.

Additional support for the plazomicin dose comes from in vivo infection models where efficacy was established in various sites of infection and

evaluated using human simulated exposures. Initial investigations focus on efficacy against enterobacteriaceae, including aminoglycoside and/or carbapenem resistant strains in the mouse urinary tract, thigh, and lung infection models. These models were associated with reductions in bacterial burden against a diversity of isolates with various resistance mechanisms. Additionally, the efficacy of human simulated exposures of plazomicin were studied in a mouse model of septicemia caused by enterobacteriaceae with a range of plazomicin MICs.

This study was designed to provide supportive evidence to the clinical study data for the bloodstream infection indication and was consistent with observed plazomicin exposures and a probability of target attainment analyses. Overall, a single dose of plazomicin monotherapy at a human equivalent exposure led to significant improvements in survival up to 96 hours and rapid clearance of bacteremia. Dr. Dr. Friedland will discuss more detailed results of the study and the clinical efficacy section describing patients with

bloodstream infections.

In summary plaza, plazomicin is a new aminoglycoside that has potent activity against the majority of enterobacteriaceae, including most aminoglycoside resistant isolates, ESBL producers, and CRE. Plazomicin efficacy has been established in a number of animal models of infection, including in studies using human simulated exposures against target pathogens. Plazomicin pharmacokinetics are predictable and similar to those observed for the aminoglycoside class overall. And finally, the probability of target attainment calculated using plazomicin PKPD targets and Monte Carlo simulations shows that the plazomicin dosing regimen is expected to result in plasma exposures consistent with efficacy against target pathogens in cUTI and BSI patients. Similar results were observed when applying the recommended dose adjustments for patients with impaired renal function.

Thank you. I'll now turn the presentation 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

analysis populations was similar in the two treatment groups. 609 patients were randomized, 306 to plazomicin and 303 to meropenem. The most frequent reason for exclusion from the mMITT population was lack of a study qualifying baseline pathogen, which is common to cUTI studies. Approximately 64 percent of patients were included in the primary analysis population, the mMITT.

Patient demographics and baseline disease characteristics of the mMITT population overall was similar in the two treatment groups and consistent with an acutely ill population with cUTI. Patients were on average 60 years old and approximately 40 percent had acute pyelonephritis. Approximately 70 percent of patients had mild or moderate renal impairment at baseline, and 12 percent had concomitant bacteremia.

The duration of IV and oral treatment was comparable between arms. Patients received a median titled treatment duration of 10 days by which a median of 6 days were IV treatment. 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.

The primary endpoint of composite cure was assessed in important subgroups, and this forest plot shows differences between treatment groups at the test of cure represented by the blue circles with the 95 percent confidence intervals. Treatment differences directionally favorite plazomicin across patient subgroups such as age and renal function, and in both cUTI and acute pyelonephritis. Of note, the comparison favored plazomicin whether or not patients received oral switch therapy.

The most common bacterial pathogens where E. coli and Klebsiella, and approximately one-quarter of pathogens had an ESBL phenotype, and a similar proportion were nonsusceptible to other aminoglycosides. Per pathogen microbiological eradication rates were high for plazomicin across the most common species. Importantly, favorable eradication rates were observed for plazomicin in common resistant subgroups such as ESBL-producing pathogens and pathogens not susceptible to currently marketed aminoglycosides.

The high cure rates for plazomicin seen in test of cure were maintained at the late follow-up visit conducted at approximately 4 weeks. Both microbiological recurrence and clinical relapse were less common with plazomicin therapy than meropenem therapy, indicating that the benefit of plazomicin was sustained out to the late follow-up visit.

In conclusion, plazomicin was noninferior to meropenem based on the co-primary endpoints at day 5 and the test of cure, where the statistically higher response rate for plazomicin suggested at test of cure, which was maintained through the late follow-up visit. Subgroup analyses supported the primary plazomicin response observed. And finally, plazomicin demonstrated high eradication rates at test of cure compared to meropenem against the most common gram-negative pathogens, including important resistance subgroups. The outcomes are shown and support the benefit of plazomicin for patients with cUTI who have limited or no alternative treatment options.

Let me now review the data supporting efficacy in the BSI indication, including results of the 007 study, also known as CARE. study 007 was the first of its kind resistant pathogen focus study. It was intended to demonstrate superiority and be sufficient for registration. Data from that study demonstrated that plazomicin was associated with reduced mortality or significant disease related complications in patients with confirmed CRE BSI compared to standard of care agent colistin.

Despite concerted efforts, study 007 proved challenging to enroll. We screened over 2100 patients to randomize 39 over a two and a half year period, which is consistent with the experience of other sponsors conducting CRE studies. One of the most challenging barriers to enrollment is obtaining consent in critically ill patients. Other barriers include unpredictable changes in CRE prevalence, which can occur naturally or through infection control measures, and the time required for confirmation of CRE infection that can

disqualify patients due to early death or excessive prior antibiotic therapy.

In addition, towards the end of the trial, the prevalence of resistance to the comparator colistin was increasing at high enrolling sites. Given the limited size of the clinical data set that could be feasibly obtained in the key target population, the totality of the data generated in the clinical and nonclinical program must be considered.

The data I'll be sharing includes efficacy from the randomized cohort of study 007, which provides the primary clinical evidence of plazomicin efficacy in patients with BSI due to CRE, and study 009, the cUTI study, which provides additional randomized control data in patients with BSI from a urinary source. Further supportive clinical data derived from efficacy in the nonrandomized BSI subset from cohort 2 of study 007 and nonclinical efficacy from a mouse septicemia model. In all, clinical efficacy data were generated in more than 50 plazomicin treated

patients with enterobacteriaceae BSI from a variety of sources.

Study 007 consisted of two cohorts, cohort 1, a randomized, controlled, open-label cohort comparing plazomicin to colistin in patients with BSI or HABP/VABP due to CRE, and cohort 2, a single-arm cohort, which was added later in the study, allowing access to plazomicin therapy for patients not eligible for enrollment in cohort 1.

Patients with suspected or confirmed infections due to CRE were randomized 1 to 1 to plazomicin or colistin, each in combination with either high dose extended infusion meropenem or tigecycline as chosen by the investigator. Plazomicin 50 milligrams per kilogram doses was subsequently adjusted based on TDM to target the prespecified AUC range. In addition, colistin dosing was optimized, including the use of a loading dose.

Patients received 7 to 14 days of IV therapy with a test of cure visit approximately 7 days after the last dose of study therapy and end of

study visit at day 28, and a long-term safety visit at day 60. Study 007 was designed to demonstrate superiority of plazomicin compared to colistin in cohort 1 with a primary endpoint of all-cause mortality at day 28 or significant disease related complications.

Our original assumptions were that the event rate in the colistin arm would 35 percent with a 12 percent absolute reduction in the plazomicin arm. As agreed to with the FDA, in the context of the high unmet need for new treatments for MDR or enterobacteriaceae infections, superiority was to be tested against a one-sided alpha 5 percent corresponding to a 90 percent confidence interval. The results I'll be sharing with you today are descriptive in nature due to the smaller than anticipated sample size.

Thirty nine patients were enrolled in cohort 1; 18 patients were randomized to plazomicin and 21 to colistin. An additional 30 patients were enrolled in cohort 1. In cohort 1, all but one 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

had BSI, the general demographics for this subpopulation was similar to those in the overall patient population.

Here I'll focus on additional characteristics of importance for this key subpopulation of bloodstream infections. Consistent with the literature describing CRE BSI, primary bacteremia was common in both treatment groups. The urinary tract and abdomen were the most common sources of secondary bacteremia. Although most patients did have indwelling intravascular catheters, only one patient in each study arm had an intravascular catheter related infection.

Here are the results of the primary endpoints 28-day all-cause mortality or significant disease related complications and a key secondary endpoint all-cause mortality alone in both the full mMITT population and the BSI subgroup. In the full population, plazomicin based therapy was associated with a 26.5 percent absolute reduction in all-cause mortality or SDRCs. The majority of events were

driven by deaths with plazomicin demonstrating a 28 percent absolute reduction in 28-day all-cause mortality compared to colistin.

In the BSI subgroup, plazomicin based therapy was associated with a 39 percent absolute reduction in all-cause mortality or SDRCs and a 33 percent absolute reduction in all-cause mortality alone compared to colistin.

The 28 day all-cause mortality rate of 40 percent in the colistin arm is consistent with our assumptions and with outcomes described in the literature with this agent, suggesting that the comparator arm behaved as expected in this study. Because we are seeking a BSI indication, the remainder of my presentation will focus on additional outcomes in this patient population.

Analysis of mortality through day 60 revealed that separation between the two treatment groups was observed early in the treatment period and sustained throughout the study with plazomicin treatment associated with a lower rate of mortality through day 60 compared with colistin. The hazard

ratio of 0.37 in favor of plazomicin, represented a 63 percent reduction in the estimated rate of mortality in patients with BSI.

Plazomicin was also associated with faster median time to clearance of CRE bacteremia and a higher proportion of plazomicin treated patients had documented clearance of CRE bacteremia by day 5. No plazomicin treated patient had positive CRE blood cultures after day 10 compared with 3 patients in the colistin group. Consistent with results of the time to clearance of bacteremia analysis, the per pathogen favorable microbiological response at test of cure was higher for plazomicin at 93 percent versus colistin at 53 percent for CRE pathogens, including those nonsusceptible to currently available aminoglycosides.

A number of baseline factors were raised by FDA as having the potential to impact the primary outcome, so I will examine these in the next couple of slides. As expected, because of the time it takes to confirm CRE infection, receipt of

antibiotic therapy prior to randomization was high in both treatment arms. Based on susceptibility data, a lower proportion of plazomicin treated patients received potentially effective prior antibiotics suggesting the prior therapy received did not bias the study in favor of the plazomicin group.

As required by the protocol, all BSI patients had at least one positive blood culture in the 96 hours prior to randomization. However, as a result of prior therapy and the intimate nature of gram-negative bacteremia, some patients had negative blood cultures in the 24 hours prior to randomization. The proportion of such patients was balanced between the two groups.

Now, let's see how these factors impact the primary outcome. Whether patients received effective prior antibiotic therapy or not, the outcomes favored plazomicin. Similarly, the treatment difference favorite plazomicin regardless of the adjunctive agent received. Looking at the impact of negative cultures in the 24 hours prior

to enrollment that was observed in some patients, such patients in the colistin arm still had poor outcomes, suggesting that the short courses of prior therapy were insufficient to impact the primary endpoint.

Given that these factors were balanced by treatment group or favored colistin and the lack of clear impact on the treatment difference, none of these factors appear to meaningfully impacted the primary outcome or explain the large treatment difference observed in favor of plazomicin therapy.

Next, let's turn to the results from study 009, which provides additional efficacy data in patients with BSI from a urinary source. Approximately 12 percent of patients enrolled in the phase 3 009 study had bacteremia due to enterobacteriaceae at baseline associated with their urinary tract infection. In this subset of patients, plazomicin demonstrated early and sustained clearance of enterobacteriaceae from the blood with 88 percent and 100 percent documented clearance at day 5 and test of cure, respectively.

Next, I'll move to the results from cohort 2 of study 007. Cohort 2 patients reflected a more heterogeneous population than cohort 1 patients. Most were male and elderly with a wide range of APACHE II scores. Half of the patients had polymicrobial infection, including 4 patients with coinfections involving pseudomonas or acinetobacter, which are not target pathogens for plazomicin. Half were primarily BSIs and all secondary BSIs had a urinary source and 3 patients had intravascular catheter related infections. The majority again received tigecycline as adjunctive therapy.

In this the subgroup of BSI patients in cohort 2, the rate of all-cause mortality at day 28 or SDRCs was 36 percent with the majority of events driven by SDRCs rather than mortality. The rate of all-cause mortality alone, or 14 percent, is supportive of the 7 percent rate observed in cohort 1 plazomicin treated patients. All SDRCs observed were persistent bacteremia.

Additional supportive evidence of efficacy

in the BSI indication comes from data generated in a mouse septicemia model. This study evaluated survival using human simulated exposures in the treatment of mouse septicemia due to enterobacteriaceae. As demonstrated by the untreated control group, this infection is nearly 100 percent lethal in the absence of therapy.

Tigecycline was also poorly effective in this model even though all assets were susceptible, showing that this model can detect poorly effective therapies in septicemia. In contrast, substantial improvements of the 96 hours survival were observed in plazomicin treated mice compared with controls for organisms with plazomicin MICs of 2 to 4.

In conclusion, the totality of data including clinical outcomes data and more than 50 plazomicin treated patients with BSI provides substantial evidence of plazomicin efficacy. In the primary efficacy analysis of cohort 1 in study 007, plazomicin was associated with clinically meaningful improvements in mortality based endpoints compared to colistin. Due to the small

sample size in cohort 1, superiority could not be statistically confirmed. However, the large survival benefit in this limited data set should be considered in the context of the severity and rarity of CRE, BSI, and the lack of alternative treatment options for this patient population.

The mortality benefit of plazomicin therapy in study 007 was supported by the high and sustained bacterial eradication rates in patients with BSI, and similarly, bacteremia eradication rates were high in the subset of cUTI patients with concurrent bacteremia in study 009. Outcomes in cohort BSI patients as well as a mouse septicemia model provide additional supportive evidence of efficacy in BSI due to enterobacteriaceae.

I'll now hand it over to Dr. Connolly to present safety data.

Applicant Presentation - Lynn Connolly

DR. CONNOLLY: Thank you. I'm Lynn Connolly, and as the head of late development at Achaogen, I lead the clinical development of plazomicin from the end of phase 2 through the NDA

submission and review. I'd now like to present the safety data for plazomicin. I will first describe for you the safety profile of plazomicin in patients with cUTI based on pooled analyses of safety data from our phase 2 and phase 3 studies in this indication.

Pooling of data from the two cUTI studies was felt to be appropriate as these patients had the same infection types, similar dosing duration, and comparable safety assessments. I will then describe the safety profile of plazomicin in patients with serious infections due to CRE. Due to the relatively small numbers of BSI patients, data for all patients, irrespective of their baseline diagnosis, were included in this analysis. And finally, I will present an analysis of topics of special interest for the aminoglycoside class, namely nephrotoxicity and ototoxicity.

In the cUTI population, the median duration of IV study drug therapy was 5 days for both the plazomicin and comparator group, which included levofloxacin and meropenem. Across treatment

groups, approximately 90 percent of patients received 4 to 7 days of IV study drug therapy. In the 007 study, the median duration of IV treatment was 12 days in both groups with the majority of patients receiving 11 to 15 days of therapy. The differences in study drug exposure support separate analyses of the safety profile of plazomicin in these two distinct patient populations.

Here is an overview of the safety profile across the pooled phase 2 and phase 3 cUTI studies. The overall incidence of adverse events, adverse events leading to discontinuation, and serious adverse events were similar between plazomicin and comparative groups. A single death occurred in the plazomicin arm study 009. This patient was a 63 old woman who presented with hematuria and lower abdominal pain that was initially attributed to acute pyelonephritis. She subsequently died on study day 18 from metastatic uterine cancer that was discovered within 48 hours following enrollments. Plazomicin was discontinued after a single dose.

The patient also experienced a serious adverse event of acute kidney injury requiring hemodialysis. This event was ongoing at the time of death and was attributed to the patient's underlying malignancy by the investigator. The cancer, the acute kidney injury, and the death were all considered unrelated to plazomicin.

Here I'm showing you adverse events and greater than or equal to 2 percent of patients in the plazomicin group. Adverse events generally occurred with low frequency or mild to moderate in severity and were balanced between plazomicin and comparator groups with the exception of a higher rate of adverse events due to renal function in the plazomicin group. The types of events were typical of a hospitalized patient population with cUTI, with the most frequently reported events being decreased renal function, diarrhea, and headache.

The imbalance in events related to renal function is consistent with known toxicities of the aminoglycoside class. I will describe the nephrotoxicity risk in more detail, including tools

to mitigate this risk later in the presentation.

The incidence of serious adverse events was low and similar between the plazomicin and comparator groups. I'm showing you here only those events that occurred in two or more patients in either treatment group. All serious adverse events resolved or were resolving at the end of study with the exception of the ongoing acute kidney injury in the patient who died from metastatic cancer. The second serious adverse event of acute kidney injury in the plazomicin group occurred after a single dose of plazomicin, and the patient subsequently experienced full recovery of renal function.

Next, I'll turn to safety in the 007 study. In patients with serious infections due to CRE, plazomicin demonstrated a favorable safety profile, including a reduced incidence of nephrotoxicity compared to colistin. Because cohort 2 was a distinct patient population from cohort 2 and lacked a comparator, I'll focus this section on the patients in the randomized cohort.

As expected in this severely ill patient

population, nearly all patients experienced at least one adverse event, and the majority experienced at least one serious adverse event. In all categories, adverse events were generally lower or comparable in the plazomicin group relative to the colistin group. Fewer plazomicin treated patients died compared to colistin treated, and no deaths were deemed related to study drugs.

Here are the reported adverse events by preferred term that occurred in 10 percent or more patients in the plazomicin group. The briefing book includes additional details for events occurring in 5 percent or more of patients. In both groups, renal function events and sepsis where the most common events reported with a higher incidence reported in colistin treated patients compared to plazomicin treated patients. A higher proportion of the renal function events were considered related to IV study drug in the colistin arm.

Overall, fewer plazomicin treated patients 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

anytime post baseline. Most of these occurred while on IV study drug therapy. In the subgroup of events that occurred while on study drug therapy, the majority in the plazomicin group recovered by the end of therapy, and all but 3 patients experienced full recovery. Each of these 3 patients had additional ongoing risk factors for nephrotoxicity that potentially contributed to their serum creatinine increases, and none of these patients required renal replacement therapy.

We conducted additional analyses in the cUTI population to characterize risk factors associated with the development of nephrotoxicity. The risk factors identified are similar to those established for other aminoglycosides. The most important is baseline renal function. Moderate renal impairment at baseline had the strongest association with the subsequent development of serum creatinine elevations. Mild renal impairment was also associated with a slight increased risk for plazomicin treated patients versus comparator treated patients, while patients with normal renal

function did not appear to be at increased risk for nephrotoxicity with plazomicin therapy.

Similar to exposure response relationship established for currently available aminoglycosides, elevated Cmin or trough early in therapy was associated with an increased risk of nephrotoxicity, particularly in patients with renal impairment of baseline. Based on these data, therapeutic drug management targeting a Cmin value less than 2 micrograms per milliliter is recommended for cUTI patients with renal impairment at baseline to help mitigate the risk of nephrotoxicity.

Let's next examine nephrotoxicity in patients with serious infections due to CRE. Consistent with the lower incidence of adverse events related to renal function reported in the plazomicin group of cohort 1, the incidence of serum creatinine increases in the plazomicin group was lower than the colistin group both at anytime post baseline and while on IV study drug therapy. The single event shown here in the plazomicin group

in cohort 1 recovered by last visit compared to half of the events in the colistin treated patients.

Based on the associations observed in the development program and decades of clinical experience with other aminoglycosides, close monitoring of renal function while receiving plazomicin is recommended, particularly in patients with renal impairment. Particular care should be taken to ensure that plazomicin doses are appropriately adjusted based on estimated renal function, and therapeutic drug management for BSI patients and the subset of cUTI patients at increased risk of nephrotoxicity is also recommended.

Next, I'll turn to ototoxicity. We monitored for ototoxicity using both objective and subjective assessments. In phase 1 and 2 studies, we used the gold standard method, pure tone audiometry including high frequency audiometry in phase 1 to detect changes in cochlear function. Based on an independent audiologist review of this

data, a similar proportion of patients in each group or approximately 2 percent had changes in audiometry for its treatment related effects could not definitively be excluded.

In terms of subjective AE reporting, no AEs consistent with potential cochlear or vestibular toxicity were reported in study 007. The incidence of AEs associated with cochlear or vestibular function in the pooled cUTI studies was balanced and low across treatment groups.

In terms of the validated questionnaires used in study 009, no patients in either group met criteria for potentially clinically significant change in the hearing or tinnitus handicap inventories. One plazomicin treated patient demonstrated a potentially significant change at end of IV therapy in the dizziness handicap inventory. However, the DHI score returned back to the baseline value of zero at the next scheduled assessment.

Based on the data collected in the development program, we cannot exclude the risk of

nephrotoxicity with plazomicin therapy. Therefore, we recommend that when starting plazomicin, the risk-benefit profile for patients possibly at increased risk be considered. Based on established risk factors of the aminoglycoside class, these include patients with a family history of hearing loss and patients with renal impairment at baseline to minimize ototoxicity risks do not exceed the recommended duration therapy.

In conclusion, in patients with cUTI, plazomicin demonstrated a comparable safety to non-nephrotoxic comparators with the exception of a higher incidence of larger reversible nephrotoxicity. In acutely ill patients with infections due to CRE, plazomicin demonstrated a favorable safety profile, including a reduced incidence of nephrotoxicity compared to colistin, a known nephrotoxic agent. A small number of events potentially consistent with ototoxicity suggests the plazomicin carries this class associated risk. Taken together, the safety profile of plazomicin in both indications support use in patients with

limited or no alternative therapies.

That concludes the data portion of this presentation, and I'd now like to turn to some concluding remarks.

Applicant Presentation - Lynn Connolly

DR. CONNOLLY: You've heard from Dr. McKinnell that alternative therapies are needed for infections due to MDR enterobacteriaceae. There has been a steady increase in infections due to these pathogens including ESBL producers and CRE in the United States due to widespread use of broad spectrum antimicrobial agents. These infections are associated with poor outcomes largely due to limitations of currently available treatment options.

Older agents are associated with poor efficacy and safety profiles as well as established resistance. Newer BL/BLI agents are active against only a subset of isolates and are not indicated for use in all infection types, including the BSI. In addition, emergence of resistance to one of these agents has been described in clinical practice.

These limitations point to the need for additional antibiotic classes with clinical evidence of efficacy against these difficult to treat pathogens. Microbiological benefits of plazomicin include in vitro activity against strains resistant to currently available aminoglycosides and the fact that plazomicin is a non-beta-lactam agent with potent activity against a variety of ESBL producers and CRE. In addition, plazomicin demonstrates rapid bactericidal activity, including synergistic killing of bacteria in vitro when used in combination with beta-lactam agents.

Plazomicin has demonstrated clinical benefits in the treatment of cUTI, including cases caused by resistant organisms demonstrating noninferiority to meropenem on the primary end points as well as higher microbiological eradication rates for ESBL-producing pathogens and a lower risk of clinical relapse. Plazomicin demonstrated a similar safety profile to meropenem in cUTI patients with the exception of a higher

incidence of nephrotoxicity. Patient factors associated with this increased risk of toxicity have been identified and are the same as those associated with other aminoglycosides, which have been used clinically for many years. TDM guided dose adjustments for this at-risk patient population are designed to minimize the risk of this toxicity.

In regards to the BSI indication, given the challenges we have discussed in generating clinical data in the target patient population, we have asked that this indication be reviewed in the context of the life-threatening nature of CRE BSI and the lack of alternative treatment options for this limited patient population.

LPAD was created to provide an approval pathway for antibacterial drugs that treat infections such as CRE BSI where it is not possible to run traditional trials. While LPAD states that the statutory approval standard must be met, it allows for the approval of an antibiotic on the basis of a favorable benefit-risk profile even when

there is greater uncertainty about the evidence due to the small number of patients available for study.

We believe that the totality of the data package in support of the BSI indication provides substantial evidence of efficacy and safety for approval in this limited patient population at high risk of death. The primary evidence of efficacy for the BSI indication comes from clinical outcomes in more than 50 patients with BSI treated with plazomicin, including randomized controlled data.

Study 007 was designed to demonstrate superiority. Though the sample size is too small to confirm this statistically, the 33 percent absolute reduction in 28-day all-cause mortality for plazomicin compared to colistin is both clinically meaningful and compelling. The high and sustained rate of clearance of bacteremia with plazomicin provides a biological plausibility to the survival benefit observed.

In addition, supportive data from patients with bacteremia from a urinary source and an

expanded population with CRE BSI, combined with extensive in vitro data, evidence of efficacy from relevant animal models, and a high probability of target attainment at clinical exposures support the conclusion that the efficacy observed in the randomized cohort of study 007 was not by chance.

Plazomicin was also associated with an overall favorable safety profile compared to colistin with fewer SAEs, including those related to renal function and sepsis or leading to death. Notably, plazomicin was associated with a reduced rate of nephrotoxicity compared to colistin therapy.

Finally, TDM guided dose adjustments for this patient population are designed to maintain efficacious exposures while minimizing the risk of potentially toxic levels. In conclusion, there is an increasing burden of infections due to MDR enterobacteriaceae in the United States. Although we have seen recent approval of agents with activity against a subset of these pathogens, currently available treatment options continue to

have limitations. Based on the data presented here today, plazomicin demonstrates a favorable benefit-risk profile for patients who have limited or no alternative due to resistance, intolerance, or failure of other treatment options for cUTI and BSI.

Thank you for your attention. We're now happy to take your questions.

Clarification Questions to the Presenters

DR. BADEN: I would like to thank the applicant for presenting a tremendous amount of data very efficiently and clearly. We can now begin clarifying questions from the committee to the applicant. We have about 30 minutes at this time before the break. I will remind the committee to please remember to state your name for the record. If you can direct questions to a specific presenter, that will make it easier. I will start with the first question, although to the committee members, please get myself or Dr. Chee's attention.

We'll have a running list. If a line of questioning emerges, please indicate if you already

follow-on question so we can develop a thought as completely as possible while respecting the overall order of questioning. So I will start with the first question while we accrue the names of others.

In the two clinical studies 009 and 007, how were catheters handled, both urinary and intravenous?

DR. CONNOLLY: In both studies, catheters were to be removed before -- so in the case of the 009 study, catheters were to be removed before completion of therapy, removed or replaced. So they were to be removed.

DR. BADEN: So let me rephrase it. Not what was desired. What happened?

DR. CONNOLLY: Yes, of course. There was high compliance with catheter management in the 009 study. And I believe we have some specific information we can share. While we're waiting for that, I will speak to catheter management in the context of the 007 study. In the 007 study, if a catheter was present at the time that the patient presented, that catheter was to be removed. And

blood cultures qualifying the patients for enrollment were to be drawn either through a peripheral site or through the placement of a brand new catheter. And we will probably have more discussion around that.

In terms of the indwelling catheters in the 009 study, approximately 15 percent of patients in both treatment groups did have indwelling catheters at baseline. Of these 58 patients in total, albeit 8, so 6 in the plazomicin group and 2 in the meropenem group had documented replacement or removal of the catheter.

DR. BADEN: Dr. Venitz?

DR. VENITZ: I have some questions first related to the information that you provided on PK and then on the dosing strategies that you're proposing. Let me start with PK then. In your summary material, you're mentioning in your population PK analysis that you found volumes of distributions to be elevated in patients. Is that, first of all, correct?

DR. CONNOLLY: That's correct.

DR. VENITZ: Do you have any rationale, any explanation for that? Do you think that's an artifact of the analysis or do you think there's any biological reasons why the volumes doubled or tripled based on average?

DR. CONNOLLY: This is actually commonly observed in patients with infection, particularly the more serious infection types, that the volume of distribution is larger due to fluid shifts in these patients. And I would like to ask one of our experts, one of our clinical pharmacology experts, provide additional detail around that.

DR. BHAVNANI: Sujata Bhavnani from the Institute for Clinical Pharmacodynamics, consultant Achaogen. Our group developed the population PK model based on healthy volunteer data and the patient data that you've seen presented today. Specifically, with regard to your question about volumes, we did see an infection type difference that was applicable to the PK parameters. We can provide more information about these volume differences and estimates, if that would be

helpful.

DR. VENITZ: No, that's okay. I just wanted to confirm that I read it right. Now, just to follow up, did you see any changes in clearance in those patients not related their renal function?

DR. BHAVNANI: We also saw an infection related type effect on clearance parameters as well.

DR. VENITZ: And which way did it go and by how much?

DR. BHAVNANI: That I will need to provide more detail.

DR. VENITZ: Was it more or less than the kidney contributed to this variability in clearance?

DR. BHAVNANI: There was an increased clearance.

DR. VENITZ: Unrelated to their renal dysfunction.

DR. BHAVNANI: There was an increased clearance related to infection type, and we saw differences between patients with urinary tract

infections and bloodstream infections. And we can provide, again, more clarity around the direction relative to infection type.

DR. VENITZ: And which way would the half-life go? Would the half-life be prolonged than in those patients relative to healthy volunteers without infections?

DR. BHAVNANI: Well, the most important effect was related to clearance. So we, as you would expect, saw increased half-life in those renally impaired patients. But with regard to infection type again, just to get back to you, I will have to provide more information.

DR. VENITZ: Thank you.

DR. BADEN: One detail I can provide around the clearances, that it was increased by 13 percent in patients with acute pyelonephritis and then decreased by about 11 percent in patients with bloodstream infections.

DR. VENITZ: So relatively small compared to what the kidney contributes.

DR. CONNOLLY: Yes, it's relatively small

compared to the impact of creatinine clearance.

DR. VENITZ: All right. Maybe we can use slide CO-45 as prop, because now I want to discuss with you what you're proposing in terms of dosing strategy. So the first adjustment, if I understand you correctly, is at baseline, you're going to measure renal function creatinine clearance --

DR. CONNOLLY: Correct.

DR. VENITZ: -- and you're going to categorize the patients into three categories based on dosing interval and milligram per kilogram.

DR. CONNOLLY: Correct.

DR. VENITZ: Now, are you going to do any further renal assessments while they are on drug to adjust the dose?

DR. CONNOLLY: So we do recommend that renal function be assessed during the course of therapy, particularly in patients who have renal impairment at baseline. We are in the patients with cUTI recommending a trough based type of monitoring that could be used instead of creatinine clearance to adjust the dose if that trough is elevated.

DR. VENITZ: Have you actually done that? So my first question is that's what you're proposing, but what have you actually done and what are you proposing that hasn't been done yet?

DR. CONNOLLY: Exactly. So we actually specifically decided not to do TDM in the 009 study, and that was in conversation with the FDA, so that we could develop exposure-response relationships for plazomicin that could be used to provide rationale for TDM for this drug specifically. It wasn't felt to be appropriate to use other relationships from other aminoglycosides.

So this is why we didn't conduct TDM and why we enrolled patients with a broader range of renal function to allow for that type of variability so that we could identify both the risk factors and thresholds of concern to use for TDM based dose adjustments.

DR. VENITZ: Right. So that would be a second strategy for cUTIs, right?

DR. CONNOLLY: Exactly. That is correct.

DR. VENITZ: But if I understand you

correctly, you're saying you can either measure trough levels or you can measure renal function as a proxy. Is that what I heard you say?

DR. CONNOLLY: So we did use renal function to guide dose adjustments during the course of the study. So we know if we dose adjust with that type of strategy, we see that 7 percent rate of nephrotoxicity, and that is higher in patients with renal impairment at baseline.

So now that we have established a relationship between -- I'll go ahead and put this up. Te patients with lower renal impairment, we see that rate of nephrotoxicity, 14 percent in the moderates, 6 percent in the milds, is higher than what would be expected at baseline, so 4 percent. And that's using the creatinine clearance guided dose adjustment.

So consistent with other aminoglycosides, we've now established a relationship between trough and that increased risk of nephrotoxicity for those patients. So that's why we're suggesting for those patients, that trough be used in a similar manner

as it is used for other aminoglycosides to try and lower their exposures early on to prevent nephrotoxicity.

DR. VENITZ: Instead of having to do daily renal assessments for the purposes of the adjusting the dose.

DR. CONNOLLY: Right.

DR. VENITZ: And that makes sense to me. But let's look at the area method that you're proposing for the BSI.

DR. CONNOLLY: So the AUC based?

DR. VENITZ: Right. My first question is, you're right now proposing to take two samples, if I understand it correctly --

DR. CONNOLLY: That's correct.

DR. VENITZ: -- and use two samples to estimate the area under the curve.

DR. CONNOLLY: Yes.

DR. VENITZ: Any idea how well two points are going to predict the 24-hour area?

DR. CONNOLLY: Yes. So let me step back and provide some of the rationale for why we approached

dosing this way in the 007 study. When we began this study, we only had PK data from patients with urinary tract infections in normal healthy volunteers, but we knew that AUC was the driver of efficacy for these patients based on our preclinical models and lots of work done with aminoglycosides.

So the dose we chose was designed to achieve and AUC value projected to be associated with efficacy based on probability of target attainment analyses. And then because we suspected, based on what we've observed for other aminoglycosides, that we would see a lot of fluctuating PK in these patients, a lot more variability in PK. And PK that is not as easily projected simply by creatinine clearance, we wanted to have TDM in place to try and assure that those AUC values were maintained within a reasonable precision of that efficacy target for these patients.

So the TDM designed for these patients was largely to ensure that we didn't have wide 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

understand how the TDM predicted AUCs from those algorithms and compared those to the AUCs from the population PK model. And those shows good agreement in the predicted exposures from the algorithm based on those two time points, and then the AUCs that were achieved in the trial. And I could just show you some of the outcomes of the AUC across days.

So here you see we're targeting an AUC 262, as Dr. Connolly mentioned, and on day 1, we're achieving a mean of roughly 262. And then throughout the course of conducting TDM in this patient population, maintaining good AUC exposures around that time, and then also decreasing the variability in the exposures and the patient population.

DR. CONNOLLY: Thank you. I think one other --

DR. VENITZ: And just to make sure that I understand this table, this is the simulation that you run on your patients after the fact where you used your two point method to predict an area, and

then you use that area to adjust the dose on those various days. Is that what I'm looking at?

DR. SEROOGY: So this is population PK data, so it's the post hoc estimated exposures showing that as we utilize TDM in the course of this study, that we were able to maintain exposure, so showing that the algorithms providing the tool to adjust the exposures got us into a good exposure.

DR. VENITZ: But did you actually use the algorithm in this study or was this done all in silico?

DR. SEROOGY: The algorithm was used in this study.

DR. VENITZ: Okay.

DR. SEROOGY: So data was received for each patient back for those two time points. They were put into an algorithm based on the protocol, and then doses were adjusted within this study based on that algorithm.

DR. VENITZ: Okay. Thank you.

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

DR. LE: Yes. First, I wanted to go back on the volume distribution with that variability that you see in healthy versus the BSI patients. Did you consider the use of loading dose in this scenario?

DR. CONNOLLY: We did not consider use of a loading dose. Our initial dose is actually designed to try and achieve those efficacious exposures from the very beginning.

DR. LE: The second question I had relates to the use of Bayesian estimation for during the TDM process here. Generally, I wanted to see when you were conducting TDM by this Cmin versus AUC, was Bayesian estimation considered in the estimation of these exposures?

DR. CONNOLLY: One thing I can state, while Dr. Bhavnani comes to the microphone, we did consider developing like a Bayesian calculator, so taking advantage of the pop PK model to guide the dose adjustment. But the challenge that came with that was that would be considered an investigational device. We already had a second

investigational device that we were using in the context of this study, the TDM assay. So for study purposes, we did not use Bayesian estimation. We used these equations that were developed in order to estimate AUC.

DR. SEROOGY: I concur with Dr. Connolly.

DR. BADEN: Dr. Palevsky, you have a follow-on?

DR. LE: I have a few more related to this. For the nephrotoxicity margin, did you consider the use of renal biomarkers at all? Because there's the nag to creatinine ratio that has been studied for aminoglycoside class.

DR. CONNOLLY: Yes, but none of those have actually been validated for use in humans for this purpose. They're still considered experimental or investigational.

DR. LE: Okay. One other question relates to the toxicity as well. As a class, you mentioned on your slides in the BSI trial, that there were cardiac effects, which is not seen with the other aminoglycosides. For example, we saw 11 percent

hypotension, atrial fibrillation, and I believe 12.5 percent deaths on cardiac effects.

Can you elaborate on that more in terms of was it dose or exposure related?

DR. CONNOLLY: Sure. So let's start with the events of cardiac arrest. Those occurred in 007 study, and it's important to remember this is a patient population who is already hospitalized with significant comorbidities, often cardiovascular disease. Those events of cardiac arrest that occurred late in the course of that study, we followed out to day 60. So all but one of those occurred beyond day 28 well distant from the receipt of plazomicin therapy. In the eyes of the investigator, these were all considered unrelated, and as I mentioned, these were all elderly subjects with underlying cardiac disease. We have also conducted a dedicated TQT study with plazomicin where we do not see clinically significant effects or impacts on the QT syndrome.

In terms of the hypotensive events, what we observed in a phase 1 study, we had a small number

of subjects who did experience hypotension near or at the end of IV infusion, and this was associated with a 10-minute IV infusion. There wasn't a clear exposure-response relationship to those events, but we did decide because of that to increase the infusion duration to 30 minutes, which is more standard for other aminoglycosides, which tend to be 30 minutes to an hour.

Since we have extended that infusion duration, we have not seen additional events occurring around or near the end of infusion in plazomicin treated patients. We did see events of hypotension in the 007 study. Again, none of those occurred in relation to dosing, and in one of those patients, the event occurred in the setting of ongoing septic shock.

DR. BADEN: Dr. Palevsky?

DR. PALEVSKY: So I have a follow-up question regarding the TDM and the AUC method. The effect of kidney function on what the AUC curve is going to look like is going to be very dramatic, someone with normal kidney function versus someone

with markedly impaired kidney function. Have you figured out how one size can fit all in terms of the AUC with those differences? If you're aiming for similar peaks, you're going to get very, very, very, very different troughs, and therefore very different AUCs.

DR. CONNOLLY: Actually, this is part of the reason why we're not aiming for peaks and troughs because absolutely we do see more variation in those values, and also because those values, unless you precisely draw that blood draw at that peak or trough, you get misguided information. So actually we think that the AUC, even in these patients with renal impairment and varying renal function, can be estimated more accurately or precisely than either the trial for the peak.

DR. PALEVSKY: But if your dosing interval has to change, and if I read what your guidance is, you're going to have dosing intervals going out to 48 hours with patients with markedly impaired kidney function. How are you basing your dosing then on an AUC of 0 to 24 hours?

DR. CONNOLLY: I see. This is the Cmin guided dose adjustment for patients with cUTI. I'm just clarifying we're just AUC --

DR. PALEVSKY: Maybe I'm misunderstanding. You're dosing recommendation based on in a patient with markedly impaired kidney function, how are you going to change it?

DR. CONNOLLY: I think I understand now.

DR. PALEVSKY: So let's take the patient not on dialysis with an eGFR of less than -- or creatinine clearance of less than 15 with a bloodstream infection. Explain how you're going to dose that and how that compares to a patient who has normal kidney function.

DR. CONNOLLY: So that patient with that very low GFR would get that 10 milligram per kilogram dose and then have TDM conducted after that first dose to estimate the AUC. And we do provide instructions that if that dose -- if the adjusted dose required for that patient is either above or below 15, that we would also change the dosing interval.

I think for additional detail around this, I would ask one of our clinical pharmacology experts to come to the microphone.

DR. PALEVSKY: It might be helpful if you have curves of the different AUCs for those characteristics. Have you developed those?

DR. SEROOGY: This is Julie Seroogy, clinical pharmacology at Achaogen. For the different dosing intervals, there's a possibility for a patient to also go on q12 hour dosing. So we have different -- the second time point is different based on those patients. So that first time point is at 2 hours post- start of infusion, and the second time point is at 8, 10, or 18 hours post start of infusion.

So specific to your example where it's poor renal function on a q48 hour dosing, that patient would get a TDM sample collected at 2 hours and at 18 hours. There are three different algorithms based on the dosing interval, so it is normalized to that q24 hour AUC.

So based on the dosing that we've achieved

in the study, as Dr. Connolly mentioned, we're really targeting an AUC range consistent across renal function, so that's done with dose adjustments and duration adjustments. So what you see here in our phase 2 and phase 3 patients are observed AUC ranges based on renal function.

DR. CONNOLLY: I think I understand what you're getting at now as well, is that in that q48 hour dosing, that shape of the AUC means that it's front-loaded for those patients.

DR. PALEVSKY: Well, you have to maintain your level at a much higher level -- well, let me phrase it differently. To achieve the same AUC, since you don't have a steep decline, you're going to have a level that is, shall we say, more constant over time.

Is that what you're aiming for with this? This is a drug that has sustained killing after the level falls, as other aminoglycosides do, and maintaining a sustained level for a prolonged period of time may not make the most sense and may actually be augmenting toxicity.

DR. CONNOLLY: Yes, I see what you're saying. And I think the important thing to remember is this would only be used in a scenario where there's no alternative option. So we're not talking about broad use for patients. And then only for a patient like that, again, where there's no alternative option and where a physician can make that determination about whether that risk-benefit profile is appropriate for that patient.

DR. BADEN: It seems that more discussion, not necessarily at this table, need to go on about the dosing. The point is well taken.

Dr. Daskalakis, you had the next question.

DR. DASKALAKIS: I actually have two questions. The first is, could you share race and ethnicity data on your studies?

DR. CONNOLLY: Sure. We have a side that looks at race and ethnicity as included in our population PK model because that would encompass all studies. Within the context of the best model, we have included -- let me go ahead and just show

you the whole thing.

The majority, as you can see here, were white. Approximately 9 percent of patients were black or African American; 4 percent Asian. This American-Alaskan Native is unfortunately an artifact of the way data was collected in our phase 2 cUTI study where patients in Latin America marked the box Americas, which then mapped -- that's largely patients from Latin America in the American Indian-Alaskan Native. So this provides the information on race and ethnicity across studies, which were included in our final population PK model.

DR. DASKALAKIS: In your clinical 007 and 009 studies, specifically, could you show those data as well?

DR. CONNOLLY: Yes, so very few patients. The vast majority of patients in those studies were white. The patients with the more variability in race come largely from the phase 2 cUTI study and from one of our phase 1 studies, the TQT study actually.

DR. DASKALAKIS: And then one brief clarifying question. On slide 74, when you have the option of positive or no culture obtained, can you comment as to how many were positive and how many had no culture?

DR. CONNOLLY: Yes. Actually, they were about split in half, so we had a third positive, a third no culture, and a third negative at the time of enrollment.

DR. DASKALAKIS: Thank you.

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

DR. SCHAENMAN: Just a follow-up question regarding the race and ethnicity. Not only were the majority of the patients in 009 white, they were from eastern Europe.

DR. CONNOLLY: Correct.

DR. SCHAENMAN: That just seems unusual for a study that's spanning multiple continents. I was just wondering if the applicant could explain why the enrollment was so lopsided for what's a relatively common cause of complicated UTI in

nursing home patients in the U.S.

DR. CONNOLLY: Oh, certainly. So this is actually a very common issue in registrational studies in the cUTI indication. Several drugs who have recently come for registration have largely enrolled these studies in eastern Europe. Even though we had the same number of sites open in the U.S. as we had open at countries in eastern Europe, the enrollment is just different.

We do think that despite the low U.S. enrollment, the data collected can be generalized to a U.S. patient population, particularly because the primary analysis excluded pathogens resistant to study drugs, thus in voiding imbalances due to geographic differences in resistance. We also know that plazomicin is not metabolized. It's cleared by the kidneys. And in our pop PK analysis, which did have greater racial diversity than this 009 study, we did not see an impact of race on plazomicin exposure or clearance.

In addition, we do have some patients from the U.S., and that was large in the phase 2 cUTI

study. And this study does also illustrate the challenges we had in enrolling. Although we had a quarter of the number of patients enrolled in the phase 2 studies and the phase 3, it took more than twice as long to enroll. We had 78 U.S. patients actually in that study, and in terms of microbiologic eradication at test of cure, if we look in the ME patient populations, which are more similar, we saw similar response rates. So again, the phase 2 outcomes do support the notion that this data can be generalized to the U.s. population.

DR. BADEN: And a follow-on. In the 007 study, with enrollment largely coming from a relatively small geographic area, the isolates that were recovered, anything about them that makes them less susceptible to colistin or more homogeneous in their genetic background in terms of responsiveness to plazomicin?

DR. CONNOLLY: So in terms of plazomicin responsiveness, not particularly. So the majority of isolates and the majority of patients that was

driven by the epidemiology of CRE being very high in Greece, most of those are KPC producers. They mostly are the ST-258 background, and that is similar to what we see in the U.s. for CRE epidemiology.

DR. BADEN: And in relation to colistin?

DR. CONNOLLY: The relation to colistin, one issue we did encounter during the study, which led to our challenges in enrolling, is that over time, we began to see increasing resistance to colistin. So at certain sites, resistance rates as high as 40 percent. We have seen reports or heard of reports of colistin resistance rate as high as 20 percent in KPC producers in the U.S. at certain centers.

DR. BADEN: Dr. Green?

DR. GREEN: Thank you. Michael Green. I have a couple of questions relating to resistance that will have a general theme and maybe to the durability of the effectiveness of this drug. So my first question is I believe you provided some data that amongst NDM producing carbapenemases,

only 66 percent of the isolates were susceptible I guess at baseline to plazomicin.

Have you characterized that mechanism of resistance?

DR. CONNOLLY: Yes, we have. In NDM producers from certain geographic areas tend to also carry a ribosomal methyltransferase. So in those NDM producers that are not susceptible to plazomicin because of the ribosomal methyltransferase, that renders them resistant to all aminoglycosides.

DR. GREEN: And to clarify, is that gene located on a transposon or plasmid, or is it chromosomally based?

DR. CONNOLLY: Generally, these are plasmid mediated.

DR. GREEN: Okay. Then the second question that I have is, do you understand why plazomicin doesn't work against pseudomonas, thetamonas [ph], and acinetobacter?

DR. CONNOLLY: Sure. We suspect this is due to efflux permeability issues with those pathogens.

So the plazomicin MICs for those organisms are actually fairly similar to other aminoglycosides. And the issue there usually is related to simply uptake or penetration of the drug into those pathogens.

DR. GREEN: And then I guess the follow-on question to those is in terms of durability, particularly for plasmid mediated resistance, I know that you're going to restrict -- your labeling is going to suggest restricting. And hopefully antimicrobial stewardship, with the increased attention it's getting by Joint Commission, CMS, is going to work. But I mean, I guess one wonders what the durability of effectiveness will be when it is a mechanism that is easily -- since it's plasmid based, resistance that's plasmid based transmits in hospitals that are pretty high rate and transmits between hospitals at a pretty high rate. So I don't know if you've had any speculation on that.

DR. CONNOLLY: No. Sure. Absolutely. I think when we look at the data that we have for the

U.S. over our three-year surveillance period and over 6,000 isolates, we found only 5 RMT producers. And that is despite decades of use of aminoglycosides in the U.S., which should be able to -- any aminoglycoside should be able to select for an RMT producer.

So we think the differences between places like the U.S. and eastern Europe where we see higher rates of resistance in general to aminoglycosides and where we picked up some of these, is that massive burden of aminoglycoside use. And I can show you some data.

This is publicly available data from the European centers for disease control and prevention. If you look across Europe at the countries that have these high rates of aminoglycoside resistance, there is a correlation with aminoglycoside consumption. So these are countries where aminoglycosides are being used more as frontline agents for multiple infection types. So one issue that we think will limit the emergence of resistance is the way that these drugs are used

and that we propose plazomicin be used in a very limited patient population.

In addition, another difference may be infection control procedures that may differ between the U.S. and some of these other places where we see very high rates of resistance.

DR. BADEN: Thank you. We will now take a 10-minute break. Panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. We'll resume at 10:52 with the agency's presentations.

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

DR. BADEN: We will now proceed. I just wanted to have a comment towards the end of the last session. There are many more questions from the committee members for the applicant. We will resume with the further clarifications after the agency's presentation and clarifying questions with the agency, and then we will resume the many other questions and clarifications that the committee would like.

So we will now proceed with the FDA presentations.

Dr. Sun?

FDA Presentation - Hengrui Sun

DR. SUN: Thank you for the opportunity to present on the efficacy of plazomicin for the treatment of complicated urinary tract infection. I will discuss the design of study 009, followed by patient disposition, demographics, and the baseline characteristics. Then I will present efficacy results and provide a summary.

This was a phase 3 randomized, double-blind, noninferiority trial to compare plazomicin and meropenem regimens for the treatment of a cUTI, including acute pyelonephritis. Patients were randomized 1 to 1 to plazomicin or meropenem group to receive IV therapy. After a minimum of 4 days of blinded IV therapy, there was an option to switch patients to open-label, oral levofloxacin for an additional 3 to 6 days to complete therapy. The maximum duration of therapy was 7 days. Clinical response and in a microbiological response

were assessed at day 5, end of IV test of cure, and late follow-up.

The co-primary endpoint were the composites of microbiological eradication and the clinical cure rate at day 5 or at the end of ivy you patients stops ivy before or on day 5 or at end of IV if patient stops IV before or on day 5, and at ToC visit. The term co-primary for this study means that noninferiority needs to be shown with the primary endpoint at both day 5 and in ToC in order to conclude efficacy.

The results of the composite endpoint was defined so that the worst response from the two components would be the result of the composite. For example, if either clinical or microbiological endpoint was a failure, then the composite would be a failure. Another example, if one endpoint was a success and the other was indeterminate, then the composite would be indeterminate.

The primary analysis population was the microbiological modified intent-to-treat population, which was defined as all randomized

patients who received any dose of study drug and have at least one qualified baseline pathogens. The pathogen needs to be susceptible to both plazomicin and meropenem.

The prespecified NI margin was 15 percent on the risk of difference scale, which is wider than the 10 percent margin recommended in FDA guidance for cUTI. This was agreed by the agency because this is an unmet need. For each of the two treatment groups, cure rates were computed. The difference of the cure rates in 95 percent confidence interval were calculated using continuity corrected disease statistics.

A total of 6 009 patients were randomized to the study, and the mMITT population included 388 patients with 191 in the plazomicin group and 197 in the meropenem group. About 99 percent of patients completed the study in both groups. For the patients who discontinued study drug early, the reasons for the premature discontinuation was generally comparable between the two groups.

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

IV therapy, the second column is for oral therapy, and the last column is for the total duration of therapy. The distribution is generally comparable between the two groups.

Results for the primary efficacy endpoint at day 5 in ToC are shown in the table. Again, for patients who stopped IV before or on day 5, end of IV response was used as day 5 response. Response at ToC reflects the treatment effect of both IV and oral therapy. Compared to the prespecified NI margin of 15 percent, both lower limits of the 95 percent confidence intervals at day 5 in ToC were larger than NI margin.

For this analysis indeterminate outcomes were treated as failure. To see whether the results are sensitive to the handling of indeterminate data, we conducted additional analysis that treat indeterminates as failure in the plazomicin group and as a success in meropenem group. Results of this analysis are not shown here. They also supported the noninferiority of plazomicin to meropenem.

The forest plot shows the risk difference in 95 percent confidence interval and each of the visits for the composite endpoints in the two components, which are the clinical response and the microbiologic response. The two blue boxes indicate the co-primary efficacy endpoint. The numerical values are in the table above. The red vertical line represents the 15 percent margin. From the plot, we can see that the composite results were driven by the microbiological response.

This table shows the microbiological eradication rates at ToC by baseline pathogen in mMITT population. The numeric value of the eradication rates for plazomicin group are generally higher compared to the meropenem group. The forest plot shows the results for the composite endpoint at day 5 and ToC for some important baseline subgroups in mMITT population. The results are generally consistent across the subgroups.

Since the maturity of patients were from

region 2 and white, subgroups of region and the race are not included in the plot. Also, because the sample size for some of the subgroups were are small, we observed the wider confidence intervals for those subgroups; for example, patients with indwelling catheter or with diabetes.

To summarize, study 009 results supported the conclusion that a plazomicin regimen is noninferior to a meropenem regimen based on a prespecified NI margin of 15 percent. The efficacy findings were robust to the handling of indeterminate data. This study was mainly conducted in eastern European countries in white patients.

My colleague Dr. Rubin will discuss the efficacy for the study of bloodstream infections. Thank you.

FDA Presentation - Daniel Rubin

DR. RUBIN: Thank you for the opportunity to present on the efficacy of plazomicin for the treatment of bloodstream infections. I will discuss the design and results of study 007,

statistical issues limiting superiority conclusions, an alternative analysis and consideration of noninferiority, and provide a summary.

This was a randomized, open-label comparison between plazomicin and colistin regimens for the treatment of infections due to carbapenem resistant enterobacteriaceae. In the original study design, this was to be a superiority trial. The original primary endpoint was day 28 all-cause mortality. Key secondary efficacy endpoints were clinical response at a test of cure visit approximately 7 days after the end of therapy, day 14 all-cause mortality, and time to death through day 28.

The primary analysis population was the microbiological modified intent-to-treat population with CRE confirmed by a central laboratory. The originally planned sample size was 286 patients in this primary analysis population with confirmed CRE. The superiority testing was to be at the one-sided 0.05 statistical significance level rather than the usual two-sided 0.05 level.

We agreed with the significance level because of the high cost of failing to detect an effective treatment in an unmet needs setting. In addition, a trial providing some evidence of superiority to colistin likely would provide persuasive evidence of superiority compared to a hypothetical placebo.

We agreed to several features of the trial because this was a superiority design. These features included the combining of patients with serious diseases of BSI or HABP/VABP. Patients could be enrolled if they had a positive culture in the 96 hours before randomization even if they had negative cultures immediately before randomization. Prior antibacterial therapy could be given for up to 72 hours. Concomitant meropenem or tigecycline was to be given for the entire 7 to 14 day duration of therapy to provide additional CRE coverage. Patients who were enrolled with unbeknownst colistin nonsusceptible infections could be included in the primary analysis. In addition, the intention-to-treat efficacy analysis did not

consider study drug discontinuations.

There were two protocol amendments in this study. The first changed the primary endpoint from day 28 all-cause mortality to a composite of either day 28 all-cause mortality or significant disease related complications. The second protocol amendment added an uncontrolled cohort to make plazomicin available to patients who were ineligible for randomization.

There were enrollment challenges in this trial. The study was halted after two years due to the pace of enrollment, and the final sample size was 37 patients in the primary analysis population of the randomized cohort. This was much smaller than the originally planned sample size of 286 patients.

The statistical analysis plan was finalized after enrollment had completed, but before the sponsor became unblinded to results of this open-label study. It stated that "while the protocol specified primary and secondary endpoints 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

bottom most infection site boxes, you can see that in the colistin group, there were 15 patients with BSI and 5 with HABP/VABP, and in the plazomicin group, there were 14 patients with BSI and 3 with HABP/VABP.

This table shows demographics in the primary analysis population of the randomized cohort, which includes both BSI patients and HABP/VABP patients. Due to the small sample size, the colistin and plazomicin groups were imbalanced on some baseline factors. For instance, the colistin group was 50 percent male and female [sic], while the plazomicin group was 70 percent male. The study was mostly conducted in Greece. The colistin group had 3 patients from sites in Italy and Turkey and none from the U.S., while the plazomicin group had one patient from the U.S. and none from Italy or Turkey. Most patients in each treatment group were over 65 years old.

As previously mentioned, there were 29 BSI patients and 8 HABP/VABP patients. The inclusion 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.

For each primary endpoint, the one-sided p-value was slightly above 0.05, and thus plazomicin would not have met criteria for declaring statistically significant superiority under either the original or amended protocol. The lower 90 percent confidence limits for differences in event rates were near zero. Note that the 90 percent confidence interval for the day 28 all-cause mortality treatment effect exceeded zero even though the one-sided p-value was above 0.05. This was due to different methods being used to construct the confidence interval and p-value.

There were only two patients in each group who survived with a failure triggered by a significant disease related complication. The two colistin group patients had persistent bacteremia and the two respective plazomicin group patients had persistent bacteremia and septic shock.

Here are results for the three key secondary efficacy endpoints. Rates of clinical care were 35 percent in both the colistin and plazomicin groups. 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

the original all-cause mortality endpoint, the results would have been near the boundary of superiority. Uncertainty was expressed using 90 percent confidence intervals. Finally, there is an issue with multiplicity when considering two primary endpoints and the BSI subgroup. Focusing on particularly favorable results such as the apparent mortality benefit in BSI could unduly favor plazomicin.

This figure shows the design for cohort 2, which was the uncontrolled cohort. Patients could have BSI, HABP/VABP, cUTI, and were all to be treated with plazomicin. There were 30 patients enrolled. All were enrolled in Greece, and like the cohort 1 patients, they had significant comorbidities, and 27 of these 30 patients had confirmed CRE infections, which were all due to Klebsiella pneumoniae. Of the 27 patients with CRE, there were 14 with BSI, 9 with HABP/VABP, and 4 with cUTI.

The mortality results for the uncontrolled 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

superiority design.

Our rationale was that this was the closest achievable to having the statistical protection of prespecification and represented an analysis of a mortality driven endpoint and a BSI driven study population. Drawbacks to this analysis were that the disease related complications in the composite might make this a less meaningful endpoint than mortality, the applicant is only seeking an indication for the BSI subgroup, and it is possible to envision more efficient analyses.

Here are the results of our analysis. The 95 percent confidence interval provides evidence that the plazomicin efficacy decrement compared to colistin for day 28 all-cause mortality, or significant disease related complications, is no worse than 6 percent. The question then becomes whether one can conclude that plazomicin is effective based on this comparison to colistin.

There are several reasons why noninferiority might be considered. The lower confidence limit of negative 6 percent was based on conservative

choices in that other choices for the endpoint and analysis population would have been more favorable to plazomicin. In addition, so called exact 95 percent confidence intervals are also conservative in that they will tend to cover the true treatment effect in more than 95 percent of repeated trials. In addition, noninferiority could still, in principle, imply a favorable benefit-to-risk profile if a very small efficacy detriment was counterbalanced by much better safety than colistin. However, any nontrivial increase in mortality risk would likely offset improved rates of reversible nephrotoxicity.

There are limitations of noninferiority analysis. An efficacy conclusion based on noninferiority would require reasonable confidence in there being a large effect of colistin beyond a hypothetical placebo in the setting of this study. There are limited data with which to quantify this colistin effect. Further, no noninferiority margin had been prespecified for this trial, although from a statistical perspective, this is an issue of

regulatory best practices rather than statistical multiplicity.

In addition, several design features that I will discuss in more detail on the next slide were agreed to when planning a superiority trial and may have impacted the magnitude of the colistin effect.

To further assess noninferiority, here are selected baseline characteristics in the primary analysis population of the randomized cohort. There are several types of patients who were enrolled in whom one might not expect an extremely large difference between colistin and a hypothetical placebo. There were only 4 patients in each group with bloodstream infections who had positive CRE blood cultures in the 24 hours before randomization. My colleague Dr. Mishra will describe this issue in more detail in his assessment of causality from examining the individual cases.

You can also see from this table that most patients received more than 36 hours of prior antibacterial therapy. From the third set of rows

in the table, it has been mentioned that all subjects were to receive concomitant meropenem or tigecycline for the duration of therapy. The last row in the table shows that 12 patients had colistin nonsusceptible Klebsiella pneumoniae.

Here are results for the primary endpoint of day 28 all-cause mortality or significant disease related complications in these subgroups. There were no notable patterns between the timing of baseline cultures and efficacy outcomes. In patients with longer durations of prior therapy, the plazomicin group had numerically better outcomes. From the third set of rows in the table, there was no noticeable impact of concomitant meropenem or tigecycline, but it's unknown what would have occurred had this double coverage been withheld. Finally, from the last row in the table, you can see that the plazomicin group had numerically better results than the colistin group in patients with colistin nonsusceptible klebsiella.

Nonadherence can also impact noninferiority

analysis. There were two patients in each treatment group with very early study drug discontinuations. The two patients in the plazomicin group discontinued on day 1 due to microbiology indicating aminoglycoside resistance and switched to regimens that included polymyxin therapy, but were counted as successes for the plazomicin group for both primary endpoints. The two colistin group patients with early discontinuations both died and were counted as failures for the colistin group.

This table shows that if excluding the two plazomicin patients who discontinued on day 1 from this small study, the confidence intervals and p-values become slightly less favorable to plazomicin.

To summarize efficacy, numerical trends favored plazomicin compared to colistin. There are statistical limitations to concluding that plazomicin has superior efficacy, including the small sample size, use of descriptive statistics and multiplicity from consideration of two primary

endpoints in the BSI subgroup. A conservative analysis is to focus on the primary endpoint and analysis population from the final protocol using 95 percent confidence intervals.

This provides evidence that the difference in rates of day 28 all-cause mortality, or significant disease related complications between plazomicin and colistin is no worse for plazomicin than 6 percent. However, noninferiority assessments are complicated by design features agreed to when planning a superiority trial. This summarizes our assessment of the statistical evidence of efficacy from this trial

My colleague Dr. Mishra will now discuss additional clinical analyses of both efficacy and safety. Thank you.

FDA Presentation - Shrimant Mishra

DR. MISHRA: Good thing is that it's summer outside, but it's still winter in this room. I should have brought my snuggie.

(Laughter.)

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

bit about the clinical review issues that came up with this NDA. I'm the main clinical reviewers. I'm just going to highlight some of the main points that we found that led to a little bit of concern about the data with the BSI indication.

Because there was a very small sample size for the BSI trial, particularly in cohort 1, we were actually able to look at all the case report forms pretty extensively. Besides just looking at the basic demographic comparisons, we were actually really able to look deeply into the blood culture records. We were able to look at the presence of lines and when they were changed. We were able to look at the source workup, dates of the study drug administration, any prior drug therapy classification, and success and failures. So we were really able to take a very comprehensive look at each of the individual cases.

What we found were two main issues. The first was there was uncertainty regarding this definition of primary bacteremia. If you look at the protocol, it very clearly outlines these

definitions, what's a primary bacteremia, what's a secondary bacteremia, what's a central line associated bacteremia? And this is all documented in the CRF.

What's missing is there was really no standardized procedure for source workup, and there may be practicality issues associated with that. But what happens is you actually have investigators who sort of did different things when they were doing their workup. So what you might have as you might have bacteremias that were defined as primary despite a fairly limited workup.

Here are two examples. There was a subject who had a femoral line in. Their only qualifying culture was a peripheral culture, which is one set. There's none taken from the femoral line, and the patient sort of characterizes as a primary bacteremia.

In another case, you have a subject with Klebsiella pneumoniae from the catheter as well as from a peripheral culture, and here is sort of a converse issue. The patient is actually still

called the primary bacteremia, and that's primarily because there were some different resistance patterns between the Klebsiella and the [indiscernible] in the peripheral culture.

So there's a little bit of uncertainty regarding these primary bacteremias. Again, this just shows you the protocol definitions that they had. And again, if you look at the central line associated BSIs, the one thing that you'll note is, typically these are defined you have to obtain either blood or catheter site exudate cultures or blood or catheter tip culture, central line and peripheral cultures that match with timing as well as in terms of differentials in colony counts.

This really is very dependent on the investigator actually obtaining this information, so what I want to show you is that we did have, again, limited source determination. So of the 14 subjects in the plazomicin arm who had BSI, 10 of them were counted as having primary bacteremias. In the colistin arm, again, of the 15 subjects who had BSI, again, 10 of them were counted as having

primary bacteremias. And if you look at the workup, at least in the plazomicin arm, 5 out of 10 of those subjects had a line, had peripheral cultures, but they really weren't done in conjunction, and yet they were called primary bacteremias.

In the colistin arm, it's even more so; 9 out of the 10 subjects had a line in, and line and peripheral cultures were not done in conjunction, and they were still called primary bacteremias. Again, this is just looking at one aspect of source workup, but again led to considerable uncertainty in how to categorize these cases.

The second main issue that we determined was beyond this issue of categorizing the bacteremias was whether some of these patients were actually bacteremic at all at baseline. In several subjects, when we looked at their CRFs, we found that in the plazomicin arm, 8 of the 14 cases, so 57 percent, and at least 3 of the 15 cases in the colistin arm , 20 percent of subjects, had negative 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

death or significant disease related complications. So we're counting all these patients as success when there's a little bit of uncertainty in terms of how infective the patient was at baseline. And you see a similar thing at the lower level with colistin patients.

Now, the sponsor has pointed out that despite whether you start with negative cultures on day 1, that's still the colistin arm still seems to have a higher rate of bacteremia as the study goes on. The one thing that I'll say is that those patients are a little bit difficult to interpret. If you look at some of these patients, they may have become transiently bacteremic for one day and there's no change in therapy. So to call those patients failures strictly on a basis of a positive culture down the line is I think a little bit tenuous. But it also still just doesn't answer the central question of you have a significant group of patients in the plazomicin arm who essentially remained negative throughout the entire study, and what do we do with those patients?

So to just quickly summarize, again, I'll just point out what my colleague Dr. Rubin said. The bottom line is the noninferiority assessments, they're complicated by design features that greet you in planning a superiority trial. So here we have this confluence of events, where we have a very small sample size that could lead to heterogeneity both in measured and unmeasured factors. You have the complication of prior therapy, and you have the heterogeneity in terms of how these patients were worked up leading to complications and uncertainty interpreting the data.

FDA Presentation - Shrimant Mishra

DR. MISHRA: I will now I guess hand it over to myself --

(Laughter.)

DR. MISHRA: -- to go into safety. A lot of the safety data has already been presented by the sponsor, and some of the other safety issues are going to be presented by some of the agency colleagues a little bit later, particularly related

to the nephrotoxicity and trough issues. So I'm just going to give a very brief overview of the clinical safety data and just highlight some of the things that we saw.

Again, we're going to just quickly talk about a drug exposure, the safety population, demographics, major safety results, and of course drug associated adverse events of interest in the aminoglycoside class, nephrotoxicity and ototoxicity.

As has been noted before, there were 6 phase 1 studies. Four of them, the clinical study reports came to us prior to the NDA submission, and this was, again, two studies in healthy volunteers that were primarily PK safety studies. There was a study in subjects with renal impairment, and there was a thorough QT study. And there were two more studies that were done, and we received the final report after the NDA submission, and these were studies looking at the mass balance as well as a drug interaction study with metformin. There's one phase 2 study in complicated urinary tract

infection, as already been discussed, and there were two phase 3 studies of complicated UTI as well as blood bloodstream infection.

I'm going to focus primarily on the phase 2 and 3 safety findings primarily in complicated UTI. I think it's been discussed earlier the bloodstream infection safety information, first of all, it's a very small sample size, and the subjects are heavily confounded by a lot of their comorbidities, which make interpreting safety data in that population a little bit more difficult. So again, I'm going to focus primarily on the phase 2 and 3 safety findings in cUTI.

We look at drug exposure. Basically the highlights to note here is that in the phase 3 studies and phase 2 cUTI studies, there was roughly 377 patients that were exposed to the 15 mg per kg dose. In the phase 3 BSI studies, there were 48 subjects that were exposed to the 15 mg per kg plazomicin dose. And there were several subjects in the phase 1 studies as well.

Again, looking at drug exposure, again,

these are not subjects who really take a aminoglycosides for a long period of time. The median duration of treatment in cUTI trials was 5 days. It was a bit longer in the BSI study. The median duration of treatment was 12 days, but by and large, the duration of treatment for these subjects with aminoglycosides is a little bit less than what we might see in clinical practice, so it's good to interpret the safety data in that context.

If we look at the subject disposition in the phase 2 and 3 cUTI trials, a quarter of the patients in the phase 3 trials in both arms discontinued IV study drug. And again, as that has been noted, that's primarily due to a lack of study qualifying pretreatment baseline culture. So this may be a subject who may have had a COAG negative staph only in their culture or streptococci only in their urine culture or had a negative urine culture. So they were discontinued from treatment. However, it's important to note that even though there was this discontinuation from study

treatment, roughly 98 percent of subjects in all the arms in and the phase 2 and phase 3 studies continued their visit out to the late fall.

Subject disposition in the BSI trial, again, you had a quarter of subjects discontinue IV study drug in the plazomicin arm, a third in the colistin arm. And the most important thing to note here is that the discontinuations were for slightly different reasons. In the plazomicin arm, it was primarily due to adverse effect or a concern about resistant pathogens, whereas in the colistin arm, it was primarily due to an insufficient therapeutic effect as well as death. Now, of course, these are very small numbers, so again, you have to view these numbers with caution. But anyway, these were the trends.

Now, if we look at following out patients out to day 60, obviously death was primarily the major reason for withdrawing from the study, and you saw that that happened more in the colistin arm.

I briefly just want to point out the

demographics of the phase 2 and phase 3 cUTI trials. And again, although the sponsor has pooled the safety data, again, we elected not to do that. And the reason why is the demographics of the two studies are different in our view. If you look at the 002 study, again, most of the patients came from both Asia as well as Latin America, whereas if you look at 009 study, almost all the patients came from eastern Europe. So obviously, that led to a little bit of differences in terms of racial makeup in the two studies.

Also, 002 study, the vast majority of patients were below the age of 65, whereas if you look at the 009 study, the patients were split more evenly between younger and older patients. Again, if you look at infection type, you see that the 002 study primarily skewed toward acute pyelonephritis, whereas in the 009 study, you saw more complicated UTI patients that were enrolled. So because of these differences, we elected not to pool the safety data for these two studies and look at them individually.

As has already been mentioned, there was only one death in the phase 2 and 3 cUTI trials. Again, this involved a patient, a 63-year-old woman admitted for pyelonephritis. She received a dose of plazomicin. This was discontinued from the study drug due to acute kidney injury, and then switched to piperacillin and tazobactam, and then meropenem. At the time of discontinuation, she was found to have metastatic uterine cancer with possible involvement of the lungs and liver. She went on hemodialysis, but on day 17 she refused, and she died the following day.

So we tend to agree with the sponsor that this patient had significant comorbidities that probably led to her death. Of course, we can't fully exclude an effect of plazomicin given its potential nephrotoxic effects and given that the patient had acute renal deterioration at the time of her death. But again, we would agree with the sponsor that there were significant comorbidities involved in this patient's death.

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

again, most of the deaths are related to either newly acquired or prior existing infection, or to end-of-life events like cardiac arrest and cardiorespiratory arrest. If you look at serious adverse events in the phase 2 and 3 cUTI trials, the one thing that we want to note is that, actually, the serious adverse event rate is very low. In terms of the plazomicin arm, really, the most noticeable thing is that there were a couple of serious adverse events related to acute kidney injury, again, highlighting the potential nephrotoxic effects of this aminoglycoside.

Now, if we look at treatment-emergent adverse events that are related to plazomicin in the phase 3 cUTI study, they fall into three categories. The first category would be just your general complaints that we see in drug trials in general, complaints of diarrhea, headache, vomiting, nausea. The second category would be the nephrotoxic events. You see a few patients who had events of blood creatinine increased, creatinine renal clearance decreased, acute kidney injury.

And the third category would be local effects, so a couple of patients with infusion site phlebitis and injection site erythema.

In the BSI trial, you saw the same thing, again, in terms of looking at treatment-emergent adverse events related to plazomicin. The main thing to note, again, in the plazomicin arm, you did have a few patients who had nephrotoxic related events, acute kidney injury, and renal impairment that were attributed to plazomicin.

So looking at this issue more broadly with the nephrotoxicity, again, for nephrotoxicity that is measured essentially, as has been done in prior trials, by looking at subject of serum creatinine greater than or equal to 0.5 milligrams per dL above baseline. So if you look at this at these patients who had had this increase -- and this could be at any time after starting treatment -- so it could be during treatment.

It could have been post-treatment -- again, reinforcing what we've already heard earlier, you see increases occurring, particularly in the UTI

trials, at a slightly larger rate in the plazomicin arm relative to the comparator, whereas in the 007 study you see these increases happening at a slightly lower rate relative to colistin. And for the most part, when you look at the plazomicin arm, most of the increases seem to be relatively mild in that point 0.5 to 1 milligram per dL range.

Again, most of this was reversible, so if you look at study 009, 9 of the 11 subjects, or 82 percent of the plazomicin subjects who had had serum increases while on therapy had improvement in their serum creatinine by the last follow-up visit.

If you look in nephrotoxicity by the RIFLE classification, again, you see a similar thing. In the UTI studies, it looks like a little bit more nephrotoxicity according to this classification relative to the meropenem and levofloxacin arms, and a little bit less in the 007 study relative to the colistin arm.

Now, the one thing I will say is it's a little bit tricky to interpret the 007 data when you're comparing plazomicin to colistin in terms of

nephrotoxicity. Because of the small sample size, there is a little bit of difference in terms of the concomitant medications that were taken. So in the colistin arm, there was a little bit of higher use of diuretics and other nephrotoxic medications. So again, you have to view this trend of less nephrotoxicity with plazomicin with a little bit of caution

Ototoxicity I think has already been discussed, again, pretty significantly by the sponsor. In terms of the phase 1 studies, there were 5 reports of transient tinnitus following a single dose of plazomicin. In the phase 2 and 3 complicated UTI trials, there were 3 reports of adverse events associated with cochlear vestibular function. There was a report of hypoacusis, tinnitus, and vertigo, but they were all somewhat atypical for aminoglycoside related ototoxicity in that they either were unilateral or that they fully resolved.

Again, as was mentioned, pure tone audiometry and electronystagmography were performed

on the phase 1 and phase 2 trials, and they were evaluated by independent experts. The bottom line from those results was that essentially there was no widespread ototoxicity that could be found in those studies. However, ototoxicity could not be fully ruled out.

The summary of the safety findings was as follows. The data from the plazomicin and clinical trials, they present a safety profile that's generally consistent with an amino lycoside class drug. The main safety signal that was observed was nephrotoxicity typical of an aminoglycoside, generally associated with reversibility. There's no clear comparison of plazomicin nephrotoxic potential relative to colistin's nephrotoxic potential. However, there's a trend suggesting less nephrotoxicity for plazomicin.

Overt ototoxicity due to plazomicin was not identified given the limited duration of treatment. There's no definitive evidence, however, that plazomicin does not have the potential for the aminoglycoside associated ototoxicity.

Now I'll hand it off to our firm colleague, Ada, here who will discuss some of the sero monitoring issues.

FDA Presentation - Luning Zhuang

DR. ZHUANG: My name is Luning Zhuang. I'm the pharmacometrics reviewer for plazomicin. My presentation will focus on the therapeutic drug monitoring for plazomicin in cUTI patients.

Plazomicin is mainly distributed in extracellular space. Protein binding is around 20 percent. Plazomicin has minimal metabolism and is predominantly eliminated by the kidney. The half-life is around 4 hours. TDM using Cmin equal to or higher than 2 microgram per milliliter during first 48 hours is proposed by applicant to mitigate the potential nephrotoxicity. Cmin based TDM was not conducted in cUTI patients in either phase 2 or phase 3 studies. However, Cmin is considered to be correlated with nephrotoxicity based on clinical experience for other approved aminoglycosides.

In the phase 3 study, plazomicin dose was adjusted daily based on creatinine clearance.

Nephrotoxicity was defined as serum creatinine increase equal to or higher than 0.5 milligram per dL from baseline. A total of 22 patients experienced nephrotoxicity in the phase 2 and phase 3 studies. Among them, 9 patients had nephrotoxicity occur after 10 days, indicating that nephrotoxicity occurred more than 3 days after plazomicin treatment had stopped.

Most of the nephrotoxicity occurred in cUTI patients with renal impairment from the phase 2 and phase 3 study. The nephrotoxicity incidence was lower in plazomicin arm than that in comparator arm in patients with creatinine clearance higher than 90 milliliters per minute. Only one patient with creatinine clearance higher than 90 milliliters per minute had nephrotoxicity. Therefore, no exposure response analysis was conducted in patients with normal renal function.

On the other hand, a significant exposure-response relationship was identified between estimated first Cmin, which is a Cmin prior to second dose and nephrotoxicity in patients with

creatinine clearance between 30 to 90 milliliter per minute. The Cmin was estimated based on population PK model, and the first Cmin was used as a PK measure in the exposure-response analysis since Cmin didn't change substantially during the treatment.

To evaluate the cutoff values for first Cmin based on TDM, classification and regression tree analysis was conducted in cUTI patients with creatinine clearance between 30 to 90 milliliter per minute. The first Cmin of three microgram per milliliter was predicted to be the critical threshold associated with high nephrotoxicity incidence. A total of the 244 patients were included in this analysis with 8.6 percent nephrotoxicity. Among them, 216 patients had first Cmin lower than 3 micrograms per milliliter and have nephrotoxicity around 5.1 percent.

Twenty-eight patients have first Cmin higher than 3 micrograms per milliliter, and their nephrotoxicity incidence was 35.7 percent. The table shows the relationship between the first Cmin

range and percentage of patients with nephrotoxicity. The nephrotoxicity for the patients with first Cmin higher than 3 micrograms per milliliter -- the nephrotoxicity was dramatically increased to 30 percent and above. The first Cmin between 2 to 3 micrograms per milliliter was associated with around 10 percent nephrotoxicity.

The two first Cmin cutoffs, 2 and 3 micrograms per milliliter was compared from different angles. A reasonable TDM cutoff should be sensitive to a lot more patients with nephrotoxicity to have dose adjustment in order to maximize the nephrotoxicity mitigation. Original TDM cutoff should also be specific to reduce unnecessary dose adjustment for patients without nephrotoxicity in order to minimize the potential efficacy loss.

Based on the current data, the incidence of nephrotoxicity was higher in patients with first Cmin equal to or higher than 3 micrograms per 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

correctly classified as dose adjustment is needed.

The first Cmin equal to higher than 3 micrograms per milliliter is helpful to minimize the potential efficacy loss, but less patients with nephrotoxicity may have dose adjustment. Well, the first Cmin equal to higher than 2 micrograms per milliliter is helpful to mitigate nephrotoxicity to a greater extent with a higher risk of advocacy loss. In brief, the cutoff 3 micrograms per milliliter is an option if efficacy loss is a major concern for TDM. The cutoff of 2 micrograms per milliliter is an option if the safety is a major concern for TDM.

Dose adjustments in cUTI patients was further evaluated using both TDM cutoffs, 2 and 3 micrograms per milliliter. Because the treatment is short and the PK samples take 24 to 36 hours to be available for TDM, more than one dose adjustment may not be clinically feasible. One dose adjustment was considered by increasing dosing interval to 1.5-fold in cUTI patients with creatinine clearance between 30 to 90 milliliter

per minute. Based on simulation, around 92 percent of patients may have seemingly lower than 2 micrograms per milliliter after one dose adjustment using 2 micrograms per milliliter as a TDM cutoff. Well, 97 percent of patients may have Cmin lower than 3 micrograms per milliliter after one dose adjustment using 3 micrograms per milliliter as a TDM cutoff.

Dosing strategy was also evaluated in patients with creatinine clearance between 15 to 30 milliliter per minute. Limited safety and efficacy data are available in patients with severe renal impairment. However, a higher risk of nephrotoxicity compared to that in patients with mild and moderate renal impairment is expected.

Since the treatment option is limited in patients with severe renal impairments, the following approaches can be considered to evaluate the dosing strategy. Leveraging the findings and knowledge from patients with creatinine clearance higher than 30 milliliters per minute, and considering the dose is given every 48 hours, TDM

should be carefully evaluated.

To summarize, it may not be necessary to perform TDM for patients with creatinine clearance higher than 90 milliliter per minute due to the lower nephrotoxicity incidence as compared to the active control. Cmin based TDM could be beneficial to mitigate nephrotoxicity in cUTI patients with creatinine clearance between 30 to 90 milliliters per minute.

Different threshold concentrations for TDM may be selected based on different benefit-risk preferences. TDM shall be further evaluated in cUTI patients with creatinine clearance between 15 to 30 milliliters per minute, although limited efficacy on the safety data are available.

Next, my clin pharm colleague, Dr. Kunyi Wu, will continue to discuss the TDM for plazomicin in BSI patients.

FDA Presentation - Kunyi Wu

DR. WU: Good morning. I'm going to talk about the therapeutic drug monitoring for plazomicin in patients with blood stream infection.

TDM was conducted in study 007. It was an AUC based TDM. The TDM range was 210 to 315. According to the applicant, the decision to use TDM was based on observed high variability of aminoglycosides PK in critically ill patients. The intent of the TDM is to avoid the risk of extremely high or low exposures that could be associated with unacceptable toxicity or poor efficacy.

The TDM range was predetermined based on plazomicin, 28 percent of the mean AUC, which is 262 in phase 2 cUTI patients with normal renal function who received the 15 milligrams per kilogram per day plazomicin. TDM strategy was modified after initiation of study 007. Based on the final protocol, doses were adjusted on day 3, day 6, and day 10 based on the estimated AUC on day 1, day 4, and day 8, respectively, in order to maintain the AUC into the target range.

The difference between the sampling time and the dose adjustment time was due to the assay turnaround time, which was 28 [indiscernible] to 36 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

adjustment, a large variability in exposure was still observed in BSI patients.

Thus far, I only discussed the overall plazomicin exposure in BSI patients in the course of the treatment. Now, let us discuss the relationship between exposure and the clinical outcome.

In trying to relate the TDM range to efficacy and safety, some difficulties were encountered. First, only a very limited number of patients were enrolled in study 007. Specifically, a total of 29 BSI patients received the plazomicin and 4 of them were on CRRT at baseline. Therefore, only 25 patients were in the PK data set, including cohort 1 and cohort 2.

Due to the limited number of patients, no exposure-response analysis can be performed for either efficacy or safety. Secondly, all BSI patients in study 007 received the plazomicin treatment with TDM. In other words, nobody received the treatment without TDM. In addition, 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

not all be due to treatment medications.

To summarize my talk, for AUC based TDM range in BSI patients, the proposed lower bound, which is 210, is sufficient to attain the PKPD target for bacterial stasis against the enterobacteriaceae for MIC up to 4 micrograms per mL. However, the proposed upper bound, which is 315, is questionable due to 30 percent incidence of nephrotoxicity.

Consideration should be given to the tolerability of the risk of nephrotoxicity in patients who have limited or no alternative treatment option. Up until now, the TDM range, low and high bound, has been evaluated. However, the clinical utility of TDM, in other words, the benefit for BSI patients' AUC to stay in the range, has not been demonstrated.

This concludes my presentation. Thank you.

Clarifying Questions to the FDA

DR. BADEN: I would like to thank the agency for also thoroughly presenting a lot of data and analyses of this compound and its development. To

the committee members, please get myself or Dr. Chee's attention so we can start a list for clarification questions for the agency. While we are creating that list, I will start with the first question to Dr Mishra.

In the 007 study, how do we understand source control? Which is what I think you were getting at with the lines being removed or not. What assessments are there of adequacy of source control at the time of initiation of treatment with the study medications?

DR. MISHRA: Well, obviously these patients are very sick. They're in the ICU. Many of them have multiple lines. It's probably maybe an impossible task to have a completely comprehensive source workup. However, I think the question is, in a case like this, we would have liked to have seen at least a limited workup, particularly as related to line associated infections. And I think in a lot of these patients, we didn't actually find that information. We really just had limited blood culture data and really nothing beyond that.

DR. BADEN: So the information wasn't clearly available.

DR. MISHRA: Yes.

DR. BADEN: Okay. Thank you.

Dr Rubin, if we were to think that colistin were no better than placebo, how does that affect your analyses of efficacy or noninferiority?

DR. RUBIN: If there was a thinking that colistin was no better than placebo in this setting of the study due to the issues that have been discussed, then it would become very difficult to conclude that plazomicin was effective based on a statistical comparison showing that it was not too much worse than colistin.

DR. BADEN: Dr. Lo Re?

DR. LO RE: Vincent Lo Re. A question for Dr. Mishra. How do we understand the uncertainty regarding the primary bacteremias? I was struck just by the fact that you noted that 57 percent of the plazomicin treated patients had either negative or no blood cultures at the time of starting treatment and remained culture negative for CREs, I

believe it was throughout the rest of the study.

So can you clarify how the review of those case report forms proceeded. And given that the inclusion criteria for study 007 allowed for presumed CRE infections, were there any concerns expressed over the potential for misclassification of bloodstream infections? It just seems unusual to conduct a study for CRE bloodstream infections without documentation of bloodstream infection from CRE. So I just wanted to get more perspective from your standpoint on the uncertainty behind this.

DR. MISHRA: Well, to the second point that you talked about in terms of not having confirmed CRE infection prior as opposed to suspected infection, I think the sponsor did try to enrich the population in terms of going to sites where they had high rates of CRE infections. And also, there were some other diagnostic tests that they could use in order to presume that it was a CRE infection. And I think for the most part, we did see that there were CRE infections, at least at baseline.

I think to answer the initial question about the uncertainty around the primary bacteremia, it's a tricky question. Again, we really comprehensively did look through the entire CRF and look through their entire hospital visit. I think the interpretation of them can essentially go one of two ways. You could essentially say that they were adequately treated because of lines replaced, and prior therapy, and really these patients really weren't terribly infected to begin with. The other, you could also possibly say that there are low levels of intermittent bacteremia that you didn't really pick up at baseline and that that was actually kept at bay, or kept under control, or eventually treated by plazomicin.

So that's the way that I approached the data in terms of how I'm looking at it. I don't think we're going to get a full answer to that question, but I think the main point to be made is that you can't ignore the uncertainty. The uncertainty is there, and there's this large population of this very small sample size that we don't really know

what to say about their infection status at baseline.

Does that help answer?

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

DR. BADEN: I realize the applicant may have clarifying information on these points. At this time, we're going to focus on questions to the agency, but please keep track of comments that will clarify issues raised, and we will certainly want to discuss them and hear them.

DR. LO RE: I have a second question for Dr. Nambiar. In your introductory comments, one of the challenges that I'm having is related to the definition of substantial evidence in this setting. And on slide 7 of your introductory comments, you noted that substantial evidence of efficacy under the LPAD pathway requires evidence consisting of adequate and well-controlled investigation, specifically data from one adequate investigation, and confirmatory evidence to constitute substantial evidence.

I'm just curious, can you clarify further

and expound upon what does the agency consider as adequate investigation, and clarify what do you think is required for confirmatory? Especially since the therapy here is limited for patients with limited or no treatment options.

Particularly for study 007, what I'm struggling with is we have one small study with no formal hypothesis testing, one uncontrolled cohort study, and mouse septicemia data. So I'm just trying to get a sense of, in terms of adequacy and confirmatory, what is the agency's thinking.

DR. NAMBIAR: The requirement is that we have adequate and well-controlled investigations. It's typically in plural, but we are also allowed to rely on one adequate and well-controlled trial if we have other supportive information. And the other supportive information can come from -- it could be another body site of infection. It could be information from, say, animal models of infection.

So there are other sources of information that we can use to support the single adequate and

well-controlled trial, but for any particular indications, whether ones considering cUTI or whether ones considering BSI, each one at least you need to have one adequate and well-controlled trial that provide the substantial evidence of effectiveness.

As we noted, the cUTI trial was an adequate and well-controlled trial. There was hypothesis testing. There was a prespecified analysis plan. The bloodstream infection study, though originally designed as a superiority study, a design of what could have been an adequate and well-controlled trial, because of the difficulties in enrollment and the study having been stopped early, at the time it was stopped, the analysis plan said that there was no intent for any kind of formal hypothesis testing. It was only meant to be a descriptive study.

DR. BADEN: Dr. Follmann?

DR. FOLLMANN: Part of what I'm struggling is similar to what Dr. Lo Re just mentioned. It has to do with the rules of the game with LPAD

pathway, and should I sort of unquestionably follow what's been given to me in terms of guidance or question those.

One thing that I thought of has to do with the unmet need. I was wrestling with the idea of you have the cUTI trial, which is noninferiority. So if it's noninferiority, we have a comparator which is viewed to be adequate and inadequate therapy. So how can there be unmet need in the cUTI population is one question.

Then related for the 007 study, I think when it was designed, there weren't the novel BL and BLIs, which we now have. So again, what's the unmet need? And the landscape that you're suggesting to us is we should have one study and sort of change the trade-off between type 1 and type 2 errors for this setting.

So explain more about the unmet need and the thinking behind the LPAD designation.

DR. NAMBIAR: So in terms of unmet need development programs, as we've outlined in our guidance, there are different avenues or approaches

that one can take. Ideally, if it were possible, one could just do a study in patients who have infections due to organisms of a particular phenotype, the phenotype that you're interested in, much like the study 007. And we've seen that from a practical standpoint that doing such a study and demonstrating superiority is very challenging.

The potential for a product to address unmet need, I think that's a determination that we base on what evidence we have that the drug can target infections of a certain type or can target organisms of a certain type. So that information will in fact come external to the trials. So it would come from animal models with infection from in vitro studies.

The UTI study is primarily to show us that the test drug does work in that particular body site of infection, and it an allcomer population study. So that study is really not designed only to address an unmet need. I think that gives you evidence that it works in a body site of infection, and all the other information external to the trial

that could potentially treat infections due to organisms that are resistant to other currently available therapies, those are the kinds of things we take into consideration, determining an unmet need.

Now, that's a little different from LPAD. So you would have to keep the two a little separate. There's an unmet need and there's LPAD. Every unmet need development program is not necessarily under the LPAD pathway.

DR. FOLLMANN: But both of these drugs are addressed for an unmet need that's part of what we're judging them on.

DR. NAMBIAR: Correct. Right. The differences for LPAD, as I had said, it's something that the sponsor has to request for an LPAD designation. It certainly has to be for the treatment of a serious infection, and then there are some other additional requirements. But the bottom line is whether you seek approval under the LPAD pathway or not, you still have to meet the statutory standards or requirement for

effectiveness.

DR. FOLLMANN: I have a couple of other questions.

DR. BADEN: Dr. Weina has a follow-on, and then we'll come back.

DR. NAMBIAR: Dr. Baden, can I just finish? There is one more thing I wanted to let you know.

DR. BADEN: Please.

DR. NAMBIAR: So I think for these programs, what we've generally done is we've taken a greater degree of uncertainty. And that's why we agreed to a wide -- a noninferiority margin. The alpha was 0.10 two-sided. So that's where the uncertainty is, but at the end of the day, even within that framework of uncertainty, we have to be able to make an assessment if the product was safe and effective.

DR. FOLLMANN: So another way you might see uncertainty, the way I might put it there's a different trade off with type 1 and type 2 errors --

DR. NAMBIAR: Correct.

DR. FOLLMANN: -- or we're more likely to take a chance on accepting a drug that might not work in this situation. So we changed sort of our calculus for evidence.

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

DR. WEINA: So just help me in my own head understand the struggle I'm having with the idea of an unmet need and noninferiority, which by definition, noninferiority means you're comparing it to something that you have something, so it's not an unmet need. Yes? No?

DR. NAMBIAR: I'll start, and maybe Ed can chime in as well. So that's the struggle, right? So even if there is an unmet need and you want to design a study, and you only want to study it in patients who have no treatment options, then you will need to do a study like study 007, because you weren't able to demonstrate superiority because here are patients who have no other treatment options.

The difficulty in doing a study just in infections due to a particular kind of organism or

a particular phenotype of interest is very difficult and challenging as we've seen from this example. So as an alternative, what we have found acceptable is if you do a noninferiority trial, at least you know that it works in whatever body site of infection you've picked. But all the other information to support the unmet need comes from what can the drug potentially treat. Can it target certain kinds of organisms for which you right now do not have too many options?

DR. WEINA: So again, we're not talking then -- we're starting to kind of skirt around the issue of, again, limited population, this is the population we're proving it in, but now we got noninferiority. I understand the trial that was designed for superiority because then you can argue unmet need difficulty with that trial, so let's make it noninferiority. But now we're talking again about off-label use, which we struggle with in a lot of our discussions with drugs that come here.

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

think about noninferiority. You have to have an active comparator because you're comparing yourself to something else that you know to be active, that you have a reliable treatment effect. So that's going to limit who can get in your trial.

You want to compare the investigational agent to an active comparator in the NI trial, and the limitation is going to be around resistance phenotypes because wouldn't have a valid comparison if the patients are resistant to the comparator, and you would certainly have ethical concerns about giving somebody a drug that you didn't think was going to be effective for a serious infection.

So the noninferiority trial when done can be a very good way to assess efficacy in a certain setting. It gives you a trial that you can enroll. It allows you to enroll patients with the usual types of drug resistance that you encounter. And then if you think about it, you may have a drug that operates via new mechanism of action. So all the attributes of that drug and something that 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.

The other thing, too, is it can be a more feasible trial. You've seen some of the issues with regards to trying to enroll a trial when you're targeting a particular resistance phenotype. That resistance phenotype may not occur to frequency where enrolling that trial can be done in a timely fashion. You can balance the trade-offs of trying to study a particular resistance phenotype or studying patients with serious infections caused by this similar type of bacteria even though they may not have a particular resistance phenotype, such a study could be more easily enrolled.

So there's a whole bunch of trade-offs here as you think about it. And then you can start to ask the question, too, about generalizability and relevance. A CRE patient population, you may want to study patients who have CRE because of particular patient characteristics. It may not necessarily be solely resistance phenotype that's driving you to want to see how the drug performs there. It may also be because these patients have

comorbidities, renal problems, diabetes, heart disease, other factors that make them different than the general population.

So you can start to ask other questions, too, like can you match those patient characteristics that would allow for a broader patient population and go beyond a particular resistance phenotype, particularly if the resistance phenotype of interest is not against the class of drug that you're trying to investigate, if that all makes sense.

So it's a complicated issue. We've sort of been through this in a variety of different settings, but just trying to summarize it sort of in a nutshell as sort of the different ways that you can think about this.

DR. WEINA: And I understand. Again, the point that I think I was trying to make is trying to fit it within this regulatory pathway of the LPAD, which really kind of argues against some of the examples that you gave, things that we've approved in the past in noninferiority and stuff.

DR. COX: So say a little bit more, if you will, just so I can understand.

DR. WEINA: I was just trying to -- again, I think all of your arguments are absolutely on the mark using our normal regulatory pathway for approval. But right now, we're considering this under the LPAD regulatory pathway for approval, which changes the math in some ways because of the fact that we have substantial evidence of effectiveness with an unmet medical need, a number of things that are all brought into the equation that we don't normally have in approving a drug because of the different regulatory pathway that's quote/unquote "recently" been approved.

DR. COX: We do take unmet need into consideration in some of the previous advisory committee meetings. That has been part of what we've talked about as we've talked about wider noninferiority margins and such. So it is part of the overall structure.

DR. BADEN: Dr. Follmann, continue.

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

would you say that the unmet need is more for the resistant pathogens that you think we'll be developing, and then we'll have this drug in the armamentarium to address its future? Because for the people in the study, they have a comparator that works with them or is thought to work for them.

DR. COX: Right, yes. I think the unmet need is present. I mean, we do have patients out there for whom there are very few treatment options. The study may not enroll those patients, but it still I think provides a good way to assess the efficacy of the drug. And then you get to the generalizability question, is that result generalizable to the broader population?

I think in many ways, yes. I mean, there are going to be some limitations, but it is a good test of efficacy and it allows you to understand how the drug works. And that's why I was thinking back 20 years ago, a drug approved, resistance phenotypes that are present today may not have been present then. But if it's a resistance mechanism

that doesn't impact upon the mechanism of the drug that you're choosing to use, most people would have a fair degree of confidence that that drug should retain its activity.

So I think we think about the unmet need currently and a good test of efficacy to see whether a drug works, and then we can use that information, I think, as to how the drug would be used today and certainly in the future, too, because we would expect that new resistance mechanisms will pop up. So a drug with a new mechanism of action may have utility now and also continuing to have utility in the future as new resistance mechanisms pop up.

DR. BADEN: But, Dr. Cox, that begs the question that the older drug that had activity still has activity if it's the comparator, and how one has a yard stick to compare to if the new mechanism obviates the activity of the older drug.

DR. COX: So I didn't quite follow. Try me one more time.

DR. BADEN: So if you use penicillin,

penicillin works well. Resistance emerges. Penicillin is now your noninferior comparator, but it has no activity against the organisms in question. And then your new agent is being compared to an antibiotic that has limited activity, but it's noninferiority, not superiority.

DR. COX: Right. So in the noninferiority trial, we would insist that the active comparator drug be one that's active. And we do look at the resistance phenotype as being a baseline characteristic. We have encountered situations where it wasn't anticipated, but there was a higher rate of resistance in the comparator arm in the study. So there it's very important for us to look at the patient populations who on their baseline characteristics are susceptible to the comparator in order for us to have a valid test of the efficacy of the drug in a noninferiority trial.

DR. NAMBIAR: And if I can just add, I think the primary analysis population for the cUTI trial patients, the organism had to be susceptible to the test drug and the comparator drug, so it was as a

valid comparison.

DR. BADEN: Dr. Follmann?

DR. FOLLMANN: So 007 is a very difficult study for us to evaluate. It's very underpowered N of 37 when the plan was to be 286, and yet it's sort of dancing around superiority with some analyses. And maybe there's some evidence for noninferiority, but it's also very fragile because of the study being so small.

So what I sometimes like to do is think, okay, this was sort of a study that couldn't be executed for exogenous reasons we could say because they couldn't accrue. So you sort of threw out the analysis plan from the window, out the window. And now we're trying to use our best judgment, I guess, as to how to interpret the evidence. And there's no plan, so different people can have different perspectives on how to interpret those best evidence. I think the FDA had a clever and sort of different way of approaching this to try and look at noninferiority for 007, recognizing its limitations and so on, but sort of a different

maneuver.

I have two minds about this. One is that, oh, it's just way underpowered; forget about it; or the other is that when you have an underpowered study, you try and use statistical methods or thinking that's more efficient and kind of glean more information from the study.

So I might be interested in the secondary endpoint of time to death, up to day 28, and so on, which was one of the analyses that you did. I was wondering if Dan had done an analysis of time to death, up to day 60, another way maybe to get more information with more endpoints. But there are different ways I guess to try and deal with a study that's super underpowered and looking at maybe more efficient endpoints or different analyses is one way that one could approach it.

So the question is have you done a time-to-event analysis using up to day 60, which I think the sponsor had done something like that.

DR. RUBIN: Your points are well taken. The time to death through day 28 was one of the key

secondary endpoints and is on my slide 15, and was favorable to plazomicin. I think there were Kaplan-Meier curves in the briefing book showing survival data out to longer times. I'm not sure if we have a p-value or hazard ratio in front of us for that.

Another kind of more efficient analysis, which was listed as an additional analysis of the primary endpoint but was not in our briefing book was a Cochran-Mantel-Haenszel test that tried to adjust for the stratification factors and also had a p-value that was more favorable for plazomicin.

So your points are well taken that there are different ways to approach them. Our thinking was that sticking with what had been specified in the final protocol was the best way to preserve the integrity of randomization and the benefits of a prespecification, but that's what we have in terms of the more efficient time.

DR. BADEN: Follow-on?

DR. FOLLMANN: Just to mention, if the sponsor could present their results. I know it's a

bit different because you were careful to say your analysis population is both HABP/VABP and bloodstream infections versus sponsor is just looking at bloodstream infections and excising the HABP/VABP group, which didn't -- maybe have increased the evidence in favor of the drug.

Anyway, if the sponsor could present their analysis like that, and it's not exactly what I want, but it's something to look at.

DR. RUBIN: Okay. I think figure 8 in the briefing book has some time-to-event data out to day 60.

Is that the sponsor's briefing book or our briefing book?

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

DR. RUBIN: Okay.

DR. FOLLMANN: Okay. Thank you.

DR. BADEN: Dr. Kartsonis, you had a follow-on question?

DR. KARTSONIS: I just wanted to make a comment to remind the committee about these kinds of studies we're doing here in carbapenem resistant

infections. This is now I think the third study that is out there that are looking at carbapenem resistant infections. All of them have struggled to recruit. All of them have enrolled about 50 to 60 patients, including one that Merck has done as well, so I can speak a little bit to that.

I think the expectation that we will have a fully powered study of hundreds of patients in carbapenem resistant infections is wishful thinking, and I do think we have to take the data we currently have and try to analyze it I think in the best way like the FDA has been trying to do as well as the sponsor has been doing. So I do want to remind folks that this is a study that went on for over a few years. The ones that Allergan did and also Merck have done have also taken three-plus years and have all recruited about 50 to 70 patients. So I do think there is a lot of value that can still be generated from these studies that we shouldn't at least lose a perspective on.

I guess the question I have is, in the face of all the data and all these uncertainties that

we've had, irrespective of how you look at the data, it does appear that there's a consistent effect for plazomicin versus the comparator. And even in the analyses, Shrimant, you mentioned the ones where on day 1, they were negative. It still appears that the mortality in the colistin arm is still ranging around 30 to 50 percent, irrespective of whether or not you knew they were positive on day 1, irrespective of whether they were negative on day 1, or whether or not they were positive on day 1.

So I do think we just have to remind ourselves that the totality of the data is an important factor here.

DR. BADEN: Thank you. There are still many more questions on our list from the committee, however, we have reached the lunch hour. So we will now break for lunch. We'll reconvene again in this room at 1:30. I will remind the committee not to discuss it amongst ourselves or with anyone else and that we will continue questions to the agency as well as to the applicant after lunch. See you

all at 1:30.

(Whereupon, at 12:41 p.m., a lunch recess was taken.)

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

(1:35 p.m.)

Open Public Hearing

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

Both the FDA and public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee on any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee

if you do not have any such relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Will speaker number 1 step up to the podium and introduce yourself? Please state your name and organization you're representing for the record.

MR. THORNHILL: Hi. My name is Barrett Thornhill. I'm the executive director of the Antimicrobial Innovation Alliance, of which

Achaogen is a member. Our coalition is a coalition of pharmaceutical innovators focused on working with Congress and the administration to help spur the development of critical need products that respond to one of our most pressing public health challenges, antimicrobial resistance.

Multidrug resistance pathogens know no boundaries. Every state is experiencing outbreaks and increased deaths. If you listen to our domestic and global experts, this crisis is going to get a lot worse. The assistant director general of the WHO has said, quote, "We are fast running out of treatment options." The UK government has released a report predicting deaths from AMR will exceed cancer in 30 years and that CMO added that without action now, quote, "We are really facing a dreadful post-antibiotic apocalypse." The agency's own Dr. Janet Woodcock has testified many times before Congress about the, quote, "fragility of the antimicrobial pipeline" and the need for a, quote, "broad continuing platform of antibiotics for a wide variety of diseases."

CRE infections are especially deadly and are occurring among our most vulnerable patients, including those in ICUs and those with prolonged hospital stays. There are at least 70,000 cases of CRE annually in the U.S. alone, and that number is expected to double within four years. More frightening is the CDC reports that CRE infections are associated with mortality rates above 50 percent.

A serious consequence, these organisms are becoming resistant to our last line of antibiotic defenses. That was the case last year when a woman in Nevada died from an infection that was resistant to 26 antibiotics. Former CDC director, Tom Frieden said, quote, "Without urgent action now, more patients will be thrust back to a time before we had effective drugs."

We talk about a pre-antibiotic era and an antibiotic era. If we're not careful, we will soon be in a post-antibiotic era; and in fact for some patients and some microbes, we are already there. Even with growing resistance and an increase in

infections, it remains an enormous economic challenge to bring a new antibiotic to market. The Presidential Advisory Council on Combatting AMR determined that the ROI for antibiotics is poor and unpredictable. A 2014 AEGIS report followed up and said the net present value of antibiotics for six leading infections has now topped $50 million, and for two types of infections, the return is actually negative.

What we need are new antibiotics that target priority pathogens. This is why plazomicin is so important. At the end of 2016, legislation which my group worked on for four years with the FDA and the IDSA, became law. The 21st Century Cures Act was passed to accelerate the discovery, development, and delivery of new treatments. Included in this bill was Section 3042 that established the LPAD pathway intended to treat patients with unmet medical needs.

Dr. Woodcock testified that, quote, "Drugs approved using an LPAD pathway will be based on a more streamlined development program that

established that the drug is safe and effective in a limited population of patients with serious or life-threatening infections and unmet medical needs." Plazomicin is precisely the type of drug Congress was thinking about when developing LPAD, and now with the opportunity to be the first drug approved for this pathway.

Bloodstream infections have flipped over 1 million patients per year, making it the single most expensive disease that U.S. treats in Medicare. This treatment under review can save lives. I urge this committee to support the licensure of plazomicin to help patients and address this growing public health crisis. Thank you for your time.

DR. BADEN: Thank you for your comments.

Will speaker number 2 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

DR. SHENDELMAN: Hi. My name is Shoshana Shendelman. I'm representing myself, and I have

nothing to disclose. First, I'd like to thank the FDA for allowing me to share our family's experience on plazomicin, and I hope that understanding our situation will help to provide some context for approval of new options for complicated infections.

My dear cousin, Dr. Fred Noband, or "Fari" as he was known to our family, was the head of neurosurgery at Lenox Hill Hospital, and he was devoted to saving the lives of others. He became a surgeon because he believed in our ability to change the world through improvements in medicine and science, and he did go on to save countless lives as a neurosurgeon. He was also a beloved son, brother, husband, and father of two young daughters.

Fari was treated for AML in 2013 and underwent several bone marrow transplants, chemotherapy, and surgical procedures. He was in remission from the cancer and scheduled to be released from the hospital within a few days. His 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

the enterobacter strain was sensitive to plazomicin, and we immediately reached out to Achaogen to access this drug.

This was on a Friday afternoon, and I still recall the late Friday night calls with the FDA, the hospital board, and the company to access this drug. It was locked in a warehouse in Pennsylvania, and we were told that if we didn't initiate the drug within 24 hours, our cousin was not going to make it.

Somehow they were able to find someone to open the warehouse and get us this drug, and we started to see an effect almost immediately after implementing plazomicin. Within a few hours, his vital signs started to improve and he began on the road to recovery. Within a few days, he awoke and soon was joking around with us as though he had not been on death's doorstep a few days prior. The ability of new antibiotics such as plazomicin to treat previously fatal infections is groundbreaking. Plazomicin can literally mean the 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

incidence of multidrug resistant infections is on the rise as everyone in this room is well aware. It's important to have as many tools in our arsenal as possible when treating complicated infections. Secondly, these infections are often fast moving, and it's important that clinicians have ready access to these drugs so that they can be implemented immediately when needed.

I work on drug development in other areas, and I've sat in this room and listened to public statements and been on the other side of that table. As a scientist, I intellectually knew about rising multidrug resistant infection numbers and lack of treatment options, but until I faced this issue up close, I hadn't recognized the urgency of the situation. And when a patient is a loved one, you start to think about drug development differently. The number of patients and incidence of disease take on a different meaning. In my opinion, plazomicin is an important new tool that should be made available to clinicians as broadly as needed. Thank you.

DR. BADEN: Thank you for your comments.

Will speaker number 3 step up to the podium and introduce yourself? Please state your name in any organization you're representing for the record.

MR. NAHUM: Good afternoon. My name is Armando Nahum, representing Achaogen. I have no financial disclosures.

Someone once said that in life, even more than education, experience is sometimes the best teacher. Well, if that is true, I can tell you with all certainty that there's no one I know that has been taught more or has been more profoundly affected by the personal devastation and particular loss caused by hospital-associated infections than my own family.

In 2006, three members of my family were impacted with hospital-associated infections in three different hospitals, in three different states, in 10 months time, culminating with the death of my son Josh. He was 27. Josh acquired a multidrug resistant organism in his cerebral spinal

fluid during his six weeks in ICU. And since 2013, the CDC has classified CRE as a serious threat to public health and one of three greatest threats to human health by the World Health Organization. And despite the global emergence of CRE, no clear consensus has emerged in regard to the method of detection, and the prevalence of CRE infection is rapidly increasing in hospitals and community settings, and my son is a testament of that.

It is important to understand that there is increasing evidence that bloodstream infections due to CRE are associated with high morbidity and mortality. So for this reason, it is imperative that we allow new antibacterial drugs to provide treatment options, especially in cases where resistance has eroded the effectiveness of existing drugs. Thank you very much.

DR. BADEN: Thank you for your comments.

Will speaker number 4 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the 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.

As we observed in recent trials, susceptibility does not always equate to success. As examples, doripenem, ceftibiprole, Tygacil, all agents with favorable microbiologic profile against key gram negatives, were unsuccessful in several other registrational trials and did not meet their primary endpoints.

As we have discussed today, we have seen a growing number of studies that have shown suboptimal outcomes with colistin when it's employed as the comparator. I believe the positive findings from the CRE bloodstream trials supports approval plazomicin, although a limited number demonstrates a mortality benefit. When I think about outcomes, you look at our patients, and that is the most difficult one to show a difference, yet across important subgroups, we were able to show a difference in mortality.

As an antibiotic steward, there's a true need for non-beta-lactam antibiotics for patients with serious gram-negative infections. Beta-lactams are highly effective and safe

antibiotics, and this is reflected in their clinical use. Their use, however, is not without consequence.

As we have discussed today, we have seen emergence in ESBL CRE and other highly resistant gram-negative bacteria. This is due in part to use of many of our broad spectrum beta-lactams, including the carbapenems and beta-lactam beta-lactamase inhibitors. Because of their broad spectrum use, we're also concerned about C. difficile colitis, which is a major concern in the healthcare environment.

In addition, we cannot use beta-lactams in all of our patients. Many patients are beta-lactam allergic and have other contraindications for their use. Therefore, there's a true unmet need as an alternative beta-lactam for patients with CRE bloodstream infections as well as complicated urinary tract infections.

I understand today's approval for a drug will be also to think about practical concerns, so we think about a lot of our drugs we use to treat

CRE dosed multiple times a day by prolonged infusions. Within the healthcare industry, there's an increased emphasis on quality and efficiency of care, so when we think about a single, once-daily drug, this has the potential to facilitate early discharge and treatment in other environments other than hospitals. So again, there's practical benefits to having other CRE drugs particularly for our non-beta-lactam patients.

Finally, I'd like to speak as a clinical pharmacist. We would welcome the addition of a new aminoglycoside. TDM is very favorable to us. Most hospitals now have a PK dosing, so I anticipate plazomicin will be readily incorporated in the practice.

Why there's some hesitancy on approving a drug with TDM. I actually see it as an advantage. As we're well aware, patients with serious gram-negative infections, there's substantial interpatient variability and pharmacokinetics. As we know, serum creatinine and GFR estimating equations on the way we dose most of these

antibiotics do not accurately reflect renal function and drug clearance of many renally eliminated drugs.

As we know, serum creatinine often lags behind true renal function in patients with rapid change of renal function and cannot be used to estimate renal function in patients with augmented renal function. A good example of this is the findings with Avycaz and its complicated intra-abdominal trial. As we saw there in patients with moderate renal impairment, we saw lower response rates, and this was due in part to rapidly improving renal function and underdosing those patients.

So there was a lot of discussion today about AUC dosing. I see this as an opportunity. I am also on the vancomycin consensus guidelines. We are moving towards AUC dosing for vancomycin. I view this as a innovative approach and the future. So again, while there may be some hesitancy with the AUC dosing, this is going to be readily incorporated into practice with vancomycin and also

plazomicin. Thank you.

DR. BADEN: Thank you for your comments.

Will speaker number 5 please step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

DR. GELFAND: Good afternoon. My name is Michael Gelfand. I'm a practicing infectious disease physician in Memphis, Tennessee. I'm also a professor at the University of Tennessee and chief of OID at Methodist University Hospital in Memphis. I was paid to travel here, but received no other compensation, just the airfare. I have no relationship with Achaogen otherwise. My remarks will be personal and will not represent an opinion of the University of Tennessee or of the Methodist healthcare system.

I'm routinely involved in the care of infectious disease patients with immunocompromised states, organ transplantation, stem cell transplantation, as well as HIV patients. When caring for these patients, we of course are all

aware of the current state of hospital infectious practice.

It is characterized by the rising resistance of gram-negative rods to multiple classes of antibiotics, including carbapenems, older aminoglycosides and polymyxins and their increasing number in elderly and immunocompromised patients. Many of these patients come to us with comorbidities. They come to us from the places such as long-term care facilities and nursing homes where resistance, including carbapenem resistance, is rising. And patients like that are then confronted with a relative paucity of therapeutic alternatives.

While a number of new beta-lactam agents have recently been approved for the treatment on label and are intended for the management of resistant gram-negative infections, the data that supported their approval did not include substantial information on carbapenem resistant bacteria of a clinical type. I think it would be highly desirable to have additional alternatives

for the treatment of carbapenem resistant gram-negative bacteria. And the reasons as a clinician to have these alternatives would include emergent resistance against older agents, including new beta-lactam agents recently introduced, especially in severe infections such as bacteremia, but also noticing recent data suggesting that this resistance is rising in the presence of pneumonia, immunocompromised state, and hemodialysism, and a desirability of being able to use combination therapy possibly to impede the emergence of resistance.

We are aware of an editorial accompanying a paper in Clinical Infectious Diseases suggesting that we'll need a bigger boat and a better boat to float our patients from an ocean of resistance. And I'm hopeful that plazomicin will be an agent that will allow as combination therapy to construct this Noah's ark of therapeutic efficacy to avoid the emergence of resistance.

We need non-beta-lactam agents for patients who are allergic to penicillin, cephalosporins, and

carbapenems. We need a convenient agent that can be given once a day. And we certainly need less toxic agents as compared to older aminoglycosides and colistin. So in my opinion, plazomicin represents these desirable characteristics that would allow us to perhaps improve the care of patients with carbapenem resistant bacteria.

Finally, I wanted to, in the period of openness, report to the committee that while I'm an American citizen, I was born in Moscow, Russia, and I don't want my remarks to be construed as an attempt at collusion --

(Laughter.)

DR. GELFAND: -- or influencing their vote on plazomicin. I also wanted to mention that while I'm relatively young, I was a personal participant in pre-antibiotic as well as antibiotic era when I was infected as a child with at that time emerging beta-lactamase positive Staph aureus and was one of the first recipients of new drug methicillin for the treatment of staphylococcal sepsis, benefiting 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

the unmet need is great.

When it comes to the unmet need -- and I think that there were quite a few presentations here. And I don't really have to add to that. The mortality that we see from gram-negative pathogens nowadays is much higher than we used to see in the past. There are multiple studies that show that resistance is a factor, and the more resistant a pathogen is, whether it's an ESBL producer or a CRE, the higher is the mortality. I think part of that is not that we don't have treatment options, but that the treatment options that we have a really not very -- are suboptimal.

I think it is important to remember that the pathogens that actually cause those urosepsis or intra-abdominal infections, or even gram-negative, catheter-related bacteremia have not changed. And there haven't been many reports about the change in their virulence, suggesting that a lot of the mortality really has to do with inappropriate therapy. And I think that when we evaluate new treatment options, we have to remember that we have

a relatively wide margin for improvement here just by improvement in treatment.

Now, my second comment has to do with effectiveness and evaluation of effectiveness, and I think there were a few comments that were similar to mine. I just want to mention that what we have been seeing and probably will continue to see our suboptimal studies. Particularly when you start to dissect them from a an independent immunology perspective, from a statistics perspective, it's really easy to kind of distance yourself in seeing the big picture and kind of dividing it into fragments, and each of the fragments doesn't really tell you a lot.

I think that we should really take a Bayesian approach when we do that, particularly when we're evaluating an antibiotic that belongs to a class for which we have a lot of experience, and actually look at in what way this antibiotic differs from other antibiotics in this class for which we have a lot of information; to what extent this difference in design has resulted in

difference in in vitro activity; and look at the safety data very carefully. But at the end of the day, I think that when you get to the clinical trial, you really have to take this Bayesian approach and ask given the change in design, given the decrease in resistance to this agent, given the mechanism of action, how should we interpret the clinical data that's available to us? And I think that you may reach somewhat different conclusions.

I think that this is particularly critical when what's considered to be best available therapy or frequently used antibiotics are suboptimal. I think many people talked about the fact that colistin or tigecycline that are so commonly used for those types of resistant pathogens in very severe infections would never have been approved by the FDA. Based on the available clinical data, there was a question of whether it's actually different from placebo. And I think that this question was very relevant because we've seen the very high mortality rate in studies when colistin has been used.

My last comment has to do with the fact that although we've seen the CRE study completed, I think that there may be better uses in clinical practice to plazomicin because if you look at many of the CRE patients in the clinical trial, they were either treated with an antibiotic for which they were resistant like a carbapenem as part of the regimen or a tigecycline type of antibiotic that doesn't really have good plasma levels and, as you know, is a static antibiotic and so forth.

While I think that in the real world, the combination of plazomicin with more active agents may actually result in better activity, I would argue that in many of the patients in the CRE study, plazomicin was actually used as an aminoglycoside monotherapy that many of us would think maybe should not be the case and should have a better combination than those studies.

So with that in mind, I think that plazomicin would be an important agent for us as infectious disease doctors. People already mentioned the fact that we have several

beta-lactams being approved, have been approved, in the pipeline, but we don't really have many of the other classes. And I think it will be particularly important to have something that we can use in synergism, particularly early in the state of infection to reduce the inoculum and improve the effectiveness of therapy. Thank you.

DR. BADEN: Thank you for your comments.

Will speaker number 7 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

DR. BURDETTE: I'm Dr Steve Burdette. I'm an infectious disease provider in Dayton, Ohio. My travel has been supported by Achaogen but not my time. I'm here representing myself. I'm a professor of medicine and the program director for infectious diseases at Wright State University, Boonshoft School of Medicine. In my 13 years in practice, I have been spending time as the medical director of both antimicrobial stewardship for the hospital as well as for the system, and I also run

infection prevention for an 800-bed level one trauma center, which is a tertiary referral place.

I oversee the antibiotic administration of dozens of patients every day, and after I leave here, I will go back to the hospital and make more rounds tonight. In my professional time, I've had the ability to serve on the Infectious Disease Society of America's guidelines committee as well as on their clinical affairs committee, and I have been on one of IDSAs task force for into microbial stewardship.

I want to start off on why we need more options for gram-negative infections. I am greatly appreciative of the FDA approving ceftolozane-tazobactam, ceftaz-avi, mero-vabor, but already we have resistance to those antibiotics. We need more options.

A lot of discussion today of colistin, a lot of discussion of the renal issues with colistin. When I use colistin, my patients don't feel well, and sometimes they don't feel well for a long time. They have various neurologic, other complications

that may or may not be pulled out in the studies. They don't like the way they feel on either colistin or polymyxin B; a lot of electrolyte issues as well that leads to more and more medications. We need more options.

We have a significant number of patients with beta-lactam allergies. The literature is very clear. Patients with beta-lactam allergies have worse outcomes because you have to go to more difficult antibiotics or antibiotic combinations. We need better options for the beta-lactam allergic patients.

There's also been some discussion of tigecycline. Tigecycline, I don't like to use it for bacteremia. I don't like to use it for urinary tract infections. I don't like to use it for sepsis. I think the literature is very clear, but sometimes with these multidrug resistant pathogens, we have to use an antibiotic like that. We need more options.

So where would plazomicin fit into this in 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

shown increased mortality, increased morbidity, and over half of the time, the empiric antibiotics are not correct. So as we get into more and more resistant gram negatives, we need to have more options to deal with those.

Lastly in closure, I have a patient I've been treating now for two weeks, spina bifida patient, has had heavy antibiotic exposure, has a couple of different very resistant gram-negative infections; just recently had a reaction to one of the options that was approved a couple of years ago through the FDA, and I'm running out of options. And his mother just asked me to pass along to you, if he pulls through this, he's going to need more options when he gets his next infection. With his spina bifida, with his chronic respiratory failure, it's not if he gets another infection, it's when. He needs future options. Thank you.

DR. BADEN: Thank you for your comments.

Will speaker number 8 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the

record.

MR. NAHUM: Good afternoon. My name is Armando Nahum, once again, representing Dr. Juan Diaz, infectious disease physician, chairman of infection prevention Florida Hospital, Orlando. Dr. Diaz has no financial disclosures.

"I am an infectious disease physician in Orlando, Florida. Unfortunately, I treat patients with multidrug resistant organisms frequent enough that it is common threat in my practice. I encounter extended spectrum beta-lactamase isolates on a nearly daily basis. However, there are other organisms that are becoming much more prevalent in clinical practice, specifically organisms such as CRE that have higher mortality, and scarce treatment options are a real and urgent threat for the Center of

Disease Control.

"The infectious disease community oftentimes is faced with limited options on treatment choices, both because of resistance and patient factors, but also because of adverse effects. In current care,

there's a lack of antimicrobials with significant activity towards these isolates or relatively few alternative agents have significant difficulties with standardized dosing, increasing MICs and sides effects including nephrotoxicity.

"Restricting utilization of carbapenems may also have a role in decreasing its resistance. I have reviewed some of the preliminary information on plazomicin, including their phase 3 trials for complicated urinary tract infections. It appears that plazomicin demonstrates a significantly higher composite cure than meropenem at the test of cure. Moreover, there was no reversible ototoxicity noted in a trial.

"In addition, expanding our armamentarium for treating bloodstream infection is extremely important at this time in our current healthcare arena. As you well know, patients with serious CRE infections have significant mortality and disease related complications. The phase 3 trials demonstrate a survival benefit with plazomicin 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

scientific and medical data and provides objective health information to patients, providers, and policymakers. Our statement today reflects our views and also that of the National Physicians Alliance. We do not accept funding from pharmaceutical companies, so we have no conflicts of interest.

Antibiotic resistant bacteria are a major public health concern. We must address this through enforced antibiotic stewardship, infection control, and development of effective and safe antibiotics that save people from deadly infections. Unfortunately, the sponsor has not proven the safety or efficacy of plazomicin for patients who have limited or no treatment options. Although there is a compelling unmet need to treat these deadly infections, we cannot lower the standards to approve this drug or any other drug that fails to demonstrate safety or efficacy through appropriate clinical research and appropriate statistical methods. That is what the law requires.

We will focus on the following questions. Number 1, do the studies show that this will work when other options are limited? In the UTI trial, plazomicin was noninferior. In other words, the older control drug was similarly effective. Since the study population could have been treated with a control drug, the study population cannot be characterized as having limited or no options. Therefore, the results provide no evidence that this newer drug will work for the intended population.

Worse, we do see a safety signal in terms of a toxic effect on the kidney for plazomicin compared to the older drug. We should not accept a more toxic drug when the older drug works as well and is less toxic. Keep in mind that the goal of noninferiority is to provide added benefits for patients such as fewer adverse events. Since a noninferior drug is no more efficacious, it should have some other proven benefit like a less serious side effect.

In the bloodstream infection trial, we also

did not demonstrate that plazomicin was safe or effective. Testing the effect of plazomicin with noninferiority or with exploratory analysis does not demonstrate that it is effective in patients with no other options. We cannot draw conclusions about the benefit or harms based on what the sponsor admits is descriptive rather than inferential data. The results are not statistically significant, meaning that these results did not rule out harm for patients and could have been due to chance alone.

Number 2, are the results valid? Interpreting these results, particularly BSI, is difficult because there was not a standard collection of data, most randomized patients had negative or no blood cultures, and the source of infection was uncertain, especially in those who had an IV catheter. Furthermore, intending population who would use this drug was not studied in these trials, so what will this drug look like in the real world? We need to clearly define the population that would be treated with this drug

based on the evidence provided. We cannot extrapolate this data from the study population who were well treated with an existing drug to the intended population.

Number 3, what evidence do we need for approval? We cannot approve this drug based on a single noninferiority study and a failed superiority study. Studies testing these drugs for unmet medical need of patients who have no other options cannot be noninferiority because by definition there is another option being tested and the new drug could even be slightly worse. It is not scientifically valid or ethical to base the claim of noninferiority on a failed superiority trial.

We urge the panel to recommend that FDA require additional well-designed superiority studies that use appropriate statistical methods to determine whether plazomicin cures infections and saves lives for patients who have no other options. With reliable methods, even small studies can show a clinically meaningful and significant benefit.

Since there is no evidence that plazomicin works or is safe for patients who have limited or no options, approval will do more harm than good. As you all know, once approved, these new drugs are often promoted and prescribed for much wider patient population. This can expose tens of thousands of patients to drugs that don't work and cause harm. Simply labeling this drug as limited population would not be sufficient to limit the drug's use to an appropriate patient population.

Thank you so much for the opportunity to share our perspective.

Clarifying Questions (continued)

DR. BADEN: Thank you. I'd like to thank all of the open public hearing speakers for sharing their thoughts, and especially those who shared their personal stories. This helps round out our perspective on why we're here. The open public hearing portion of the meeting is now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful

consideration of the data before the committee as well as the public comments.

Given that we were not able to complete the clarification elements with both presenting groups, there are a few more questions for the agency that we'll complete, and then we will return to the questions we have for the applicant. So where we left the agency questions, Dr. Le, I think you were next.

DR. LE: Yes. I really enjoyed the FDA's exploration of the data, particularly as it relates to the TDM, both for toxicity and efficacy. In particular for the toxicity, the threshold that you used during CART, identifying Cmin, resulted in improved specificity, did you by any chance evaluate it from -- because it's obvious that it's exposure-response related, right, and increasing dose or exposure relate -- did you by any chance to do a CART for the AUC as well?

DR. LIU: It's Chao Liu, the pharmacometric team leader for this review. So we did assess the correlation between the AUC and the nephrotoxicity

that also show the cause associations. So in terms of finding out one classifier to predict the nephrotoxicity, we're still operating the characteristic analysis, and it shows that trough concentration in 24 hours to have a better predictive power as compared with AUC. So we choose the trough concentration as a predictor to correlate with the nephrotoxicity.

DR. LE: The reason why I ask that is because what's proposed here is two different TDM processes, one that's more Cmin based and the other one is AUC based. Whereas the Cmin clearly identifies a threshold for nephrotoxicity, what is that for AUC? Because if I'm going by AUC for efficacy, well, I have the AUC unless I extrapolate it to the Cmin to make that correlation to nephrotoxicity. Because most patients with this BSI will likely be on higher dose or a higher exposure by AUC. So that's why it's nice to have that information in there for some correlation.

DR. LIU: Right. We did some exploratory analysis that quantitatively correlates the trough

concentration with the AUC, and we see that there is some correlation between the trough concentration and AUC. Though, in terms of using an explorer matrix to predict the nephrotoxicity, we do see a better predictive power using trough concentration as compared with the AUC. So although these two explore matrices were correlated, trough concentration correlates better with the nephrotoxicity risk as compared with say AUC.

DR. LE: Thank you for that. Now related to the effectiveness side, I know that you were trying to select the lower end by using the static rather than the one log kill, and you were comparing this for bloodstream infection. I'm not sure in clinical practice if we would target stasis when we're treating a patient with bloodstream infection rather than a one log kill.

Can you comment on that?

DR. WU: Sure. My name us Kunyi Wu. I'm a clinical pharmacology reviewer for plazomicin. As Achaogen talked about, they already talked about

the great uncertainty in animal PKPD targets, regarding the animal PKPD target to the gram-negative BSI. And to my knowledge, the relationship between the animal PKPD target to the clinical PKPD target, especially regarding the gram-negative BSI has not been established.

So to answer your question, because of the severity of the infection, as you mentioned, especially in BSI patients, we did think about not only the medium for the PKPD target values for bacterial stasis. We thought about the 75th percentile of the PKPD targets for stasis, and also we take the one log kill into consideration.

Could I have the backup slide number 6? Maybe it's 5. I can't remember exactly what number; 7, try. Sorry.

(Laughter.)

DR. WU: Yes, this one. The up table shows the median value for PKPD targets, stasis and also 1 log kill. You can tell the 1 log kill number is 89. The median value for PKPD stasis for 1 log kill is 89. The lower table shows the target AUC

value to achieve the attainment for 1 log kill, where MIC equals 2 is 178. And that the lower bound for TDM range is 210. 210 is higher than 178, so the lower bound is high enough to achieve the value for PKPD targets where MIC equals 2.

DR. BADEN: Thank you. Dr Daskalakis?

DR. DASKALAKIS: I think this is a fairly simple question -- Demetre Daskalakis -- for the FDA. Is there any concern that in the bloodstream infection, the only bacteria other than one is a klebsiella?

DR. MISHRA: I guess the short answer to that question is no. I mean, in general, that's sort of what we expected in terms of what they were able to recruit, so, no, it's not surprising.

DR. DASKALAKIS: Thanks.

DR. BADEN: Thank you. Dr. Honnegger?

DR. HONNEGGER: Sorry. I have a couple of questions. I'll try to be brief. One brief for Dr. Nambiar. As far as the LPAD or LPAD mechanism, because of the known uncertainty going into these approvals, is there additional built-in mechanism

for post-approval monitoring for drugs that go through this pathway?

DR. NAMBIAR: Just under the LPAD pathway, there is no requirement for postmarket studies, unlike accelerated approval where's there requirement for a confirmatory postmarket study. But certainly in any instance when we have concerns, especially from a safety standpoint or any other unanswered questions, postmarket studies could be done, but there isn't a requirement under LPAD, if that's your question.

DR. HONNEGGER: Thank you.

The next question is about, because they allow -- because it's been made clear that it's difficult to study CRE bacteremia in treatment, it's hard to get big numbers, and then you want to know what are other supportive studies you'd want to see, would it be considered -- right now, normally, we wouldn't use an aminoglycoside first line for bacteremia. It usually is a beta-lactam, if you can. Would a noninferiority study comparing this drug with a beta-lactam in known bacteremia

that's not necessarily highly resistant, that's susceptible to beta-lactams, be permitted?

DR. NAMBIAR: Let me make sure I understand the question. So you're saying can someone design a noninferiority trial in sort of an allcomer population in gram-negative bacteremia, and not necessarily just the CRE studies? Is that your question?

DR. HONNEGGER: Yes. This isn't my expertise on gram-negative bacteremia, but going into a study where we use upfront aminoglycoside I don't think is commonly practiced now. It was in the past, and sometimes it's used after identification of the organism now, but it's not common.

DR. COX: Just in general, yes, you can design studies that don't target a particular resistance phenotype. People oftentimes refer to that as usual drug resistance because the organisms that we encounter on a daily basis usually have some type of resistance to something along the way. It may not be the particular problematic or

concerning resistance mechanisms that are sort of on the forefront today.

So in a variety of different indications, yes, you could design a study. And one of the things that you might think about when designing such a study to look at the usual or prevailing resistance phenotypes, not necessarily the ones that occur infrequently, might be you try and enrich the study for patients that had comorbidities, that had greater underlying conditions, that had greater severity of illness.

So you might not get the particular resistance phenotype you're looking for, but you might make a study that would be more enrollable because there'd be a larger pool of patients out there to try and get information that would help you to understand how the drug works against particular pathogens and in inpatients who have particular acuity of illness. If the drug's mechanism of action is orthogonal, unrelated to the mechanism of resistance that's a particular problem, that could be a way to do a feasible trial

to get some very good quality data to understand how the drug works.

DR. HONNEGGER: Thank you. And then just lastly for Dr. Mishra, in terms of your analysis -- I appreciate you going into the cases in detail since they're small numbers for the bloodstream infections. Your analysis in terms of there being differences in the number of patients who had no documented bacteremia at day 1 or thereafter, but that was different than what we saw from the company about what was their baseline -- it could be, like you said, that they could have no subsequent bacteremia because the drug was actually having an effect. But to have baseline, is it true that the proportion of patients with ongoing bacteremia was similar between colistin and plazomicin?

DR. MISHRA: Let me make sure I --

DR. HONNEGGER: Or when the drug was started, the proportion of patients that still had ongoing bacteremia documented was similar between the groups.

DR. MISHRA: Right. There were 4 patients in each arm that had positive bacteremia at 24 hours prior to starting. I guess that's one way to sort of look at that question.

DR. HONNEGGER: Okay. And then you talked about differences in the diagnosis of line infections in the group and that there were maybe some discrepancies. But as far as the proportion of patients who had central lines -- maybe they all did -- and the proportion of patients that actually got their lines pulled, was that similar regardless of whether they were called a primary- or a line-associated infection?

DR. MISHRA: That I'd probably have to look into more detail. I don't want just tell you straight off. There were patients who had lines replaced. I can't tell you the proportion between the two in terms of whether that happened on day 1e. When I was more looking at that calculation, I was looking more specifically about when that happened around the time of starting drug to see if potentially it could have affected the rest of

their course. But there were patients who had lines that were changed during the course of their drug, after starting it as well.

DR. HONNEGGER: Thank you.

DR. BADEN: Dr Gripshover?

DR. GRIPSHOVER: I'm not sure if mine is for the agency.

DR. BADEN: Well, I have you on the agency list. If not, then we'll come back to the applicant.

DR. GRIPSHOVER: Okay. It can sort of go either way I think because it's about the pharmacology. In terms of the bacteremias that were in the UTI study -- and that's why it might be the agency -- do we have data on the pharmacokinetics in there? If we approve this for a urinary tract, people are going to probably use it for bacteremias. And I'm thinking did we have any data to be able to help how we're going to monitor it if we are using AUC.

Do we have any data in terms of efficacy and drugs on in particular the bacteremias? But I

don't know if the pharmacology was even collected on them.

DR. ZHUANG: Hi. This is pharmacometrics reviewer from FDA. Can you clarify your questions? You're asking the relationship between exposure and efficacy in cUTI patients? Is that your question?

DR. GRIPSHOVER: Yes, actually in the bacteremic ones.

DR. BADEN: No, no, the bacteremic UTI.

DR. GRIPSHOVER: UTI. So in study 009 in the UTI study, there were I believe 24 --

DR. BADEN: There were 46 bacteremias divided between the two groups.

DR. GRIPSHOVER: -- yes, between the two groups.

DR. BADEN: How did they behave?

DR. ZHUANG: Actually, we didn't conduct a subgroup analysis for exposure -- to identify the relationship between exposure and efficacy. But for the general cUTI patients, we conducted exposure-response analysis for efficacy. So for that part, we didn't see any trend. There's a

slight relationship, but because these are only under one dose, it's only one dose available for all the patients. But for the subpopulation, we didn't conduct any analysis yet, so we don't know.

DR. BADEN: Thank you. Dr. Schaenman for the agency side.

DR. SCHAENMAN: Yes. This is a question for Dr. Nambiar, I believe. I think as clinicians who have faced MDR infections, we all appreciate the importance on a systems basis for the LPAD; we all support that idea. But I think as some of my colleagues have raised, we're kind of struggling with how to actually apply that framework in practice.

So I'm interested to know if this is the first drug that's come up under LPAD as opposed to the QIDP or if there are other precedents that you could tell us about that might give us some guidance in how we go through answering the two questions before us.

DR. NAMBIAR: So you're right. This is the first application we have received specifically

asking for approval under LPAD. QIDP is a little different. QIDP is a designation that is granted for certain products. For indications, it is not related necessarily to an approval process. What QIDP gives you in this context was a priority review, which is why the application received a priority review.

Does that help?

DR. SCHAENMAN: So I guess any other words of advice or guidance, since this we'll be setting a precedent then for other LPAD applicants.

DR. NAMBIAR: Yes. Would you like me to go through what LPAD does provide and doesn't provide? Would that help to just go through it again?

DR. BADEN: Maybe we can save that for when we get to the question, when we actually look at the formal question.

DR. NAMBIAR: Okay.

DR. BADEN: Thank you. Dr. Green, did you have a last question for the agency before we can go back to the applicant?

DR. GREEN: I do, and I don't know if

Dr. Mishra can do this or not. When he was doing his presentation on a case-by-case basis, we started off with a total of 29 bloodstream infections in 007. But after he got through kind of walking through it, I was left with the sense that if you were to look at your evaluable patient population, it was less than 29.

I don't know whether you're willing to or not, but can you tell us the number of patients you actually thought were evaluable after you sort of went through all your concerns and contingencies about these patients?

DR. MISHRA: Well, I don't think that I would say that I thought that absolutely none of the patients were not evaluable. I think I still would look at the whole set of 29 as being an evaluable population. I think the bigger question was, yes, I did feel that there was a strong or a large percentage of that population where the uncertainty was higher.

Is that a way to answer that question? I mean, I won't fully discount these patients that

had completely negative cultures and say that they were not evaluable.

DR. GREEN: Thank you. I think you answered the question, at least for me.

DR. BADEN: We have completed the list of remaining questions from the agency's presentation and we can turn back to the questions we have for the applicant. I know the applicant have a series of clarifications from issues raised since they were sharing their thoughts, so please, Dr. Connolly.

DR. CONNOLLY: Thanks for the opportunity to provide some clarifications. I would first like to provide you with some additional information about this catheter and primary BSI issue. We also did do a case-by-case analysis of these patients, and I want to start with the plazomicin treated patients who are characterized as either primary bacteremias or potential catheter related bacteremias.

So the first was considered to have a primary BSI because their catheter was pulled and 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

neutropenic with a potential gut translocation source. A second patient considered primary by the investigator had persistent bacteremia despite removal of the catheter with another potential GI source and a complicated course after hiatal hernia surgery with peritonitis requiring small bowel resection, so another possible gut source.

Another primary BSI with bacteremia persisting after removal of the initial catheter, another one persisting with bacteremia at the time of line removal who had a colonic perforation and polymicrobial blood cultures that included bacteroides, so suggesting this was a gut source; two more who had primary BSIs because the culture from the catheter tip that was removed was negative, and then a culture that cleared without removal of the catheter.

As you can see for several of these patients, consequences were severe. Four of these patients actually went on to die by day 28 despite the uncertainty around the source of their 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

the catheters remained in beyond day 1, so to speak, while the others had them removed, or these are just primary bacteremias?

DR. CONNOLLY: No, these are primary bacteremias, and I wanted to share how the catheters were handled.

DR. BADEN: I see. And on the colistin group, if I understand correctly from the agency's presentation, 8 of the 21 colistin treated patients, the colistin MIC was greater than 2.

DR. CONNOLLY: Yes, that's correct. So patients were enrolled in the study based on local laboratory data. So the local laboratories were using several different colistin susceptibility testing methodologies, and we only discovered after when we ran these in the central laboratory that they were resistant to colistin.

We have looked at the impact of this on the primary outcome, so I can show you here. If we remove those and look at patients who had colistin susceptible baseline pathogens, we still see a high rate of mortality, so 56 percent for colistin

treated patients despite Colistin susceptibility, so to look at the impact of that.

DR. BADEN: Dr. Clark, you had a follow-on question?

DR. CLARK: Yes. On the primary BSIs, despite what you presented there, those criteria don't seem to meet what the definitions of catheter related or primary bacteremia were in the studies. Is that correct?

DR. CONNOLLY: So correct. Ultimately, the investigators needed to provide an assessment, and when they couldn't determine the source, they called it primary.

DR. CLARK: And one other question on susceptibilities. Is it true that all the patients who got meropenem in both groups had MICs less than 8?

DR. CONNOLLY: No, that is not the case. Although that was the recommendation provided to the investigators, some of those patients had meropenem MICs above 8; in fact, I believe all of them did who got meropenem.

DR. CLARK: Can you tell us what the MICFs were between the two groups, colistin and plazomicin?

DR. CONNOLLY: For meropenem, who received meropenem, in general, they were greater than 32.

DR. CLARK: For all patients? There was no difference I'm saying between the colistin group --

DR. CONNOLLY: No, there was no difference. So meropenem MIC greater than equal to 8 was 71 percent and 81 percent for the plazomicin and colistin treatment group.

DR. CLARK: Okay. Thank you.

DR. BADEN: Please continue with the clarifications.

DR. CONNOLLY: Sure. I did want to clarify also about the culture status at baseline just to be sure we are clear what that looked like. One important thing to remember about this study, the way it was designed was to test plazomicin against colistin as definitive therapy for CRE infections 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

then in the colistin arm, we see that 3 of the 6 patients, despite negative cultures at the time of enrollment, go on to meet the primary endpoint in the study.

DR. BADEN: Any questions on these data? Dr. Lo Re?

DR. LO RE: Vincent Lo Re. So given that the inclusion criteria for this study was presumed or confirmed carbapenem resistant enterobacteriaceae, in the subgroup of individuals where there was no blood cultures, what were the triggers that the clinicians made to indicate that these were presumed carbapenem resistant isolates?

DR. CONNOLLY: So let me clarify, every one of these patients did have a positive culture for CRE. The issue is that those cultures were often taken. So what would happen in the study is the patient would present with signs and symptoms of illness. These are hospitalized patients. Cultures would be drawn. They would be started on empiric therapy. And only when that initial blood culture turned positive for CRE or there was some

microbiological confirmation that it was likely CRE, were they then considered for randomization in this study. At the time of randomization, a second culture was drawn to determine whether that patient was still bacteremic.

So the cultures that qualify them for enrollment in the study were taken up to 96 hours prior to actual randomization, but then we took a second culture at the time of randomization to determine what proportion of patients would still have positive cultures, and that's what we're looking at here.

DR. LO RE: So when Dr. Mishra was noting that 57 percent of the plazomicin group did not have a evidence of either active CRE bacteremia at the time of enrollment or during the drug treatment, that neglected that there was prior culture results for CRE available.

DR. CONNOLLY: Exactly. He was referring to the cultures taken at the time of randomization and then post-baseline. He was not referring to the cultures that were taken that actually qualified

the patient for enrollment into the study.

DR. LO RE: That's helpful. Thank you.

DR. BADEN: Dr. Kartsonis, you had a comment on this?

DR. KARTSONIS: Yes. I just wanted to make one comment about this, about studies like this for bacteremia or candidemia that historically have been done. If you actually look at the data, if you take most of the candidemia studies, or you look at the one bacteremia in the study that was done with daptomycin in the past, not everybody's going to have culture on the day they get randomized into the study.

The candidemia studies did allow for 4 days of prior therapy, and the prior daptomycin study allowed for up to 48 hours. So indeed, in both of those studies, you do have a number of patients at the time of randomization who already have negative cultures. This is completely common and very consistent with what have been done with other studies in the past. And if you actually look at the efficacy on all of those studies, it didn't

matter on day 1 whether or not they still had positive cultures or not. So it's an important factor to keep in mind as well.

DR. LO RE: Just one other follow-up question.

DR. BADEN: Yes, Dr. Lo Re?

DR. LO RE: Can you just give us a sense of what the median time prior to enrollment of the people who did not have either CRE bacteremia isolated at the time of enrollment or during treatment was? How far prior to enrollment was that? Was it relatively recent or was it 7 days, 14 days before? I'm just wanted to get a sense.

DR. CONNOLLY: Oh, no. The farthest out it could be was 96 hours, that culture. And some of them were certainly closer, and I don't have it up at the top of mind. But we also did stratify patients based on whether they received less than 36 hours of empiric therapy, so new therapy for this new infection or greater than 36 hours. We do have data around that.

DR. BADEN: Dr. Clark, you had a follow-on?

DR. CLARK: I just had a question for Dr. Kartsonis. When you talk about the studies for daptomycin or a treatment of candidemia, those were much larger studies, and probably the numbers of patients who had negative cultures are a much smaller percentage.

DR. KARTSONIS: Yes. And if you actually look at the candidemia studies, including the one I ran for caspofungin, up to 30 percent of the patients on day 1 had a negative culture. So it's completely common that you have to account for those factors, and it's consistent with the prior studies that have been done for fluconazol, micafungin, anidulafungin, and what have you. Yes, they are much larger studies. Obviously, they are not inferiority based.

DR. BADEN: Dr. Connolly, along the issue of prior treatment in positive culture, how much colistin -- could these patients have received colistin previously, not just in the 24 to 96 hours before enrollment?

DR. CONNOLLY: So yes, these patients could

have received colistin previously for an unrelated infection.

DR. BADEN: How many of them had?

DR. CONNOLLY: There were I believe 3 in the colistin arm who had previously received colistin in the time period around enrollment for another infection.

DR. BADEN: Thank you. Please go on with your clarifications.

DR. CONNOLLY: Sure. I would also like to share with you a Kaplan-Meier curve. I think this was requested looking at -- so this is in that primary analysis population. This includes all patients, so both the BSI and HABP/VABP. So this is preserving that original intent.

Looking at death through day 28 and through day 60, what we've included here are hazard ratios through day 20 and through day 60, as well as p-values from one-sided log rank tests.

DR. BADEN: Dr. Follmann?

DR. FOLLMANN: So a clarifying question. This is the bloodstream infection group?

DR. CONNOLLY: No, this is the entire primary analysis population. This includes both the bloodstream and HABP/VABP patients.

DR. FOLLMANN: Thank you.

DR. CONNOLLY: I'd also like to ask Dr. Satlin to come to the podium. There's been a lot of discussion here around unmet need and how do these data sets potentially address that, and how to think about them. So I'd like to ask him to make some comments.

DR. SATLIN: Hi, everyone. I'm Michael Satlin. I'm an infectious disease physician at Weill Cornell Medicine in New York City, and I am a paid consultant by Achaogen. I think where I practice here actually matters because New York City has been the epicenter for CRE. In fact, we've been facing patients infected with these organisms for over a decade.

I think a lot of great points were made about the
unmet need in the public speaking session. One additional point I would like to add is that even

with the new beta-lactam beta-lactamase inhibitors, those are primarily only active against the KPCC CRE, and we certainly have patients who are infected with non-KPCC CRE for which currently colistin is our primary treatment option.

I'd like to also share with you a perspective about some struggling with the uncertainty of whether plazomicin is superior to colistin or less toxic than colistin. We have been managing patients with CRE infection for over a decade. We have nearly 100 patients a year with CRE infection in our hospital, and we published a study last year.

It was a multicenter study in New York City, published in AAC, where we found that despite a decade of experience in managing patients with CRE infection, by relying on colistin based therapies, we are still seeing a 50 percent mortality rate, and that's despite all the things we've been trying to learn about the polymyxins. And it made us start to wonder, are these patients just so sick 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

clearly we need additional drugs. We need plazomicin, and I think being able to offer our patients plazomicin instead of colistin is a major benefit to obviously the patients and also the clinicians that take care of them.

DR. BADEN: Thank you. Other points you wanted to clarify, Dr. Connolly? Because we have more questions.

DR. CONNOLLY: Of course. I had one last point of clarification. I did want to clarify our intentions around the AUC based TDM for BSI patients, as well as provide some information that may help with how do we think about clinical utility for this type of a TDM for these patients.

So as mentioned, we are targeting an AUC range that's around at 210 to 315, and that is based on the TDM algorithms that have been developed and the AUC range roughly observed in the study. I think our original intent for this type of TDM was to try and reduce the variability and exposures that these patients see due to their dynamic changing physiology from their critical

illness. So because we can do a randomized controlled trial now of TDM without TDM with these patients, what we can do is take all of the PK data and our population PK model and run simulations, and ask ourselves what would have happened if we didn't do TDM in these patients.

So what I'm showing you here are AUC values on the Y-axis over time, so with the initial dose, the first TDM, the second, and the third. In the blue boxes, we're showing without TDM, and in the red with TDM. So just to orient you to this, this is based on the data collected from BSI patients and run through that pop PK model.

So what we see happening in the absence of TDM over time is we see increasing AUCs, increasing exposures for these patients, including extreme high AUCs that may place them at increased risk of nephrotoxicity. With the application of TDM, we reduce that variability and those extremes.

I'm not trying to imply that this is actually a therapeutic window. I know that's something that you're very interested in getting

to, so two of the main purposes of TDM here is reducing that variability and avoiding those extreme high exposures.

DR. BADEN: Dr. Gripshover?

DR. GRIPSHOVER: Just a quick clarifying question. It looks like most of them were actually too high. Is that if we didn't change? So did you look at Cmin also?

DR. CONNOLLY: Yes. You're correct. The tendency is if we don't change, we see increases in exposures over time. There is some variability on the low end as well. It's a little bit hard to see what the gray dots, but we see as we go over time, there are more extremes on the low end as well. But you're right. The bias is towards the high end.

DR. BADEN: Dr. Rej?

DR. REJ: This is Robert Rej. A question about the assay that you used for the TDM studies, is that bout equivalent to the microsphere assay that you're contemplating as a companion device under 510(k)?

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

patient population because that population was too small, as we have all acknowledged, to run a robust exposure-response relationship. But I can share with you the relationship to AUC that we characterize with cUTI patients, just to clarify.

Shown here, this is looking at pooled cUTI studies and the incidence of nephrotoxicity with increasing the AUC. So if we recall the background rate in the meropenem and levofloxacin arms was around 4 percent of patients experiencing serum creatinine elevations. And here where we start to see a real jump up is around that 400 range to 10 percent, and then above that at 540 percent. So it's a sort of shallow relationship, but you can see it really does jump up when you hit 500 and above.

DR. BADEN: Thank you.

DR. CONNOLLY: Thank you.

DR. BADEN: Then we will resume where there were more clarifying questions from panel members. Dr. Honnegger?

DR. HONNEGGER: [Inaudible - off

mic] -- applicant?

DR. BADEN: Applicant, yes, the applicant questions.

DR. HONNEGGER: Regarding bloodstream infections in the 009 study, we have time to clearance -- just looking for more data on bloodstream infections. Do you have the time to clearance plotted for these patients and any other measures of their outcome? I think they all survived.

DR. CONNOLLY: In the 009 patient study, none of these bacteremias led to death. And the blood cultures were not drawn as frequently, so what we have around the outcomes for these patients is we were able to show clearance of bacteremia at those two time points, day 5 and test of cure. We can also look at their outcomes in terms of their primary infection, so I'll show you that here.

This is the composite cure rate in cUTI patients with concurrent bacteremia at the test of cure visit showing 72 percent, uh, in the plazomicin arm as opposed to 56 percent in the

meropenem arm, keeping in mind this is a small subset.

DR. BADEN: Do you have a comparable for the day 5, comparable graphic?

DR. CONNOLLY: Yes. Here's what I can show you actually, so this is interesting. I can show you over time --

DR. BADEN: Thank you.

DR. CONNOLLY: -- what competent cure looks like in patients with concurrent bacteremia. And interestingly, these curves overlap substantially others then at day 5, where meropenem, there's a higher rate of response in the meropenem arm, but then we see that flip as we move out over time with a higher response rate for plazomicin at test of cure and long-term follow-up.

DR. BADEN: Thank you. Dr Follmann?

DR. FOLLMANN: Yes. I was curious about the choice of the endpoint for the cUTI study where you used a composite of clinical cure plus microbiological eradication, which is a biomarker, not a direct reflection of a patient's clinical

course. To me, it would have been more natural to look at the clinical outcome by itself without imposing traditional microbiology on it.

Was it thought that was a harbinger of the future, that they would be more likely not to relapse? If so, why wouldn't you just look at a later clinical endpoint?

Those are my questions about the choice of that composite endpoint. I would have just used clinical cure, and maybe the FDA would comment on this as well.

DR. CONNOLLY: Sure. What I would say was this was consistent with the guidance document from FDA.

DR. FOLLMANN: So why did the guidance suggest that kind of endpoint as opposed to just a straight cure endpoint?

DR. COX: I'll give it a shot, Joe, but you help me out. So most of the data that we used to develop the noninferiority margin, a lot of the trials look at microbiological cure. We actually struggled to find ones that also included on a

level where we could make sense out of combined clinical and microbiological cure together.

So we do feel that we do have a clinical endpoint here and that there is a clinical component to this. And if we think about the drug, its mechanism of action is actually to treat the bacteria that's causing the infection, so it's a pretty reasonable thing to also look at are we eradicating the bacteria in the setting of a urinary tract infection.

The other thing we learned as we started to look at this, and some folks have pointed this out to us, is that you can actually look at some non-antibacterial treatments that make people clinically feel better. You can give NSAIDs or whatever, and people will feel better, but that doesn't necessarily treat the urinary tract infection.

So we actually think it's a pretty good endpoint to be looking at the microbiologic outcome, is the antibacterial drug essentially treating the bacteria, and then also is the patient

feeling better, and are the symptoms urinary tract infection essentially going away. So we think it's a pretty good endpoint to include both components, the microbiological and the clinical. I

DR. FOLLMANN: I had one other question for the sponsor. By arm, do you have who ended up on dialysis in 007 for the colistin arm and your drug, plazomicin?

DR. CONNOLLY: At baseline, we had 4 patients on the plazomicin receiving CRRT, and I believe there were two patients in the colistin arm receiving CRRT at baseline.

DR. FOLLMANN: I didn't mean at baseline. I meant after the end of the study or at the end of follow-up, how many were on dialysis?

DR. CONNOLLY: Post-baseline use of CRRT.

DR. FOLLMANN: Yes.

DR. CONNOLLY: I do believe we have the data for post-baseline. And there certainly were patients who required CRRT after enrollment in both treatment groups. I do know sometimes the indication provided for receipt of CRRT was sepsis;

at other times, it was for renal adverse events.

Here we go. Let me bring that up. So any CRRT -- and I believe this is post-baseline -- we have one patient in the plazomicin group in cohort 1 and 3 and the colistin group, and the subset for which CRRT was indicated for a renal adverse event were 2 out of the 3 in the colistin group. And then we also have the data here for cohort 2 plazomicin treated patients, 3 requiring CRRT post-baseline; 2 of those were for a renal adverse event.

DR. FOLLMANN: Thank you.

DR. BADEN: Dr. Palevsky?

DR. PALEVSKY: So a clarifying question regarding the use of CRRT for, quote, "sepsis," because the data does not support that there is a role for sepsis. Do you know anything about dosing of the CRRT? Because if it's being done as CBBH at a high dose for cytokine manipulation, that could be having a very major effect on your clearances of the drug and an effect on efficacy.

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

nephrotoxicity, and where are we drawing the line?

DR. CONNOLLY: Sure. So in terms of labeling, that's certainly an ongoing discussion with FDA. Our position would be that TDM would be recommended for patients with renal impairment at baseline. So those patients who experienced an increased risk of nephrotoxicity. And based on the data we're showing here, that would include severe, moderate, and potentially mild renal impairment.

DR. SCHAENMAN: So meaning less than 90.

DR. CONNOLLY: Yes.

DR. SCHAENMAN: I just wanted to point out that there is some renal impairment, even if patients are starting with normal renal function. And of course these patients are often a moving target. They might have come concomitant nephrotoxic medications. They might be older. Especially in the setting of transplantation, where people are often on calcineurin inhibitors, we often see a lot of nephrotoxicity that comes out in the setting of treatment.

Could I also see slide 100? It's just the

next slide right after this. In addition to some nephrotoxicity in the mild or zero renal insufficiency patients, you can also see that there's a real heterogeneity of Cmin in the patients initially. So this is just raising concern for me in terms of TDM and also the question of applicability because this is, again, primarily this white population.

Although I think you did show safety from your phase 2 study, I'm just wondering, can we extrapolate from this in a non-Caucasian population, especially African Americans, in terms of how can we safely dose this drug?

DR. CONNOLLY: Sure. So in terms of African Americans in particular, 9 percent of the patients included in the population PK analysis were African American or black, and we did look at race as a covariate for exposures. So that's the data we have to rely on currently to say that exposures are not impacted by race.

Also, one thing around TDM is this is really 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

perhaps the patients who had that persistent cure were slightly overdosed during the initial treatment period.

DR. CONNOLLY: Oh, sure. We didn't do that exact correlation asking if the patients who were cures at Test of
Cure were those who had elevated Cmins, although the numbers there probably don't add up when we see that the proportion of patients who had elevated Cmins early compared to the high rates of response at test of cure that are sustained to the long-term follow-up.

We do have some hypotheses around why an aminoglycoside or even any concentration dependent-killing agent might have a persistent effect. One is due to the differences in the way these antibiotics kill bacteria. So with a concentration-dependent agent, the higher the concentration you get, the more bacteria killing you see, whereas with a drug like meropenem, once you are above that MIC, as long as you're there, you don't increase with more drug killing. So it

may be that initial killing, and killing of the potential reservoirs is greater with a concentration-dependent drug such plazomicin.

In addition, we know from our human ADME studies that plazomicin persists in the urine for a prolonged period of time after dosing, whereas meropenem, a less stable drug, that's not likely the case. And this observation is very consistent actually with what we see for beta-lactams in this indication. We see very similar response rates for doripenem, avi-caz [ph] out at that test of cure visit where you lose that efficacy from end of therapy or the day 5 visit down to test of cure. And where we've seen maintenance is with those concentration-dependent killing agents.

DR. BADEN: Dr. Palevsky, you have follow-on?

DR. PAVLESKY: Yes, thank you. All of your assessments of kidney function relevant for dosing guidelines were based on a Cockcroft-Gault creatinine clearance estimates. Yet in clinical practice, what's generally reported are eGFR, which

don't necessarily correlate with the Cockcroft-Gault creatinine clearance.

Do you have a plan for how you're going to address that in terms of labeling and guidance should this come to market?

DR. CONNOLLY: Sure. What we have currently proposed in the labeling, and certainly because we did use Cockcroft-Gault, and particularly for obese patients, we used ideal body weight in that equation, currently the proposal is to stick with what we did in the clinical trial to ensure that those exposures are consistent with what were achieved in that context.

DR. BADEN: Dr. Clark, do you have a follow-on?

DR. CLARK: I had a question about the converse [indiscernible] situation. Were there any patients who had undetectable levels, trough levels, well below 1, and were there correlates with outcome in those patients?

DR. CONNOLLY: Oh, in the cUTI study? Oh, 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

whether the renal assays of plazomicin had an effect on that, so that's something we'd have to consider.

DR. CONNOLLY: Yes. I could potentially pull that up for you. We did look at a series of endogenous -- with the selectivity of other drugs as well as endogenous, and I believe it had no effect on plazomicin. I think your question was for the other way around, right?

DR. REJ: Yes. My question is that someone aminoglycosides affect the creatinine measurement, and I was wondering whether the effects of this drug as an interference have been looked at.

DR. CONNOLLY: Let me see if I can clarify. So if you're asking whether the presence of the aminoglycoside in the sample interferes with the creatinine test, yes, we have not addressed that yet. That is not something that we're aware of.

DR. REJ: [Inaudible - off mic] -- you haven't?

DR. CONNOLLY: We have not.

DR. REJ: You have not.

DR. CONNOLLY: Yes.

DR. BADEN: We are short on time, however, I do want to push through and clarify everything we can. Dr. Kartsonis, did you have a question from earlier?

DR. KARTSONIS: Yes. My question was with regard to the microbiology. In protocol 7, do We know if the isolates that were recruited were mostly KP2's or KP3's? And also do we have any efficacy regarding metallo-beta-lactamase producing organisms from protocol 7 maybe in the other cohort?

DR. CONNOLLY: So yes. We did have a small proportion of patients who had infections due to non-KPC-producing organisms. Just looking at what we have here. I'll start with this.

So certainly, KPC was -- so what I'm showing you here is actually the isolates from study 007, and then the isolates from surveillance. In 007, they were largely KPC. We did have some MBLs, VIMs, and MDMs often in combination with the KPC. And then we had a couple of OXA-48 in that study.

DR. BADEN: Presumably given the numbers, this is a couple per group.

DR. CONNOLLY: Oh, absolutely, yes.

DR. REJ: Any word on the efficacy?

DR. CONNOLLY: Yes, that's what we're looking at here, yes.

DR. REJ: Okay. Sorry.

DR. CONNOLLY: Okay. Here we go. So this is microbiological response at test of cure in BSI patients with carbapenemase-positive pathogens. So we can look in cohort 1. You can see KPC predominantly an 89 percent rate for plazomicin versus 36 for colistin. And then we can go down the line.

So as I mentioned, when we see the VIM or MDM, it's in combination with another carbapenemase. So KPC plus VIM, we had 3 patients in the plazomicin group who had good outcomes, and we had one NDM plus VIM in the plazomicin group and one in the colistin group.

DR. REJ: Thank you.

DR. BADEN: One more question about the

microbiology. You had mentioned earlier that the resistance was largely due to RMTs to the plazomicin plasma. In the in vitro data, it looked like some percent of isolates were or became resistant. In the in vitro data, the isolates that became resistant, was it also the RMT mechanism or were there other mechanisms at play?

DR. CONNOLLY: No. So what we do in vitro selection, in vitro selection for resistance, what we generally see are isolates that have plazomicin MICs in the 8 to 16 to 32 range, and those are being characterized molecularly to try and ferret out the mechanisms, but it is not the presence of an RMT. And then interestingly, when we look in surveillance, we very rarely see isolates at that MIC range. It's really in surveillance when we see resistance, a vast majority of those have an RMT.

DR. BADEN: RMT. But in the in vitro, you were able to select for a resistant organism through a different mechanism.

DR. CONNOLLY: Yes, absolutely, like most gram-negative agents, that's relatively

straightforward.

DR. BADEN: Great. Dr. Rej, did you have a follow-on question from this morning?

DR. REJ: [Inaudible - off mic].

DR. BADEN: Great. Dr Lo Re?

DR. LO RE: Just a question. So given the challenges of enrollment in study 7, I know that an amendment was made to include an additional uncontrolled cohort. Could you just take me through the thinking on the decision of why the decision was made to include that uncontrolled cohort versus, for example, changing inclusion criteria? I just was trying to get a sense of how you thought these data would be or should be interpreted in the context of the very different cohort 1.

DR. CONNOLLY: Sure. So cohort 2 was actually added at the request of multiple investigators who felt they had patients who could potentially benefit from plazomicin therapy because they had no options, but who were not eligible for enrollment in cohort 1. So in some ways, cohort 2

is almost like an expanded access cohort.

Two of the groups of patients in there, patients with known colistin resistant pathogens would not be appropriate to put them in the randomized controlled arm. In addition, patients who had polymicrobial infections that involved acinetobacter or pseudomonas, which are not target pathogens for plazomicin, were allowed in cohort 2 but not in cohort 1.

The other types of patients who were allowed in are a very distinct population, so cUTI patients. The reason we didn't include cUTI patients in cohort 1 is because they have a very low rate of mortality compared to BSI and HABP/VABP. So we were challenged to figure out an endpoint that could be applied across all of those infection types. So that's how the cUTI patients were included in cohort 2.

Then finally the low APACHE II scores less than 15, again, because we had a mortality based end point in cohort 1, we had to ensure a sufficient severity of disease so that we could

potentially demonstrate difference on a mortality-based endpoint.

DR. BADEN: Great. Any more questions from committee members? Dr. Palevsky?

DR. PAVLESKY: So a couple hopefully quick questions. In the materials that were provided ahead of the meeting, there is discussion of plazomicin inhibition of the MATE2-K transporter. Inhibition of that transporter can actually alter creatinine secretion, which then draws into question the use of a creatinine based determination of AKI.

Do you have any information on how much of an interference with creatinine secretion there is, how it varies based on level of kidney function, and do you have any data using another marker of kidney function such as cystatin C that's not affected by the transporter?

DR. CONNOLLY: Sure. I'll start with the really simple one, your second one, do we have data using cystatin C or other markers? No, we do not 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,

particularly patients who have a severe acute illness, may after their illness have a decrease in creatinine production? So even if you recover to the same serum creatinine, you haven't recovered kidney function.

DR. CONNOLLY: Sure. I'd actually like to ask Dr. Dwyer to address the question specifically around the definition we used.

DR. DWYER: Jamie Dwyer, Vanderbilt. I'm a nephrologist.

So you're correct. There are various definitions for the recovery of nephrotoxicity. We used a 0.5 milligram per deciliter increase from baseline at any time across the study. We categorized the subjects into three groups: full recovery, partial recovery, and then a persistent elevation.

Full recovery was that the last post-baseline serum creatinine value had to be less than 0.5 milligrams per deciliter above the baseline value. Partial recovery, getting to a point you made earlier, was that the last

post-baseline serum creatinine value had to be greater than or equal to 0.3 less than the peak, but that did not meet the definition for full recovery. And then persistent elevation was criteria that met neither the definition of the other two.

DR. PAVLESKY: But you have no data on creatinine production and whether recovery is affected particularly in the more severely ill patients because of the underlying critical illness decreasing creatinine production.

DR. CONNOLLY: Right now. You're correct.

DR. PAVLESKY: Then just one other question. You used the 0.5 definition rather than using the current consensus AKIN/KDIGO definitions. Is there reason for that, recognizing that there's a dispute about the best definition to use?

DR. CONNOLLY: So we also did apply RIFLE criteria. I mean, these are not --

DR. PAVLESKY: The RIFLE being surpassed more than a decade ago by AKIN, and then subsequently KDIGO.

DR. CONNOLLY: Yes. So essentially we chose the 0.5 five milligram per deciliter and also the RIFLE because these were values we had seen used in similar drug labels, even recent ones such as the new tenofovir label, for these types of drugs. So we tried to look at precedents in this space, and we applied similar definitions.

DR. BADEN: Dr. Le?

DR. LE: I have a question regarding what you mentioned earlier for the use of weight for the cUTI studies. For those greater than 125 percent, you still use ideal body weight, correct, in your --

DR. CONNOLLY: We used the ideal body weight in the creatinine clearance calculation, and we used an adjusted body weight for calculation of the dose.

DR. LE: Okay. Did you use at all the ideal body weight plus the 40 percent? Is that to adjust the body weight for the dose --

DR. CONNOLLY: That's the adjusted body weight.

DR. LE: -- but not the creatinine clearance?

DR. CONNOLLY: Correct. And in doing so, what we found ultimately is that the AUC distribution for patients with high BMI versus low, we were able to achieve very similar AUCs across those patients using this type of correction for obesity.

DR. LE: And you can certainly apply this for the UTI. Would you be considering the same for the BSI patients, where a higher exposure may be needed?

DR. CONNOLLY: No. For calculation of the initial dose, this is recommended for all patients for that initial dose.

Questions to the Committee and Discussion

DR. BADEN: I think we have answered all clarification questions, and we can move forward now with consideration of the questions.

We'll now proceed to the questions to the committee. We will be using an electronic voting system for this meeting. Once we begin the vote,

the buttons will start flashing and will continue to flash even after you've entered your vote. Please press the button -- we're not going to vote quite yet because we need to look at the question, and then we will vote.

We see the question here. Yes?

DR. FOLLMANN: I thought we were going to get a little clarification.

DR. BADEN: Correct. That's where I'm going. I'm just looking at the guidance.

(Laughter.)

DR. BADEN: So I wanted to present the question, and then we will ask Dr. Nambiar to discuss a little bit about the LPAD rules and guidance as to how we should weigh the evidence in light of this pathway and the precedent we're setting.

DR. NAMBIAR: Thank you, Dr. Baden. So what I think I can do is just review the information I presented this morning about LPAD.

There are the three key requirements and then some additional requirements that regard

labeling and promotional materials. The three requirements for LPAD are that the drug is intended to treat a serious or life-threatening infection in a limited population of patients with unmet needs. The standards for approval under the 505(c) and (d) standards for licensure under 351 the Public Health Service Act are met. So there's no change in our standards for approval. There needs to be a written request from the sponsor that the drug be approved as a limited-population drug.

Just to review with you what the standards for approval are, the sponsor must provide substantial evidence of effectiveness for the drugs intended use and sufficient information to conclude that it is safe for use under conditions prescribed, recommended, or suggested in the proposed labeling. For us to consider a product, a drug to be safe and effective, we look for substantial evidence of effectiveness for treatment of the proposed indication, and the benefits for the proposed population should outweigh the risks.

In terms of the additional requirements,

labeling will indicate the safety and effectiveness has only been demonstrated with respect to a limited population. And as I said, promotional materials need to be submitted 30 days prior to dissemination of such materials.

Are there any questions I can clarify?

DR. BADEN: Dr. Schaenman, Dr. Follmann, questions about this pathway, or any other member of the committee?

(No response.)

DR. BADEN: Okay. A question I have is there is also in the background a device question related to the TDM. Presumably, that is not relevant to this consideration. That's a separate discussion, but a companion ID, I assume.

DR. NAMBIAR: For today's discussion, we were not planning to touch upon aspects of the device.

DR. BADEN: Okay. So if no other questions -- and I do want to note that Dr. Venitz had to leave and that we will now proceed to the voting.

The lights will flash. Please press the button firmly that corresponds to your vote. If you're unsure of your vote or wish to change your vote, you may press the corresponding button until the vote is closed. After everyone has completed their vote, the vote will be locked. The vote will then be displayed on the screen. The DFO will read the vote from the screen record. Next, we'll go around the room and each individual who voted will state their name and vote into the record. You can also state the reason you voted as you did if you want to. We'll continue in the same manner until all questions have been answered.

The first question is before us. I assume there are no questions about the wording, so we will move forward with voting.

(Voting.)

DR. CHEE: We have question 1, 15 yeses, zero nos, zero or abstain of course, and 1 no vote.

DR. BADEN: We will start with Dr. Palevsky, and with the next vote, we'll start from the other side.

DR. PAVLESKY: So obviously it's clear I must have voted yes, with some concerns that we need more information, speaking as a nephrologist, on pharmacokinetics, how best to monitor the drug for preventing nephrotoxicity. I'm uncomfortable with remaining tied to Cockcroft-Gault creatinine clearance, and I think that the company needs to look at dosing recommendations based on circa 2018, means of assessing kidney function, and potentially look at other markers for nephrotoxicity and markers of kidney function such as the statin C.

DR. BADEN: Dr. Le?

DR. LE: I voted yes primarily because it does appear qualified for the definition of LPAD with one well-controlled control trial with other information that's available there. I like the fact that there is somewhat of a TDM incorporated into this that kind of provides a safeguard in terms of monitoring for nephrotoxicity in patients with cUTI.

DR. BADEN: Thank you. Dr. Schaenman?

DR. SCHAENMAN: I also voted yes. I did

feel that evidence was provided supporting safety and effectiveness for this particular indication. Although there was only a single noninferiority trial presented, I thought that the in vitro studies using clinical isolates, the animal studies as well as the limited bloodstream infection data all supported the idea that the drug was effective, and especially in the framework of the LPAD labeling plan and the clear unmet need of having additional treatments for MDR gram-negative infections.

May we talk about labeling suggestions? Okay. I would suggest that the packaging mention limitations of the clinical trial, including generalizability to nonwhite population. As was mentioned previously, I do think that TDM should be suggested given the interpatient variability observed even in patients with relatively minor or even normal renal function, but especially for those with renal insufficiency to ensure efficacy and avoiding nephrotoxicity in patients with urinary tract infection. And I would also like to

add that postmarketing studies would be very beneficial.

DR. BADEN: Dr. Lo Re?

DR. LO RE: Vincent Lo Re. I voted yes. I thought that the phase 3 study 009 sufficiently demonstrated noninferiority to meropenem and higher composite cure rates and microbiological eradication rates at test of cure, especially for key resistant subgroups. I thought there appeared to be few SAEs, which generally appeared to reflect the aminoglycoside class. And I thought that just given the continued emergence of resistance to both old and new antimicrobial agents, limited existing treatment options and a continued need for additional antibiotic options for persons with complicated UTIs, that this new antibiotic will fill that important unmet need. And I would agree with Dr. Schaenman that additional postmarketing studies on safety would be valuable.

DR. BADEN: Dr. Daskalakis?

DR. DAKSKALAKIS: Demetre Daskalakis. I also voted yes on the grounds that study 009 did

demonstrate noninferiority, and I think it represented an adequately powered study to make that assertion. I think that from the perspective of complicated urinary tract infection, this drug is important and adds to the limited armamentarium that we have for resistant organisms.

From the perspective of labeling, I think that there needs to be clear guidance about therapeutic drug monitoring, and I think that there are still some discussions happening. So I think if there is ambiguity, it's best to implement therapeutic drug monitoring across the board rather than base it on creatinine clearance if that becomes an area of a lot of conversation. It's easier for clinicians to understand that they create a subgroup of individuals who may or may not qualify for that monitoring.

I would also recommend clear guidance on bacteremic UTIs just to make it clear from the perspective of duration of therapy. That may be something that the labeling should also include. And I would also comment that it's worth, I think

in the setting, to not only advise clinicians about a limited population, but also to comment that it's probably wise to limit the exposure of this agent to whatever is necessary for therapeutic purposes.

We don't have a lot of experience nor a lot of long duration therapy in UTIs, so I think it's important to comment to limit the group and also limit the time people are on the drug. And finally, I think it's also important to make a comment about ototoxicity and the fact that we don't really know very much. So I think that a non-statement on this will mean that clinicians may think that this is not a problem. And since we don't know, I think it needs to be clearly stated in the labeling. Thank you.

DR. BADEN: Dr. Baden. I also voted yes, and I echo the earlier comments. The comments that I would highlight, the safety data set are quite limited, however, the study offered was reasonable for the question being asked and is clinically relevant.

I would presume that this agent has the

similar toxicity as this class of drugs aminoglycosides until date are generated otherwise, echoing a Dr. Daskalakis' comment that ototoxicity, vestibular toxicity, those other toxicities should be presumed until data can be generated that they are or not a concern.

This also lends itself to the TDM and monitoring analogous to the class, again, until data are generated that can better direct practice. I also think there needs to be better data generated on the microbiologic effect and characterizing organisms and the different resistant mechanisms, as that will be important in better understanding activity going forward.

Dr. Weina?

DR. WEINA: Peter Weina. I obviously voted yes as well. I still struggle with the issue of the idea of unmet needs, and that's after availing myself of the 2017 guidance for industry issued by the FDA and actually speaking of the noninferiority complex -- no --

(Laughter.)

DR. WEINA: -- the noninferiority trials and how to utilize them for the unmet medical need. I'm a little bit of a cynic, and regarding the labeling, totally agreeing what has been previously said, the clinicians are the worst when it comes to it. The lawyers are really good at reading the labels; we're not. And we have to make sure that it specifically says exactly what we want it to say because, otherwise, it's going to end up being used in every way but what it's for. So that's all.

DR. BADEN: Dr. Honnegger?

DR. HONNEGGER: Jonathan Honnegger. I also voted yes, for the same reasons that have been mentioned before. I felt it met the criteria or the LPAD pathway. I welcome a drug that treats the CRE multidrug resistant organisms. I also just want to add, in additional studies, I just want to remind there is obviously no pediatric data yet, so I would encourage that to be done.

DR. BADEN: Dr Green?

DR. GREEN: Michael Green. I voted yes. Today's meeting brought the committee face to face

with the crisis of multidrug resistant bacteria, their terrible impact on patient outcome, the response of our legislator, the FDA, and perhaps most importantly, the pharmaceutical industry to address the crisis. Results of 009 study in my mind clearly showed that plazomicin met the noninferiority endpoints that were built into this protocol.

I actually was comfortable with the unmet need standard being met and wasn't bothered by the use of meropenem when one looks at the fact that approximately 80 percent of the isolates were ESBL positive and 75 percent of the isolates were aminoglycoside resistant in both the plazomicin and the comparator group. I think the approval of plazomicin with an indication for complicated UTI provides an important new tool against the epidemic of CRE, and I'm thankful for that.

Then to mimic my colleague to my left, I hope and trust that future studies in the pediatric population are being planned because we need them, too. Thanks.

DR. BADEN: Dr. Gripshover?

DR. GRIPSHOVER: Hi. I voted yes because as everyone else, I felt that study 009 did show efficacy and did [indiscernible] mean that it was noninferior to meropenem. I think it showed reasonable in the UTI, especially if people had normal renal function and over the short duration of treatment because it really was a short duration of treatment, 5 days for most people.

So I think that label should highlight that we went to limit it to susceptible organisms and use a special caution with renal insufficiency.

DR. BADEN: Dr. Clark?

DR. CLARK: Yes. I voted yes. I think approval is appropriate for the limited population suggested in the sponsor's proposed indication for complicated UTI. And while there may be some generalized ability concerns given the demographics, I thought the data were convincing in terms of noninferiority of plazomicin to the comparator. I also thought it was reassuring that bacteremic of patients ultimately cleared their

bloodstream infection with plazomicin.

I'm interested in seeing future data in immunocompromised patients, especially renal transplant recipients who have very high rates of UTI, especially recurrent UTIs and those due to MDR gram negatives. I disagree with monitoring drug levels probably in all patients and have some concerns about the ototoxicity issue that should be noted in the labeling.

DR. BADEN: Dr. Follmann?

DR. FOLLMANN: This is Dean Follmann. I voted yes. After some thought about the unmet need and the back and forth on that, I thought it made sense to accept the limited pathways argument that the FDA had for this. So the single trial with the endpoints that they required were met pretty easily. I felt the safety profile was acceptable. I appreciated the explanation of the composite endpoint that Ed gave, and I also was comforted by looking at the clinical endpoint at late follow-up visit, which also showed it easily met the noninferiority margin. So I felt comfortable

voting yes.

DR. BADEN: Dr. Hawkins?

DR. HAWKINS: Yes. I felt comfortable voting the affirmative. And although it may be obvious, I think it's very, very important that in our hospitals, we're also limited by who could write and prescribe these drugs. I think it's very, very important in the labeling, where possible, to indicate that only individuals trained, such as infectious disease or other specialists, be the ones that write this drug.

DR. BADEN: Ms. Dunn?

MS. DUNN: Yes. Five years ago, I had a very serious blood infection and was on an intravenous antibiotic routine of multiple medications for about 10 weeks. So I did live through some of this, not quite as serious as what we've been talking about today, but it was still pretty serious for me. I am concerned about labeling and dosing for the patients, but I do believe that this is a hopeful drug for patients who are in a very critical state. So it's good to

know that there's something out there on the horizon for them and hopefully will be available soon. So I definitely feel that the benefit outweighs the risk. Thank you.

DR. BADEN: Dr. Rej?

DR. REJ: I obviously also voted yes for many of the reasons that were expressed around the table. And I think that the evidence presented meets the bar for approval in this category. I think that definitely the criteria for the TDM component needs to be clarified and be much more specific. And again, even though it's a minority of aminoglycosides that interfere with certain creatinine measurements, I think the sponsor should look to be sure that there is no interference with the measurement of creatinine.

DR. BADEN: So I'm asked to summarize after each vote. The arguments against, none; the arguments for, unmet need, a well-controlled trial was offered, however much more data are needed, including better safety data, dosing data, renal monitoring data, microbiologic activity data.

However, those should be encouraged upon the applicant to help generate those data in the future.

We can move to question 2. Has the applicant provided substantial evidence of the safety and effectiveness of plazomicin for the treatment of bloodstream infections in patients with limited or no treatment options? If yes, please provide any recommendations regarding labeling. If no, what additional studies, analyses, are needed?

Any questions about the question?

(No response.)

DR. BADEN: If not, then we can proceed to voting the same process as previously.

(Voting.)

DR. CHEE: Question 2, you have 4 yeses, 11 nos, zero abstain, and 1 no vote.

DR. BADEN: One no voting. Okay. So we will start with Dr Rej.

DR. REJ: So I did vote yes, but after considerable deliberation, I felt in the end the

data met the criteria needed for approval for this category of drug. And again, all my comments about the TDM part for question 1 apply here, too.

MS. DUNN: I voted yes.

DR. BADEN: Dr. Hawkins?

DR. HAWKINS: Dr. Hawkins. I voted no. I had difficulty with patients and substantial benefit. I had trouble with that; need more patients, and I understand the limitations are indicated by our panelists in the industry.

DR. BADEN: Dr. Follmann?

DR. FOLLMANN: I'm Dean Follmann. I voted no. This is a tough decision for me in that going in this morning, I was leaning towards yes, but ultimately I think it hinged on looking at the word "substantial." I felt ultimately this was a quite underpowered study and sort of danced around superiority, but it wasn't convincing I guess. There were 17 maybe different analyses that you could look at to support or not support this, and I'm a little uncomfortable when you're in that gray 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

obviously. In terms of additional analyses, I liked the time-to-event analysis that we talked about. The sponsor presented that. There was slight mention in the FDA documents about an ordinal outcome. That might be another way to take the existing data you have and try and glean a little more information about it.

Another thing that was touched on in the FDA comments is to use covariates of regression analysis to try and either increase the power of the study or to -- I thought of this maybe as a way to bring in cohort 1 -- I mean bringing in cohort 2 in the analysis, so we have cohort 1 and bring in cohort 2 and sort of use observational study type techniques to look at the blended cohort.

I don't know if I strongly advocate that because I just don't know how comparable they are, and I know you can't level the playing field with very many covariates, maybe one or so. So given you have the data, I would probably do that, but I wouldn't accept it uncritically, as I'm sure you wouldn't. So that's about all I have.

DR. BADEN: Thank you. Dr Clark?

DR. CLARK: I also voted no. My concerns are similar to Dr. Follmann's. It was a very difficult decision given the need for new agents, but I didn't feel that the applicant met the standard of substantial evidence of safety and efficacy with an adequate and well-controlled study.

I was influenced by the case details that were provided by the FDA, which I thought were very helpful, the uncertainty about plazomicin treatment effect due to the small sample size and all the potential confounders such as lack of documented positive blood cultures within 24 hours of drug initiation and the prior potentially effective therapies. I also was not convinced that the noninferiority analysis was an adequate basis for approval given the initial study design and confounding factors that might have impacted outcomes with colistin.

DR. BADEN: Dr. Gripshover?

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,

too, because I think that that was a little bit unclear as well.

DR. GREEN: Michael Green. I voted no. Because of the clear need, I was really tempted to vote yes, and actually I came here today thinking that I was going to vote yes. But this study clearly had a number of limitations that impacted the interpretation of results to support the approval for a bloodstream infection indication. The changes in the protocol, the modifications in the original statistical plan clearly created challenges. But I think the limitation that I just could not overcome were the small numbers. At most, we have a study of 29 patients with bloodstream infection, and at worse we have a study of less than that. So while we desperately need new drugs, I just don't think we have enough data to approve for this indication.

I also thought that one might be able to apply the model of what was just done for complicated UTI to bloodstream infections. If you wanted to open the door a little wider to both have

a little bit more restricted but still have a broad population for which there's no shortage, you could maybe even say go after ESBL positive bloodstream infections. But to get those numbers, I think it would be fine to do noninferiority.

As I stated, for the complicated UTI comment, I don't have a problem using meropenem as a comparator. I think if you're down to having to use meropenem, there's a clear need because it's not going to last for very long, so we could bring it on board. We obviously desperately need it. But I just have a hard time saying yes as a labeled indication on a total of 29 patients. Thank you.

DR. BADEN: Dr. Honnegger?

DR. HONNEGGER: Jonathan Honnegger. I also voted no for the same reasons, and I made my decision last minute. It was very difficult. I wanted to vote yes because this treats CRE. I believe the supportive data are really there obviously in the UTI and the in vitro microbiological data.

Also in less ill patient who had bacteremia

in the setting of a UTI or those with APACHE score of less than 15, it appeared to do well and supportive data. It was just a lack of an adequate well-controlled trial. I just didn't feel it was adequate in the numbers, 14 versus 15 in the comparator group. And that was hard, too, because this trial had a very impressive numerical effect on a very meaningful endpoint of mortality.

As far as that primary trial, they're going to have to figure out some mechanism to do this, and unfortunately doing this now in retrospect, whether it's a slightly larger design trial for CRE or a noninferiority trial in patients who don't necessarily have CRE.

DR. BADEN: Pete Weina. I voted no. Unlike the complicated UTI one where we had a really nice, I thought, noninferiority trial and where the concentrations of the unchanged drug in the urine makes complete sense for clearing the bacteria, I believe this particular trial for bloodstream didn't meet FDA's guidance of substantial evidence, where the definition of evidence is adequate and

well controlled. As a clinician, I'd love to have more tools, but I'm uncomfortable with the data as presented. I failed to see the sponsor met the standard that is set forward for us.

As I said, I'm a cynic, and I believe an approval is an approval, is an approval, and even drugs with black box warnings are used all over the place until the lawyers start dropping lawsuits or denigrated when compared to another drug. So my recommendation for additional studies and analyses are just to keep track of all the bloodstream infections that the drug is going to end up being used for if it gets approved for UTIs. Thank you.

DR. BADEN: Dr. Baden. I voted yes, and I seem to routinely find myself in the minority.

(Laughter.)

DR. BADEN: However, I hope and I think we are a thoughtful minority. So I have many of the same views as the prior statement, prior panel members and their comments, but a slightly different synthesis. I think that there are many issues with the study design, the change in the

study design, the smallness of this study, the focus of a single country, single population, small number of organisms, lack of clarity, and the limitations in disentangling source control, line management, underlying condition, an organism susceptibility and resistance to the comparator. However, we are left with the data we have, not the data I want.

There were 2100 participants screened. This is not a trivial undertaking and this is not a trivial problem that we are faced with in terms of the unmet need of gram-negative resistance, and as I mentioned in my concerns with the design, those intrinsically increased the complexity to have the perfect study, so we have an imperfect study. But the totality of the data, including the in vitro data, the animal model, the understanding of the mechanism, the understanding of prior agents in the class and activity, the 009 bacteremic data, plus the 007 having a mortality endpoint, to me the totality of those data are compelling that there is meaningful activity of this agent for an unmet

need.

Having said that, there are many, many questions that need to be further explored and understood as I already alluded to and as others have alluded to. But for those reasons, I voted yes,

Dr. Daskalakis?

DR. DASKALAKIS: Demetre Daskalakis. I also voted yes, and a lot of the reasons -- many of the same reasons that Dr. Baden just discussed. I think we all acknowledge that the study is very limited as far as CRE, but I read the question very literally, which reads, has the applicant provided substantial evidence of the safety and effectiveness of plazomicin for the treatment of bloodstream infections in patients with limited or no treatment options?

The totality of the data to me says yes. It doesn't say CRE. It says for limited options in treatment. So from my perspective, I think that we have a fairly good signal that this agent has activity against CRE and also a very good signal

that it is effective in bacteremic ETI. We have animal models and also in vitro models that support it as well.

So from my perspective, I voted yes, again, looking at the totality of the data and not just one isolated study. So I think that in my opinion, though there is more work to do, the totality of the evidence does demonstrate substantial proof that this agent does work and that it does have a very good safety profile.

I'll continue on that track of following the question literally and say if this does go on to approval, I think definitely, as I said for UTI, there has to be extraordinary clarity on therapeutic drug monitoring for this drug; so whatever ends up happening from this perspective for septicemia, for bacteremia.

I also just want to say from the perspective of the future of this pathway for applicants, I hope that our vote here doesn't discourage individuals from pursuing this type of approval for drugs that are so critical. There is clearly a

need, and I want to echo the comment that people will be using this for bacteremic infections that are not urinary tract infections, so it will be very important for us to track what this looks like and then potentially reconsider if this does not get labeled to include bacteremia as not related to urinary tract infections. Thank you.

DR. BADEN: Thank you. Dr Lo Re?

DR. LO RE: So I voted no, and for me it came down to what were the criteria for substantial evidence. For me, I did not feel that study 007 provided substantial evidence for the efficacy of plazomicin for the treatment of bloodstream infections. I had concerns regarding study 007's overall very small sample size; the uncertainty of the primary bacteremia diagnoses in the trial that were expressed by the agency; the problem of nonadherence where some people were switching to alternative regimens early on; the limitations in the statistical analyses that were also highlighted by the FDA; and the largely descriptive nature of the study results, all of which to me made

interpretability of those results challenging and introduced a high degree of uncertainty.

I appreciate that the sample sizes are going to be small for these studies of antimicrobial drugs for these highly resistant organisms, but to me, this study had too many, far too many, limitations to assure the efficacy of plazomicin for bloodstream infections.

I also thought that study 007's cohort 2, which was so different from cohort 1 and with no control group, for me made further evaluation of this group for efficacy difficult. I don't think that this should be the bar that we set for the limited population for the antibacterial drugs pathway. And I think the challenge for the agency going forward is to probably more effectively articulate what the bar should be. But I personally thought that additional data evaluating plazomicin's efficacy in a larger sample of patients with bloodstream infections are needed before we can support a positive benefit-risk for this indication.

DR. BADEN: Dr. Schaenman?

DR. SCHAENMAN: I also voted no for very similar reasons. I also struggled with this vote. Considering the current crisis and the lack of alternatives, it was very difficult. However, I also felt that we had not reached the threshold of substantial evidence in demonstrating effectiveness.

We've already talked about the many problems of trial 007. There was a numerical trend towards efficacy, which was quite encouraging, but the trial did not reach the predetermined goals. Everybody has mentioned the small study size. There was heterogeneity in the inclusion, in the length of time that patients received drugs. And although Dr. Kartsonis did caution us that this is common in candidemia or bacteremia drugs, given the small study size, I felt that it really did limit our ability to interpret the results.

As was mentioned before, the initial plan as a superiority study followed by two study amendments that were quite impactful leading to

ultimately a descriptive study only, all of this undercut the ability of the sponsor to reach that threshold of substantial evidence, but again, further guidance from FDA as to exactly what that looks like would be helpful.

I did want to say, however, that I thought that the safety data was quite reasonable, and given the limited number of choices and alternatives including colistin, meropenem, tigecycline, I thought that in terms of safety, substantial evidence was shown that the drug was safe, again, within the context of need to treat CRE. So that all led to my vote of no.

In terms of additional studies that would be required, it may be that where we are now compared to where we were in 2011 or even 2014, as this crisis continues to enfold in metropolitan areas including New York City, perhaps it will be easier to enroll a reasonably powered study to test the question of efficacy in bacteremia.

DR. BADEN: Dr. Le?

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?

So integrating those variables in to give a more estimate of what the nephrotoxicity would be in this population.

Lastly, it may or may not be a signal, but the 8 adverse events of greater than 10 percent was reported in 007 cohort 1 with some of the cardiac effects. So it would be prudent just to monitor that.

DR. BADEN: Thank you. Dr. Palevsky?

DR. PALEVSKY: So I also voted no with some degree of reluctance because I would really like a drug as an alternative to using colistin. However, I don't think that the threshold for efficacy and safety was met with a 29-patient study. My comments echo those of multiple that have been made. I am absolutely convinced that if the agency provides the approval based on our recommendation for urinary tract infections, I will see this used in my ICU for bacteremic infections. But I think that it has not met the labeling requirement, and we just need, a larger -- not enormous but a larger study.

I do have concerns over the approach for therapeutic drug monitoring, and I think you need extensive data on how the AUC over 24 hours plays out at different levels of kidney function or patients who are on renal replacement therapy. I also think you need to have data on the use of this drug in patients on other modalities of renal replacement therapy other than continue with therapy, although that didn't influence my decision.

DR. BADEN: Thank you

So as you have heard, 4 yes, 11 no. The primary no arguments were the data are not substantial, multiple additional analyses are needed, the small sample size was just too small, and the multiple changes in the design further undercut the interpretability of the data. TDM will be needed in any case.

On the yes side, it has to do with the totality of the data, the difficulty of doing the studies, the tremendous unmet need, and activity for bacteremia in the setting of limited other

options, and the need to encourage more development in this space given the unmet need.

So that concludes the business of the committee. Before we adjourn, any last comments from the agency?

DR. NAMBIAR: Thank you, Dr. Baden. We just wanted to thank the committee for all their useful feedback and very thoughtful suggestions. I would also like to thank the applicant for all the work they've done on this NDA and for their presentations today, and also extend our sincere thanks to the presenters at the open public hearing. We wish you all safe travels, and we'll see you in a few months.

Adjournment

DR. BADEN: Thank you, and the meeting is now adjourned.

(Whereupon, at 4:09 p.m., the meeting was adjourned.)