FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEETING
(AMDAC)

Wednesday, October 16, 2019
8:00 a.m. to 4:02 p.m.

FDA White Oak Campus
White Oak Conference Center
Building 31, The Great Room
10903 New Hampshire Avenue
Silver Spring, Maryland
Meeting Roster

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PROCEDINGS
(8:00 a.m.)

Call to Order

Introduction of Committee

DR. BADEN: It is 8:00; if everyone can please take their seats.

Good morning. I would first like to remind everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so. I would also like to identify the FDA press contact, Jeremy Kahn. If you are present, please stand. No Jeremy.

My name is Lindsey Baden, and I will be chairing today's meeting. I will now call the Antimicrobial Drugs Advisory Committee to order. We'll start by going around the table and introducing ourselves. We'll start with the FDA to my left and go around the table.

DR. FARLEY: Good morning. John Farley, acting director, Office of Antimicrobial Products, CDER, FDA.

DR. NAMBIAR: Good morning. Sumathi
Nambiar, director, Division of Anti-Infective Products, CDER, FDA.

DR. WEINSTEIN: Good morning. Ed Weinstein, clinical team leader, Division of Anti-Infective Products.

DR. NASEER: Shabnam Naseer, clinical reviewer, Division of Anti-Infective Products.

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

DR. SUVARNA: Kalavati Suvarna, clinical microbiology reviewer, Division of Anti-Infective Products, CDER, FDA.

DR. SIBERRY: George Siberry, pediatric infectious disease physician at the Global Health Bureau USAID, panel member.

DR. OFOTOKUN: Igho Ofotokun, adult infectious diseases, Emory University, Atlanta, panel member.

DR. GREEN: Michael Green, pediatric infectious diseases, transplant infectious diseases, UPMC, Children's Hospital Pittsburgh, and the University of Pittsburgh School of Medicine.
DR. BADEN: Is Dr. Smith on the phone?

DR. SMITH: I am. Good morning.

DR. BADEN: Will you please introduce yourself?

DR. SMITH: Sure. Good morning. My name is Davey Smith. I'm an adult infectious disease doctor and chief of infectious diseases at UC San Diego.

DR. WEINA: Peter Weina, adult infectious disease, Defense Health Headquarters.

DR. HOTAKI: Lauren Hotaki, designated federal officer.

DR. BADEN: Lindsey Baden, adult infectious diseases, Brigham and Women's Hospital, Dana-Farber Cancer Institute, Harvard Medical School in Boston, Massachusetts.

DR. GRIPSHOVER: Barb Gripshover, adult infectious diseases at University Hospital's Cleveland Medical Center, Case Western Reserve University.

DR. CLARK: Nina Clark, adult infectious diseases at Loyola University Medical Center in
Stritch School of Medicine at Maywood, Illinois.

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

DR. LE: Jennifer Le, pediatric infectious diseases, professor of clinical pharmacy at UC San Diego.

DR. WALKER: Good morning. Roblena Walker, CEO, EMAGAHA, Inc., Atlanta, Georgia, consumer representative.

MS. THOMAS: Good morning. Jill Thomas, patient representative.


DR. DELEO: Good morning. I'm Frank DeLeo, chief at the laboratory of bacteriology at NIAID in the National Institutes of Health.

DR. MAY: Susanne May, professor of biostatistics at the University of Washington in Seattle.

DR. MOORE: Tom Moore, infectious disease physician in Wichita, Kansas.
DR. KARTSONIS: Good morning. Nick Kartsonis, clinical infectious diseases and vaccines at Merck Research Labs, Merck and Company, Incorporated, and I serve as the industry rep.

DR. BADEN: 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 will 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.

Dr. Hotaki will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

DR. HOTAKI: 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 for this committee's compliance with federal ethics and conflict of interest laws, covered by but not
limited to those found at 18 U.S.C. 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 U.S.C. 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 a special government employee's services outweighs his or her potential financial conflict 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 discussion of today's meeting, members and temporary voting members of the committee have been screened for potential financial conflicts 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 U.S.C. 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 209445, cefiderocol lyophilized powder for intravenous administration, submitted by Shionogi, Inc., proposed for the treatment of complicated urinary tract infections, including pyelonephritis due to gram-negative bacteria in patients with limited or no alternative treatment options.

This is a particular matters meeting during which specific matters related to Shionogi'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 Research Laboratories, 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 interest, 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 proceed with the FDA opening remarks from Dr. Weinstein. And while Dr. Weinstein comes to the podium, I just want to thank both the applicant and the agency for very thorough briefing documents, which will lead to a vigorous discussion today about the issues at hand. And I'd like to thank the committee members for taking the time to join us in this important activity.

Dr. Weinstein?

FDA Introductory Comments – Edward Weinstein

DR. WEINSTEIN: Thank you. Good morning. My name is Ed Weinstein, and I'm a clinical team leader in the Division of Anti-Infective Products. Thank you for traveling all the way to White Oak today and spending the day with us to discuss cefiderocol.

The NDA number is 209445. The applicant is Shionogi. The product has qualified infectious disease product designation for complicated urinary tract infections, hospital-acquired bacterial
pneumonia, ventilator-associated bacterial pneumonia, and bloodstream infections. This NDA was granted priority review, as the product has QIDP designation.

The proposed indication is for use as a single agent in patients aged 18 years or older for the treatment of complicated urinary tract infections, or cUTIs, including pyelonephritis caused by susceptible gram-negative microorganisms.

As only limited clinical safety and efficacy data for cefiderocol are currently available, cefiderocol should be reserved for use in patients who have limited or no alternative treatment options. The proposed dosing is 2 grams intravenously every 8 hours, with dose adjustments for patients with augmented renal clearance, as well as renal impairment, including end-stage renal disease.

The development program included six phase 1 studies, including a lung penetration study, a thorough QT study, and renal impairment study. There were two active controlled clinical
trials in adult patients.

The cUTI trial compared cefiderocol to imipenem/cilastatin in patients with carbapenem-susceptible gram-negative pathogens. The CREDIBLE study, otherwise called CREDIBLE-CR, compared cefiderocol to the best available therapy in patients infected with carbapenem-resistant pathogens across body sites.

CREDIBLE completed enrollment during the review cycle. There was no clinical study report submitted.

There was one phase 3 trial in adults with nosocomial pneumonia due to carbapenem-susceptible gram-negative pathogens, called APEKS-NP. This trial recently completed enrollment, and only summary mortality data were submitted.

Taking a look at the cUTI trial, it was 2 to 1 randomized, double-blind, a non-inferiority trial comparing cefiderocol to imipenem/cilastatin for 7 to 14 days of treatment. The trial design was generally consistent with the FDA and cUTI guidance. There was no IV to oral anti-bacterial
therapy switch permitted during the trial, and dose adjustments were based upon the creatinine clearance.

The primary endpoint was a composite of microbiologic eradication and clinical cure rate in the microbiological intent-to-treat population at the test of cure. This visit occurred approximately 7 days after the last dose of study drug.

Given the potential of cefiderocol to address an unmet clinical need, the agency agreed that a single clinical trial would provide sufficient evidence of efficacy for a limited-use cUTI indication. The prespecified, non-inferiority margin was 15 percent.

Taking a quick look at the overall results of the cUTI trial at the test of cure, we have the following table. The top line is the composite response. Cefiderocol produced a 72.6 percent success rate as compared to the imipenem/cilastatin comparator that was 54.6 percent. The treatment difference was 18.6 percent, and if you notice, the
lower boundary of the confidence interval is greater than zero, which is consistent with statistical superiority.

Looking at the second row, the microbiologic response, you see the treatment difference is 17.3 percent, and this is what drove the composite response difference. The clinical response difference was 2.4 percent or roughly similar between the two treatment groups.

Taking a look at the second trial, the CREDIBLE trial, it was 2 to 1 randomized, and open-label trial comparing cefiderocol to the best available therapy. We're going to call it BAT or B-A-T.

This was across body sites for the treatment of carbapenem-resistant gram-negative pathogens. No formal hypothesis testing was prespecified. A colistin-based regimen was used as BAT in the majority of subjects.

Cefiderocol dosing regimen was the same as the cUTI regimen, except the infusion time was extended from 2 hours to 3 hours. Seven to 14 days
of treatment was intended, but it was permitted to be extended up to 21 days of treatment with a clinical justification.

The primary endpoint depended upon the site of infection. For the pneumonia or the bloodstream infection, the clinical outcome at the test of cure was the primary endpoint. For patients with cUTI, the microbiological outcome at the test of cure was the primary endpoint.

The following table shows the key result from this trial. There was a mortality imbalance, so it was disfavorable to cefiderocol, and this occurred at each one of the study days that was examined, including day 14, day 28, and day 49 that loosely corresponded to the end of study.

You'll notice in the lower portion of the table that this mortality imbalance did not extend to patients with complicated urinary tract infections.

The safety assessment considered each of the trials separately, and there are reasons for this. There were substantial differences between
the trials such as the type and the severity of the infection, the duration of treatment, the patient population, the fact that multiple comparators were used in the BAT regimen, and the use of concomitant medications.

The safety of cefiderocol in the cUTI trial was generally consistent with the cephalosporin class. Potential safety signals included reduced seizure threshold, hepatotoxicity, C. diff colitis, and hypersensitivity reactions.

This brings us to the outline for the day. We'll start with presentations by the applicant, followed by presentations by the FDA review team. Dr. Suvarna will provide some microbiologic considerations followed by each of the trials presented individually. Dr. Rubin will present efficacy, and Dr. Naseer will present safety findings.

At that point, we'll take clarifying questions from the committee. We'll break for lunch. We'll return to an open public hearing, and finally the questions to the committee.
To give a preview of the questions to the committee, there are two. The first is a discussion question. Please discuss your evaluation of the mortality imbalance observed in the CREDIBLE study with respect to the overall risk-benefit assessment for cefiderocol and provide recommendations for labeling and/or the need for additional studies.

The second question is a voting question. Has the applicant provided substantial evidence of the efficacy and sufficient evidence of the safety of cefiderocol for the treatment of complicated urinary tract infections, including pyelonephritis, in patients with limited or no alternative treatment options? If yes, please provide any recommendations concerning the labeling. If no, what additional studies or analyses are needed?

Thank you very much. At this point, we'll proceed with the applicant presentations.

DR. BADEN: Thank you, Dr. Weinstein.

While Dr. Nagata takes the podium, 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 relationship that they may have with the applicant, such as consulting fees, travel expenses, honoraria, and interest in the 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 will now proceed with Shionogi's presentations.
Applicant Presentation – Tsutae Nagata

DR. NAGATA: Multi-drug resistance, particularly a carbapenem resistance, is a growing problem in the United States and around the world. Penicillin was discovered in 1928. The first carbapenem became available in 1985 for the treatment of complex bacterial infections.

Physicians need new antibiotics with novel approaches to overcome the multiple resistance mechanisms that make these superbugs so hard to treat.

Good morning. I am Tsutae Den Nagata, chief medical officer at Shionogi. I'm a physician with a urologist specialty, and I still see patients in a clinic in Japan. In my hospital days, I treated patients in the ICU, including those with complicated urinary tract infections. Infections were challenging due to resistance then and are even more challenging today.

Developing antibiotics that can overcome resistance is a priority of mine, with my top priority being cefiderocol. My team and I are
excited to work with this committee to bring to
patients and clinicians an innovative treatment
option to help cure infections to relieve suffering
and save lives.

Cefiderocol is a new cephalosporin, and its
activity against resistant strains led to FDA
granting a qualified infectious disease product,
also known as QIDP designation. Through
discussions with the FDA, we agreed that the best
route to making this important medication available
to patients would be a streamlined development
program focused on a clinical trial in
site-specific infections where statistical
comparison with existing medicine is possible.

Streamlined development enables approval
with a limited-use indication based on a single
pivotal study with strong support from
microbiological and pharmacokinetic and
pharmacodynamic assessments.

The pivotal study for this streamlined
approach was a cUTI study. This study enrolled
patients at risk for MDR pathogens and demonstrated
the primary endpoint of non-inferiority compared
with high-dose imipenem. It also met statistical
criteria for demonstrating superiority to imipenem.

The cUTI study forms the basis for the
indication being sought. It is a 448-patient
double-blind study to assess clinical outcome and
microbiological outcome in patients with
carbapenem-susceptible cUTI.

APEKS-NP is a study that was recently
completed and is the basis for approval of a future
indication in nosocomial pneumonia in the United
States. The primary endpoint in this double-blind
study was to assess all-cause mortality in
300 patients with carbapenem-susceptible HAP, VAP,
and HCAP. Although the top-line results have been
provided to the FDA, the full study report has not
yet been submitted for review.

The CREDIBLE-CR study is a recently
completed open-label study of 150 patients with
three infection types and forms the basis for a
pathogen-focused indication for approval in Europe.
The study assessed the effect of cefiderocol by
measuring, as the primary objective of the study, clinical outcome and microbiological outcome in seriously ill patients with infections with carbapenem-resistant bacteria.

These patients had complex illnesses and included those who would normally be excluded from clinical trials, as their prognoses are so poor. This resulted in a heterogeneous population, which limits rigorous comparison between treatment arms.

The best available therapy arm was used for descriptive comparison, and no inferential testing of statistical hypothesis was planned. We observed a difference in all-cause mortality between the two treatment arms in this study, which will be discussed in detail later.

Shionogi has three planned pediatric studies. We are currently collaborating with investigators on a trial in adults with bloodstream infections. A phase 1 study is ongoing to assess cefiderocol in epithelial lining fluid in patients with mechanical ventilation.

In addition to clinical studies, Shionogi
has been also providing cefiderocol unsolicited, upon request from physicians, for patients who have serious carbapenem-resistant gram-negative infections and are not eligible for clinical studies. They have to have no other treatment options for their infections. The briefing document describes 74 of these compassionate-use patients.

Today's presentation will focus on the cUTI indication, which is for the treatment of complicated urinary tract infections, including pyelonephritis, in adult patients caused by gram-negative pathogens.

Consistent with a streamlined development pathway, the cefiderocol indication will only be for use where limited or no alternative treatment options are available. The recommended dose and dosing regimen of cefiderocol is 2 grams administered every 8 hours by intravenous infusion over 3 hours. Dose adjustments are recommended for patients with renal impairment, as well as augmented renal clearance.
After this introduction, Dr. Karam from Louisiana State University School of Medicine will describe the pressing need for new antibiotics to treat serious cUTI indications caused by resistant pathogens.

Next, Dr. Roger Echols will show the data that demonstrate how cefiderocol overcomes resistance and how that translates into microbiological activity and target attainment.

Then Dr. Simon Portsmouth will present the result of the double-blind cUTI study that demonstrated non-inferiority efficacy and the favorable safety profile as expected for a cephalosporin, followed by a description of the recently completed open-label CREDIBLE-CR study. He will then briefly discuss the recently completed double-blind APEKS-NP study, which is not under review by the FDA.

Finally, Dr. Paterson from the University of Queensland will present how the benefits of cefiderocol outweigh its risks for the treatment of cUTI. Thank you very much.
DR. KARAM: Hello. My name is George Karam. I'm an infectious disease physician with the Louisiana State University School of Medicine in New Orleans, but I'm based in Baton Rouge with 36 years of experience in infectious diseases.

Antimicrobial resistance is a medical crisis that requires immediate attention, and carbapenem-resistant species are a major driver of the problem.

As an infectious disease physician, I see firsthand the consequences of carbapenem-resistant gram-negative infections, such as complicated UTI, which lead to both increased morbidity and mortality, as patients infected with these resistant pathogens have longer hospital and ICU length of stays and generally worse outcomes.

Unfortunately, there are few good choices for the treatment of these antibiotic-resistant complicated UTIs.

Complicated urinary tract infections occur in patients that have an abnormal urinary tract,
such as obstruction, stones, have a bladder
catheter or instrumentation, immunosuppression or
neurogenic conditions that impair bladder emptying.
These are not uncomplicated infections like
cystitis.

Recurrence of infections are common despite
multiple courses of antibiotics with apparent
activity. Indeed, these repeated courses of
antibiotics are the drivers for the development of
resistance among many urinary tract pathogens.

Complicated UTIs can spread to the
bloodstream, where they can cause sepsis due to
bacteremia. cUTIs impose a significant clinical
burden within the practice of medicine, leading to
over 400,000 hospitalizations each year in the
United States. Over the past 15 years, there's
been a 50 percent increase in the number of
patients hospitalized with cUTI. Over 85 percent
of cUTIs are caused by gram-negative pathogens such
as E. coli, Klebsiella pneumoniae, pseudomonas, and
others.

cUTI is the most common cause of sepsis in
patients over 65 years of age, and cUTI is the most common cause of severe sepsis, which has a mortality rate of 25 percent or higher. This could increase significantly if the patient has multiple co-morbidities or has a carbapenem-resistant pathogen.

Carbapenem resistance in cUTI has been associated with increased mortality. The availability of large electronic databases allows for a detailed understanding of the bacterial etiology and outcomes of complicated UTI.

Data from 180 U.S. hospitals in the Premiere Healthcare System provide information on over half a million gram-negative infections. Almost two-thirds of the pathogens came from urinary tract infections.

From this pool of 500,000 gram-negative infections, 6.7 percent were carbapenem resistant. While the rate of carbapenem resistance in urine is not as high as other infection sites like the lung, the absolute number of CR pathogens in the urine is substantial, representing 29 percent of all CR
infections.

Of these urine CR pathogens, 60 percent were non-fermenters such as Pseudomonas aeruginosa, Stenotrophomonas maltophilia, and Acinetobacter baumannii. Several of these pathogens are at the top of the list of the 2017 World Health Organization priority pathogens.

These pathogens possess resistant traits that urgently require new treatments. The top three with the critical need are carbapenem-resistant acinetobacter, carbapenem-resistant pseudomonas, and carbapenem-resistant in ESBL, producing enterobacteriaceae such as Klebsiella pneumoniae.

Carbapenem resistance is associated with worse outcomes for cUTI. In order to assess the outcomes of cUTI, we examined the Premiere Healthcare Electronic Database, which encompasses patient outcomes in microbiologic information from 180 hospitals in the United States.

Data collected from 2010 through 2015 identified over 245,000 cUTIs and showed that
Carbapenem-resistant cUTIs resulted in longer stays in hospital in the ICU.

Additionally, patients with carbapenem-resistant UTIs were less likely to be discharged home and more likely to be discharged to another long-term healthcare facility or to hospice. Moreover, mortality rates among carbapenem-resistant infections was doubled, 8 percent compared to 4 percent with susceptible strains.

Important in clinical medicine are those variables that are modifiable. A relevant question is whether the rate of death due to carbapenem-resistant enterobacteriaceae can be positively impacted. A recent published report sheds light on this.

An analysis of the Premiere database from July 2011 to September 2014; 50,000 patients, who were admitted with serious infections due to enterobacteriaceae, were evaluated. Of these, 52.6 percent had cUTI and 0.9 percent were carbapenem resistant.

The major finding of this review is that
delays in providing appropriate therapy are an important driver of mortality. This highlights the importance of providing initial therapy that is active against the infecting pathogen, especially for resistant strains.

In the five years that have ensued since these data were collected, the rates for carbapenem-resistant pathogens has increased, accentuating the need for effective agents that might modify an outcome like death due to an infection by resistant pathogens.

Gram-negative bacteria develop resistance to beta-lactams through three primary mechanisms: porin channel mutations that limit drug injury, overexpression of efflux pumps that expel drugs, and expression of beta-lactamases that inactivate drugs. And while the recent emphasis has been to develop new antibiotics that address the problem of beta-lactamases, all three mechanisms often coexist within a single pathogen.

As a result, overcoming beta-lactamase enzymes may not by itself overcome carbapenem
resistance. This is particularly a problem amongst the non-fermenters. The carbapenemase production may not be the predominant resistance mechanism. This suggests that a new approach is needed that can overcome all three mechanisms of carbapenem resistance.

All gram-negative species have outer membranes that are impermeable to antibiotics. Porin channels allow passive diffusion of beta-lactams across the bacterial outer membrane into the periplasm. Bacteria can reduce the number of porin channels expressed in the outer membrane or the porin channels can mutate to restrict injury.

Once the antibiotic crosses into the periplasmic space, the bacteria can expel the antibiotics, including carbapenems, via efflux pumps. The presence of antibiotics that result in a selection of bacteria with an increased efflux pump has been described.

Antibiotics that go into the periplasmic space that are not expelled by efflux pumps may be subject to enzymatic degradation by beta-
lactamases, the most common type of beta-lactam resistance.

There are more than 2600 beta-lactamase enzymes. Fortunately, the number of beta-lactamases that inactivate carbapenems, the carbapenemases, is much lower.

The carbapenemases fall in three different Ambler classes of beta-lactamases. Classes A and D are serine beta-lactamases, including KPCs and OXAs. Class B are the metallocarbapenemases, including NDM, VIM, and IMP. There are currently no approved antibiotics that could overcome resistance caused by the metallos, making them the most difficult to treat.

Class C beta-lactamases are not carbapenemases. However, when they occur in conjunction with porin channel closure and overexpression of efflux pumps, together they confer carbapenem resistance, and this is the primary mechanism of carbapenem resistance in pseudomonas.

The polymyxins were introduced in the 1960s
to treat gram-negative infections, but were largely withdrawn due to nephrotoxicity and neurotoxicity. The aminoglycosides followed, but they can cause renal and otologic toxicity.

In the 1980s, third-generation cephalosporins, fluoroquinolones, and carbapenems largely replaced aminoglycosides to treat gram-negative infections. But by the late '80s and early '90s, resistance emerged to the third-generation cephalosporins and fluoroquinolones.

As a result, carbapenem use increased. And then in the 2000s, there was an increase in carbapenem resistance, particularly among enterobacteriaceae due to carbapenemase enzymes such as KPC. This led to the return to the polymyxins, including colistin, despite their toxicity. And now, we see the emergence of resistance to polymyxins so that even these last-resort treatments are failing.

As a result of global concern and awareness of the critical need for new antibiotics and FDA's
updated guidance for the development of antibiotics, several new antibiotics have been developed and approved in the United States, many of which have activity against certain types of gram-negative resistant pathogens.

While this is very important and a positive development, gaps in treatment still exist. Unfortunately, none of the new therapies effectively covers all of the mechanisms of resistance. None of them has reliable activity against pathogens that overexpress efflux pumps or have porin channel closures. And none of them has activity against metallo-carbapenemases, a resistance mechanism that is spreading dramatically worldwide.

These new drugs do not cover many of the OXA enzymes such as OXA 23, which is a prime mediator of resistance to acinetobacter, and they lack activity against stenotrophomonas, which has intrinsic resistance to beta-lactams, including carbapenems.

The pharmacokinetics of some new agent such
as eravacycline, while active against some carbapenem-resistant species, does not achieve adequate concentrations in the urine. Because of the increase of resistance to beta-lactams and fluoroquinolones, there has been a resurgence in the use of polymyxins despite their toxicity. With this increased use, we now see high levels of resistance to polymyxins.

In recent surveillance data of gram-negatives collected in North America and Europe, there were gaps in coverage, even when including recently approved antibiotics. While a disproportionate amount of this resistance was based on the isolates from Europe, it is noteworthy that such potential for developing resistance is already occurring in certain sites in the United States.

In this study, ceftazidime/avibactam was the best agent for CRE, but it still covered only 78 percent of the pathogens. Similarly, ceftazidime/avibactam and ceftolozane/tazobactam were only active against 76 percent of carbapenem-
resistant Pseudomonas aeruginosa isolates.

Neither of these agents had activity against Acinetobacter baumannii that was significant. These data highlight the challenges seen with non-fermenters. None of the available antibiotics is reliably active against stenotrophomonas.

Antibiotic resistance is a global crisis with three pathogens recognized to be of critical importance. These are carbapenem-resistant Pseudomonas aeruginosa, carbapenem-resistant Acinetobacter baumannii, and carbapenem-resistant ESBL-producing enterobacteriaceae. Each of these organisms can cause complicated UTI.

Carbapenem resistance in cUTI results in increased morbidity and mortality. There are limited treatment options, particularly for organisms producing metallo-carbapenemases or that have resistance mediated by porin channels or efflux pumps. Relying on old drugs with substantial toxicity is not a solution. There is an urgent need for new treatment options that
address all three mechanisms of carbapenem resistance.

Applicant Presentation - Roger Echols

DR. ECHOLS: Thanks, George.

Hello. My name is Roger Echols. I'm an infectious disease physician long involved in antibiotic drug development, and I've been working very closely with Shionogi on the development of cefiderocol since 2012.

Cefiderocol is unique in that it can overcome the three primary mechanisms of resistance to beta-lactam antibiotics, including carbapenems, found in gram-negative bacteria. The microbiology and PK/PD profile of cefiderocol are especially important for this application that is following a streamlined development pathway with heavy reliance on robust in vitro and in vivo nonclinical efficacy and the pharmacodynamic correlation with human drug exposure.

The nonclinical studies demonstrate that cefiderocol can effectively treat gram-negative infections, including those caused by carbapenem-
resistant enterobacteriaceae, and carbapenem-resistant non-fermenters such as Pseudomonas aeruginosa and Acinetobacter baumannii.

Cefiderocol is a siderophore cephalosporin. As a siderophore, cefiderocol binds to free iron and is efficiently transported across the outer membrane unique to gram-negative bacteria. This provides a unique method of cell entry and overcomes a porin channel mechanism of resistance that blocks antibiotic entry into the cell.

Cefiderocol also overcomes the efflux pump mechanism of resistance that rapidly removes other antibiotics from the periplasmic space, enabling cefiderocol to remain in the cell. And most importantly, the chemical structure with specific side chains make cefiderocol resistant to the beta-lactamase enzymes that inactivate beta-lactam antibiotics. So it's stable against all classes of beta-lactamases, including carbapenemases.

Cefiderocol is the first antibiotic to overcome all three mechanisms of beta-lactam resistance to gram-negative bacteria. This
translates to low MICs and potent activity for nearly all gram-negative pathogens.

All gram-negative bacteria possess an outer membrane, which blocks entry of small water-soluble molecules such as antibiotics. There are porin channels, shown in yellow, which allow for passive diffusion of antibiotics. In addition, there are specific selective channels, shown in dark blue, for essential nutrients such as iron. Since these selective channels are essential for bacteria's survival, they are more efficient than porin channels due to active transport.

The initial response by the host bacterial invasion involves the innate immune system, whereby the bacteria are recognized by macrophages and, in turn, produce chemical messengers called cytokines, which increase the production of iron-binding proteins, such as lactoferrin, in an effort to starve the bacteria of this essential nutrient.

In response, the bacteria increase their production of siderophore molecules in an effort to scavenge for any available iron in the environment.
Once these bacterial siderophores bind to iron, they are transported into the cell via specialized iron transport channels.

Cefiderocol is a cephalosporin antibiotic with a catechol moiety, shown in green, covalently attached at the three-position side chain. Between the two hydroxy groups, it binds one molecule of free iron.

Cefiderocol enters the bacteria by active transport via the iron siderophore transporters, leveraging the bacteria's essential need for iron, therefore overcoming porin channel mutations. This is referred to as the Trojan horse approach.

Efflux pumps are a second type of resistance mechanism and gram-negative bacteria to exclude or remove the antibiotic from the periplasmic space. Cefiderocol retains its activity against gram-negative pathogens with higher numbers of efflux pumps.

The third and most important beta-lactam resistance mechanism in gram-negative bacteria is the expression of beta-lactamases, including...
carbapenemases, which inactivate the antibiotic. Cefiderocol binds to penicillin-binding proteins, creating a lethal effect due to inhibition of new cell wall synthesis.

Cefiderocol has demonstrated stability against inactivation by all classes of beta-lactamases and retains activity against gram-negative pathogens, expressing serine carbapenemases such as KPC or OXA, as well as pathogens expressing metallo-carbapenemases such as IMP, VIM, and NDM, where there is a significant unmet need for antibiotics that resist these enzymes.

Shionogi has conducted three consecutive years of surveillance studies in North America and Europe, totaling nearly 30,000 clinical isolates. Among these randomly selected strains of gram-negative pathogens, 99.6 percent were susceptible to cefiderocol at an MIC of 4 micrograms or less.

There is a broad distribution of MICs across the gram-negative bacteria spectrum,
including enterobacteriaceae and the non-fermenter, pseudomonas, acinetobacter, and Stenotrophomonas maltophilia. However, because the target for cefiderocol use is carbapenem-resistant gram negatives, the subset of carbapenem non-susceptible organisms from these same studies were analyzed in greater detail.

In this subset of carbapenem non-susceptible gram-negative pathogens, the activity of cefiderocol was preserved with 97.7 percent of these clinical isolates susceptible to cefiderocol at an MIC of 4 micrograms or less.

Because cefiderocol is not a beta-lactamase inhibitor and addresses all three mechanisms of resistance, only cefiderocol is broadly active for problematic carbapenem non-susceptible organisms, which represent the unmet medical need.

The comparator antibiotics and the sidero wild type or WT studies included recently marketed antibiotics such as ceftazidime/avibactam, and although this drug is quite active against KPC-producing enterobacteriaceae, it is not so
active against other types of CREs. Neither ceftazidime/avibactam nor ceftolozane/tazobactam retain much activity against carbapenem-resistant Pseudomonas aeruginosa.

Also noteworthy is the cross-resistance to fluoroquinolones, and perhaps most alarming to colistin, that is considered the last line of treatment for carbapenem-resistant infections. Finally, for Stenotrophomonas maltophilia, of the antibiotics tested, only cefiderocol provides reliable activity.

In a separate surveillance study called SIDERO-CR, or for carbapenem resistance, selecting only carbapenem non-susceptible strains, we identified the specific carbapenemase enzymes causing carbapenem resistance using molecular analyses.

These data show that cefiderocol activity has the same MIC distribution against these strains which contain specific carbapenemase enzymes compared to carbapenem-resistant strains without carbapenemases, shown here in black. These data
demonstrate that the presence of any of these carbapenemase enzymes does not result in resistance to cefiderocol.

The development of resistance to a new antibiotic is always of concern. Shionogi has investigated the potential for resistance development to cefiderocol using several experimental methods, both conventional and some unique to cefiderocol.

Both the serial passage and frequency of resistance from large inocula studies showed a low propensity for resistance development, including carbapenem-resistant strains. A chemostat model, which reproduces human pharmacokinetic exposure, also showed little emergence of resistance.

Knock-out experiments deleting specific iron transport genes did not result in cefiderocol-resistant strains, and a study of adaptive resistance, in other words, an observation described with several hydroxypyridones, siderophore monobactams, where the in vitro and in vivo activity did not correlate, this study did
not show the same phenomena with cefiderocol.

Finally, in in vivo murine thigh efficacy study with extended treatment duration examined residual bacteria for phenotypic or molecular changes, and with rare exception, there were no changes in MIC or genomic sequencing.

Unlike other cephalosporins, cefiderocol has limited activity against gram-positive and anaerobic bacteria and could be considered a narrow-spectrum gram-negative antibiotic. In clinical practice, for mixed infections, additional antibiotics with gram-positive or anaerobic activity should be added.

The selection of a dose and dosing regimen for antibiotics is often based on empirical evidence from phase 1 and phase 2 clinical trials. Rigorous PK/PD analyses are often performed only after the drug is marketed.

Cefiderocol is being developed under a streamlined development program with limited clinical trial data. Also, cefiderocol development includes patients with life-threatening infections,
so getting the dose regimen right the first time was paramount.

We first established in a neutropenic murine thigh dose fractionation study the pharmacodynamic parameter, which confirms that the percent time of a dosing interval, where the free plasma concentration exceeded the MIC of the pathogen, was most relevant to cefiderocol. The 58 percent free drug time above MIC for this strain of Pseudomonas aeruginosa is consistent with other anti-pseudomonas cephalosporins.

We then conducted a series of dose-response studies in both murine thigh and lung, using multi-drug-resistant strains of enterobacteriaceae and non-fermenters. And while the range of bactericidal activity varied somewhat, there was no difference between the two infection sites.

From these studies, we chose a conservative estimate of 75 percent free drug time above MIC as the pharmacodynamic target for cefiderocol. Because percent time of free drug above MIC is the pharmacodynamic target for all beta-lactams, it has
become best practice to extend the infusion
duration when treating antibiotic-resistant
infections.

We can illustrate this using the human PK
of cefiderocol. By extending the infusion time to
3 hours, we can achieve concentrations exceeding
8 micrograms for 75 percent of the dosing interval
compared to 4 micrograms with the 1-hour infusion.

We confirmed the superior efficacy of the
extended infusion in a rat pneumonia study.
Immunocompetent rats were connected by catheter to
a computer-programmed infusion system that could
exactly mimic the human PK drug exposure.

Using this model, we could directly compare
the efficacy of the 3-hour infusion, in purple,
with the 1-hour infusion, in red, for clinical
isolates with higher MICs to cefiderocol. The
3-hour infusion achieved multiple log bacterial
killing against organisms with MICs as high as
16 micrograms per mL.

For further confirmation of the 75 percent
target pharmacodynamic parameter, we use the murine
thigh model, again reproducing in mice the drug
exposure comparable to a 2-gram dose infused over
3 hours in humans. This was a large experiment
involving nearly 100 strains of bacteria chosen to
represent a broad range of MICs across different
bacterial species, including Pseudomonas aeruginosa
and Acinetobacter baumannii.

Ninety-six percent of the 67 strains with
MICs less than or equal to 4 showed bactericidal
efficacy, whereas those strains with MICs greater
than 4 had diminished activity. There was no
apparent difference between bacterial species.
This experiment strongly supports the relationship
between time above MIC across a broad range of
bacteria susceptible to cefiderocol.

We could then calculate the probability of
achieving this efficacy threshold in patients using
PK data from healthy subjects, as well as patients
enrolled in the clinical studies. Against a
background of nearly 5,000 carbapenem non-
susceptible clinical isolates, we can estimate,
probability that the 2-gram dose infused over 3 hours would cover bacteria with MICs up to 8 micrograms per mL.

The results demonstrate that the plasma concentrations of cefiderocol achieve the conservative target of 75 percent free time above MIC for 8 micrograms or less.

Six clinical pharmacology studies were conducted to support the use of cefiderocol. Cefiderocol has the predictable pharmacokinetics of a cephalosporin. It's linear, and 90 percent of the drug is excreted unchanged in the urine, allowing patient-specific dosing adjustment based on renal function.

Sixty percent of cefiderocol is bound to plasma proteins. There is no clinically relevant PK impact of age, gender, race, or body weight. A comprehensive in vitro drug-drug interaction assessment and three phase 1 drug-drug interaction clinical studies demonstrate there are no clinically relevant drug interactions via metabolic enzymes or drug transporters.
Additionally, no QT prolongation was observed in a clinical study using a supratherapeutic dose of 4 grams. In phase 1 human trials, the drug was well tolerated and had a safety profile similar to other cephalosporins.

Cefiderocol is the only antibiotic that overcomes all three mechanisms of carbapenem resistance through the combination of its siderophore cell entry and its stability to all classes of beta-lactamase enzymes.

The numerous animal infection models, particularly those using in human drug exposure, demonstrate the efficacy against all types of carbapenem-resistant infections. And the data from the preclinical studies used in human drug exposure confirm the PK/PD relationship and enable precise estimates of the probability of target attainment.

These data meet and exceed the requirements for robust in vitro and in vivo preclinical efficacy and the pharmacodynamic correlation for streamlined development. There is a low propensity for the development of resistance.
The PK/PD and probability of target attainment was confirmed in patients, and the resulting dose and regimen can potentially treat nearly all carbapenem-resistant infections.

**Applicant Presentation – Simon Portsmouth**

DR. PORTSMOUTH: Thank you. Good morning. My name is Simon Portsmouth, and I'm an executive medical director at Shionogi, based in New Jersey. I was a clinician in HIV medicine and genital urinary medicine in London for 16 years, and then for the past 10 years have been working on infectious disease drug development. I've been with Shionogi for the past 4 years and was the cUTI study lead in the cefiderocol development program.

Cefiderocol is effective in the treatment of complicated urinary tract infections as demonstrated in the cUTI study. The cUTI study was a pivotal, double-blind, randomized non-inferiority study in 450 hospitalized patients. The sample size of 300 patients on cefiderocol and 150 in the comparator arm was designed to support the demonstration of non-inferiority and provide an
adequate safety database.

Subjects were randomized 2 to 1 to either 2 grams of cefiderocol with adjustment for renal function, or 1 gram/1 gram of imipenem/cilastatin, both administered every 8 hours for 7 to 14 days, and no oral antibiotic step-down was permitted.

The primary endpoint was a composite of microbiological eradication and clinical response assessed at the test-of-cure visit 7 days after stopping IV treatment in the microbiological intent-to-treat population. This is defined as those with a qualifying gram-negative pathogen in complicated UTI who received at least one dose of study drug.

A microbiologically evaluable population, which is those that adhered to aspects of the protocol such as correct treatment duration, was also evaluated as a sensitivity analysis. Secondary endpoints included responses at other time points, and responses split by microbiological response and clinical response alone.

The endpoints in design followed the cUTI
guidance and the comparator was 1 gram/1 gram of imipenem/cilastatin, the highest dose recommended, and was the labeled dose indicator for the treatment of pseudomonas infection at the time this study commenced. Subjects with known imipenem-resistant infections were excluded.

There were certain design features unique to this study. These features were implemented in order to make this appropriate as a clinical study for an antibiotic to be used in serious infection. The study enrolled seriously ill and more difficult-to-treat patients, reflective of the intent-to-treat population with MDR gram-negative infections.

The specific design features that accomplished this included limiting the proportion of subjects with acute uncomplicated pyelonephritis, which is often diagnosed in younger female patients with antibiotic-susceptible E. coli, and so it's usually easier to treat, to no more than 30 percent in each treatment arm and having few exclusion criteria.
The baseline characteristics were consistent with more complicated infections. Most patients were over 65 years of age and 24 percent over 75 years of age in both groups, with equivalence of enrollment of male and female patients.

The proportion with acute uncomplicated pyelonephritis, which is defined as upper urinary tract infection without complicating factors, was 25.8 percent in the cefiderocol arm and 29.4 percent in the imipenem arm.

Overall, combining those with acute uncomplicated pyelonephritis and those with complicated urinary tract infection with pyelonephritis, between 51 and 53 percent of the overall population had pyelonephritis.

Of the factors leading to the complication, between 25 and 32 percent had a history of stones, 14 to 18 percent with urinary catheters, and 32 to 34 percent had obstructive uropathy, and 7 percent in each group had a concomitant bloodstream infection.
Overall, between 50 and 57 percent of subjects had some degree of renal impairment. Approximately one-third in each group had mild impairment, 16 to 19 percent had moderate, and approximately 3 percent had severe renal impairment.

The pathogens identified as the cause of infection were diverse and often drug resistant. For E. coli and klebsiella, baseline resistance was well balanced between the treatment groups. Of the E. coli, which was the commonest pathogen, around 38 percent were levofloxacin resistant and 17 percent were cefepime resistant in both groups.

Klebsiella pneumoniae was the next most frequent pathogen, and levofloxacin and cefepime resistance was balanced between 53 and 56 percent. Pseudomonas aeruginosa was identified more frequently in the cefiderocol arm.

Subjects with known imipenem-resistant infections were excluded by the protocol, however, susceptibility results were often only available post-randomization. A baseline, 5 klebsiella
isolates in the cefiderocol arm and 1 isolate in the imipenem arm, turned out to be imipenem resistant. Of the Pseudomonas, 3 isolates in the cefiderocol arm and 1 in the imipenem arm were also imipenem resistant. There was only one other imipenem-resistant organism in the imipenem treatment arm.

As far as the study disposition is concerned, over 93 percent in each group completed treatment. The median treatment duration in both treatment arms was 9 days. Two patients in each group had a treatment interruption, and approximately 17 percent required a dose adjustment for renal function changes during the study.

The major reasons for discontinuation were loss to follow-up, withdrawal by subject, and adverse event in 5 cefiderocol-treated and 3 imipenem-treated patients.

Cefiderocol met the statistical requirements for non-inferiority for the primary endpoint; that is a composite of microbiological eradication and clinical response at the test of
cure. The results in the microbiological intent-to-treat population showed that 72.6 percent of patients receiving cefiderocol met the primary endpoint compared with 54.6 percent of those treated with imipenem/cilastatin, an adjusted treatment difference of 18.58 percent.

The baseline-adjusted difference of 18.58 percent, which is an adjustment by baseline characteristics, where the absolute difference was 18 percent, was in favor of cefiderocol with a lower bound of the 95 percent confidence interval at plus 8.23, well above the non-inferiority margin of minus 15, indicated in the guidance for the limited-use indication.

The lower bound of the confidence interval excludes zero, which is shown by the confidence interval bars being to the right of zero, and a post hoc analysis is consistent with the superiority of cefiderocol over imipenem/cilastatin.

The composite response was driven by the microbiological efficacy. Here are the
microbiological outcome results alone, which mirror the composite results, with the lower bound of the confidence interval well to the right of zero.

The sensitivity analysis carried out on the microbiologically valuable population supports the primary and the analysis results. Two additional sensitivity analyses were conducted, one to exclude all subjects with an indeterminate response at test of cure, and one to assess the clinical response using subject-reported symptoms, which was a patient-reported outcome tool we instituted in the study to compare with the physician-assessed clinical response, which was the clinical assessment for the primary endpoint.

All analyses showed consistency with the primary response with the lower bound of the confidence interval well to the right of zero and favoring cefiderocol.

The response in the imipenem arm was as expected in this patient population, with more difficult-to-treat infections and with significant co-morbidities and complicating factors.
The conclusion that imipenem did not underperform is illustrated by the responses to imipenem in the easier-to-treat acute uncomplicated pyelonephritis subgroup, where almost 70 percent of imipenem-treated patients had a clinical and microbiological response. This is consistent with the expected response for imipenem with these easier-to-treat infections.

Several subgroup analyses were conducted and all showed consistency with the primary endpoint results, including an extended spectrum, beta-lactamase-producing organisms, which made up approximately 25 percent of organisms, shown at the bottom of this forest plot, with a treatment difference of 16.12 percent.

Further examination of the results supported the primary efficacy endpoint. There was a consistent treatment difference in favor of cefiderocol across all of the prespecified subgroups, including gender, age over 65 and 75, and by baseline pathogen.

The point estimates for the treatment
difference in each of these subgroups are all to the right of zero. Four of the klebsiella in the cefiderocol arm were NDM producers, and all of these had a clinical response.

These are the composite response by causative pathogen. For E. coli and klebsiella, the most frequently observed pathogens, the treatment difference between both arms was preserved. For pseudomonas, there were only 4 single isolates in the imipenem arm compared with 15 in the cefiderocol group, and responses between groups appear to be matched at around 50 percent. Other pathogens were in single numbers, so a comparison cannot be made.

Clinical responses over time are shown at each time point. At test of cure, clinical responses were similar at 89.7 percent for cefiderocol and 87.4 percent for imipenem/cilastatin. At later follow-up, the cefiderocol response was 81.3 percent, and for imipenem, this was 72.3 percent, a 9 percent difference.
Cefiderocol demonstrated non-inferiority to imipenem, with a lower bound of the confidence interval not crossing zero, and so well above the non-inferiority margin. Cefiderocol was effective both clinically and microbiologically in this population of patients with complicated urinary tract infections, where just over half had pyelonephritis and who are at risk of multi-drug-resistant infections. These were patients with complicated infections, requiring hospitalization, who were mostly elderly and had co-morbidities.

Microbiological assessment showed that many of them had resistant or multi-drug-resistant pathogens, and the response difference was consistent in this subgroup, as well as for other pathogens in demographic subgroups.

The treatment difference compared with imipenem was a consistent finding across subgroups and in sensitivity analyses. So the efficacy of cefiderocol supports its use for the treatment of complicated urinary tract infections.
The cUTI study had an independent data safety monitoring board, and based on the results of the study, the safety of cefiderocol is well characterized and also supports its use for the treatment of cUTI. The rates, types, and severity of adverse events were what would be expected for a cephalosporin, and it was generally well tolerated.

Around 94 percent of patients in both groups completed all study visits, and overall, the safety of cefiderocol compared favorably with imipenem. Rates of adverse events were similar between the treatment groups.

Forty-one percent of cefiderocol-treated patients were reported to have an adverse event compared with 51 percent in the imipenem-treated patients. Serious adverse event rates were also similar, 4.7 percent for cefiderocol compared with 8.1 percent in the imipenem group. Discontinuation due to adverse events was 2 percent or less and similar between the treatment arms.

The most common adverse events were generally mild to moderate in severity. The most
frequent adverse event was diarrhea, reported for
4.3 percent of cefiderocol-treated patients
compared with 6.1 percent of those on imipenem.
One cefiderocol-treated patient was reported to
have C. diff infection compared with 5 in the
imipenem arm.

The only serious adverse events that
occurred in more than one subject was C. difficile
colitis in two imipenem recipients; otherwise, each
SAE was reported for one subject only. Only one
serious adverse event was considered treatment
related, and this was a non-severe occurrence of
C. diff diarrhea in a cefiderocol-treated patient.

There was one death in the study, and this
was in a cefiderocol-treated patient. This patient
had complicated UTI without pyelonephritis and
concomitant bacteremia at baseline. This was a
76-year-old male patient who had a medical history
of extrapyramidal disorder and was taking levodopa,
insulin-dependent diabetes, cerebrovascular
disorder, previous stroke, chronic kidney disease,
and epilepsy. ECGs done on day 1 and day 6 reports
to have no significant abnormalities, and there was no QTc prolongation.

The patient died due to a cardiorespiratory arrest on day 7 of treatment, considered by the investigator to be a cardiac event and not related to treatment, and no autopsy was performed.

Further exploration of safety in prespecified subgroups confirmed the overall safety of cefiderocol. Adverse events common to beta-lactam antibiotics were reviewed. No patients were reported with anaphylaxis, and no cases of Hy's law or drug-induced liver injury were observed.

One cefiderocol recipient with a history of epilepsy had a single seizure during treatment. The seizure occurred on day 7 of treatment, and treatment was completed uneventfully for a further 3 days. Pharmacokinetic measurements show that the patient was not overexposed to cefiderocol. One subject was reported with hypersensitivity, which was in fact limited to itching alone with no rash after the first dose, and the patient was
discontinued from any further dosing.

Since cefiderocol has a catechol moiety that complexes with free ferric iron, we looked at serum iron between baseline and test of cure 7 days after the end of treatment. In both groups, serum iron appear to increase over time, as did transferrin, which is as expected during the treatment of an acute infection.

There were no appreciable differences in hemoglobin, hematocrit, or total iron-binding capacity between the groups, which was measured at every time point.

Additionally, we tested hepcidin. Hepcidin is a key regulator of iron homeostasis. Hepcidin was observed to decrease in both groups in parallel. Hepcidin is an acute phase reactant, and so declines with a resolution of an infectious process, and no differences between the groups was noted.

We monitored post-treatment urine cultures for the possible development of resistance to cefiderocol. Even though 7 subjects had increases
in MIC, the highest MIC reached was 1 microgram per mL, and all remained susceptible. There was one subject with a new infection at follow-up, a pseudomonas with a cefiderocol MIC at 8, but electrophoresis showed that this was not present at the baseline visit. So there was no development of resistance to cefiderocol during the study.

Cefiderocol was generally safe and well tolerated in the cUTI study with a safety profile consistent with the cephalosporin class. There were no events observed that were unique to cefiderocol, including no events associated with iron metabolism and homeostasis.

Adverse events and serious adverse events were comparable between the cefiderocol and the imipenem groups. So the safety profile of cefiderocol supports its use for cUTI, including use in an elderly population with co-morbidities.

The cUTI study tested the efficacy of cefiderocol in a carbapenem-sensitive infection using an established comparator. Two additional studies have been conducted, an open-label,
pathogen-focused study in carbapenem-resistant gram-negative infections and a double-blind study of cefiderocol compared with high-dose extended infusion meropenem in patients with HAP, BAP, and HCAP, and both of these studies will be discussed next.

The CREDIBLE-CR study was an open-label study of cefiderocol or best available therapy, which I will call BAT from now on, in severe infections in hospitalized patients with carbapenem-resistant gram-negative pathogens. This is an unmet need due to the limited options for treatments of these infections, which are associated with a high mortality, as these are often opportunistic infections in debilitated and critically ill patients.

The minimum criterion for study enrollment was evidence of any carbapenem-resistant gram-negative pathogen based on susceptibility testing, rapid diagnostic tests, or microbiological surveillance, or hospital antibiogram. Three infection types were enrolled. Fifty percent had
HAP/VAP/HCAP, 31 percent had BIS sepsis, and 19 percent had complicated urinary tract infections.

BIS/sepsis encompassed any infection other than HAP/VAP/HCAP and cUTI, and included bacteremia and non-bacteremic sepsis. Pneumonia or cUTI with bacteremia was separately categorized. Osteomyelitis and endocarditis were excluded, as these require more than 21 days of treatment. Meningitis in patients with cystic fibrosis were also exclusions.

The study allowed enrollment of patients with progressive underlying disease and end-of-life conditions with prolonged hospitalization and who were often mechanically ventilated. This resulted in a heterogeneous group of patients with such severe conditions, as decompensated end-stage liver disease; patients with metastatic cancer, including to the brain and skin; an inoperable esophageal rupture; Stevens-Johnson syndrome; 56 percent burns with smoke inhalation; patients with shock prior to and at randomization; patients with major trauma,
including major trauma with catastrophic head injuries; and ischemic bowel with perforations following emergency surgery for abdominal aortic aneurysm rupture.

These are patients who would generally be excluded from conventional clinical studies, but represent those at risk of nosocomial carbapenem-resistant infections; and often, these patients have conditions where source control would be impossible. These patients have a high mortality despite treatment, often.

The assumption in this trial was that the identified bacteria was causing disease, although the possibility exists that this could be colonization in an otherwise debilitated patient. Patients were stratified according to infection site, APACHE II score, and geographic region, but not by pathogen. Other factors were not stratified for, including mechanical ventilation status, shock prior to and at randomization, or location in ICU.

The primary objective of the study was to provide sufficient evidence of efficacy in the
treatment of serious and potentially life-threatening carbapenem-resistant gram-negative infections from a variety of infection types and that of an appropriate safety profile for those indications.

The study collected detailed patient-level information. It was not designed to detect statistical differences between the treatment groups for any of the outcomes by inferential testing. However, as part of the safety and efficacy assessments, descriptive statistics of the results are provided.

This is the design of the study. Patients were randomized 2 to 1 to either cefiderocol or best available therapy. Cefiderocol could be given with one adjunctive gram-negative antibiotic, but not with polymyxin, or a cephalosporin, or a carbapenem, but was given as monotherapy, usually. Best available therapy was a regimen of up to 3 gram-negative antibiotics.

The primary endpoint was clinical outcome at test of cure, 7 days after the end of treatment.
for HAP/VAP/HCAP and BIS/sepsis groups, and microbiological outcome for cUTI. The following populations were defined in the CREDIBLE-CR study. The safety, or ITT population, is all patients who received at least one dose of study treatment. This was 150 patients, 101 randomized to cefiderocol, and 49 to BAT.

The micro-ITT population is a subset of the ITT population and includes all patients with a baseline gram-negative pathogen from an appropriate clinical specimen, and there are 130 patients in this group.

The primary efficacy population was the CR micro-ITT population or carbapenem-resistant micro-ITT population. This is a subset of the micro-ITT population and includes all patients with a baseline gram-negative pathogen confirmed to be carbapenem resistant by a central laboratory. This consisted of 118 patients overall, which was 78 percent of the randomized population, and is further subdivided into 59 patients with HAP/VAP/HCAP, 37 with BSI/sepsis, and 22 with cUTI.
As far as the baseline characteristics are concerned, the median age was similar between the cefiderocol and the BAT arms, but there were fewer patients over the age of 65, at 44.9 percent in the BAT group than in the cefiderocol group, where it was 63.4 percent.

The median creatinine clearance was higher in the BAT group at 69.4 mLs per minute than in the cefiderocol group, where it was 59.2. There were no clear differences in other characteristics, including APACHE II score, SOFAS score, or CPIS score in the HAP/VAP population.

Acinetobacter baumannii was the most frequently isolated pathogen. Klebsiella pneumoniae and Pseudomonas aeruginosa were the next most frequently isolated, and there is no Stenotrophomonas maltophilia in the BAT arm. Of the 5 stenotrophomonas patients in the cefiderocol arm, 4 had mixed infections.

These are the study drug regimens. 82.5 percent of patients in the cefiderocol group received cefiderocol monotherapy, shown on the
left, and the rest received cefiderocol with one additional gram-negative antibiotic. In the BAT arm, 28 percent received monotherapy with 6 patients, or 15.8 percent, receiving colistin alone. Overall, 65.8 percent of BAT patients received a colistin-based regimen, and there were 25 different BAT regimens included.

Clinical and microbiological outcomes for all infection types at each study time point were generally similar between the treatment arms. The clinical cure and microbiological eradication rates at test of cure 7 days after the end of treatment, here shown with cefiderocol in blue, show similar rates of cure and microbiological eradication for the HAP/VAP/HCAP on BSI/sepsis groups and cUTI.

In the cUTI subset, the microbiological eradication rate was 52.9 percent for cefiderocol and 20 percent for BAT, although evaluation for this efficacy endpoint is limited by the sample size of just 5 patients in the cUTI BAT group.

The low microbiological response rates do not necessarily represent persistence. They are
often due to the large number of indeterminate responses. So these efficacy findings were consistent with those other study time points, including the end of treatment and later follow-up.

Outcomes by pathogen were broadly similar between the treatment groups. Clinical cure rates for acinetobacter, pseudomonas, and klebsiella are shown on the left with microbiological eradication for those three pathogens on the right.

There were 8 NDM-producing enterobacteriaceae in the cefiderocol arm and 4 in the BAT group. Six of the 8 had a clinical cure, a microbiological response, and of the 4 in the BAT group, none responded. These are on the far left of each graph.

As shown in the middle of each graph, there were 14 KPC producers in the cefiderocol group compared with 7 in the BAT group, and the response as shown here in the middle of both graphs, with clinical response on the left and microbiological response on the right, was similar between the treatment groups.
On the right of each graph, porin channel mutations was seen in 15 in the cefiderocol group and 9 in the BAT group. Clinical responses were similar, but microbiological eradication was 7 out of 15 for cefiderocol and 1 out of 9 for BAT.

These are the clinical cure and microbiological eradication rates for all of the metallo-carbapenemases, including NDM, VIM, and IMP for the CREDIBLE-CR study. At each time point, we see a clear advantage for both clinical and microbiological endpoints for these difficult-to-treat pathogens.

The overall safety in the CREDIBLE study will be discussed, followed by an evaluation of all-cause and infection-related mortality in the study.

This table provides an overview of adverse events for the safety population in the study. In the safety population, most patients in both groups were reported to have adverse events, more than 90 percent in both groups.

Treatment-related adverse events were
reported for 14.9 percent of cefiderocol-treated patients and 22.4 percent of BAT-treated patients. Around half of patients in both groups had serious adverse events, although treatment-related serious adverse events were lower for cefiderocol compared to BAT.

Discontinuation due to adverse events was 9.9 percent in the cefiderocol group and 6.1 percent in the BAT group, and discontinuations due to treatment-related adverse events occurred in 3 and 2 patients, respectively.

Adverse events leading to death were reported for 33.7 percent of patients in the cefiderocol group and 18.4 percent in the BAT group, and a single patient could have more than one adverse event that led to death.

Two patients in the study met the biochemical criteria for Hy's law, but not the clinical criteria. The first of these two cases was admitted to hospital with hepatic failure due to hepatitis B infection and was not on antivirals. The patient was treated with cefiderocol for
hospital-acquired pneumonia and developed hepatic encephalopathy on day 2 with a co-incident gastrointestinal bleed, and had severe edema due to pre-existing hypoalbuminemia. These changes in biochemistry coincided with the gastrointestinal bleed.

The patient continued to be treated with cefiderocol until day 9 with no further worsening of the biochemical parameters. The patient experienced a clinical cure of infection, a test of cure, and then died due to refractory hepatic failure on day 35, 26 days after the end of treatment. The biochemical abnormalities and subsequent death due to hepatic failure were not considered to be related to cefiderocol treatment.

The second patient had ALT and bilirubin levels meeting the biochemical thresholds for Hy's law. This was a patient who had a traumatic liver injury associated with major multiple trauma, including a catastrophic head injury. Three doses of cefiderocol were given on days 1 and 2, and the patient developed hyponatremia on day 2 and died on
day 6 due to the multiple trauma and skull fracture. So these abnormal liver test values were not considered related to cefiderocol.

Kidney safety will be discussed next.

Patients coming into the study were heavily pretreated, often with nephrotoxic drugs, including colistin. So around 80 percent in each group had some degree of baseline renal impairment, and most BAT regimens contain colistin. On-treatment changes in creatinine were followed through the study.

This table shows changes from baseline in serum creatinine. Cefiderocol is on the left and BAT is on the right. The BAT group has a higher percentage of 2 to 3 times change from baseline at 16.3 percent compared with 5 percent for BAT [sic]. A greater than 3 times increase was seen in 4.1 percent in the BAT group and 1 percent in the cefiderocol group, so this is consistent with the use of colistin in the BAT group.

This table was shown before, but shown again to point out that adverse events leading to
death were higher for cefiderocol than for BAT. Adverse events leading to death were reported for 33.7 percent of patients in the cefiderocol group and 18.4 percent in the BAT group.

There were two hepatobiliary disorders leading to death in the cefiderocol arm and none in the BAT arm. The first of these patients was already discussed and had hepatitis B. The second case was another patient with untreated hepatitis B, cirrhosis of the liver, and had a prior history of hepatic encephalopathy, spontaneous bacterial peritonitis, and esophageal varicosity bleeding.

The patient had a pulseless cardiac arrest, was in septic shock 4 days before being randomized to cefiderocol with a diagnosis of VAP, and had cefiderocol-resistant Acinetobacter nosocomialis, sensitive Pseudomonas aeruginosa, and Chryseobacterium indologenes.

On day 1 of treatment, severe worsening of liver failure was reported. On day 4, sputum was positive for stenotrophomonas, Acinetobacter
nosocomialis, and pseudomonas, but the outcome of clinical cure was reported. On day 5, the serious adverse event of worsening septic shock was reported, and a DNR order was agreed. On day 8, the patient died due to worsening liver failure and septic shock following a palliative extubation.

In addition to the hepatobiliary adverse event leading to death, this patient was also reported with septic shock as an infection and infestations adverse event leading to death.

Of the adverse events leading to death, the largest difference between the two groups was seen in the events in the system organ class classification of infections and infestations. These could include worsening for progression of infections that the patient was randomized into the study with or the development of new infections. There were no appreciable differences in other system classes, including cardiac, and renal, and urinary disorders.

The difference in infection and infestation-related adverse events leading to death
between the two groups predominantly come from pneumonia or septic shock and includes new infections, including gram-positive and fungal infections. These events reflect the higher all-cause mortality in the cefiderocol arm.

To further explore infection-related mortality, we will discuss all-cause mortality, and following this, attributable mortality assessed by a blinded adjudication committee.

At each of the time points in the CREDIBLE study, the all-cause mortality in the cefiderocol group was higher than in the BAT group. At day 14, the all-cause mortality was 18.4 percent for cefiderocol compared with 12.2 percent for BAT. At day 28, the all-cause mortality was 24.8 percent for cefiderocol and 18.4 percent for BAT. At day 49, it was 33.7 percent for cefiderocol compared with 20.4 percent for BAT.

Deaths after the end of the study were not systematically collected in the study, but 6 additional deaths, 4 in BAT-treated patients and 2 in cefiderocol-treated patients, were spontaneously
reported to the company.

The investigator, providing direct patient care, our review, and the independent data safety monitoring board assessed that none of the cefiderocol deaths were considered to be adverse drug reactions.

We looked at all-cause mortality by infection type, i.e., pneumonia, BSI/sepsis, and cUTI. The rate of all-cause deaths was higher in the cefiderocol group for pneumonia, HAP/VAP/HCAP on the left at each time point, and for patients with BSI/sepsis shown in the middle, but not for those with cUTI, which is shown on the right.

The CREDIBLE-CR study was open label, and, therefore, the treatment regimen was known to the investigators, to Shionogi, and to the DSMB, so there could have been biased in interpreting attributability of all-cause mortality.

For this reason, an independent blinded adjudication committee was convened to review the deaths in the study and address attributable mortality; that is, if the death was attributable
or not to the gram-negative infection that the
patient was randomized into the study with.

The adjudication committee consisted of
three practicing medical experts who were
professors of infectious disease, internal
medicine, or critical care medicine, and who were
blinded to study treatment and unaware of the
aggregate results in the ongoing trial, including
the mortality.

They were provided with detailed patient
narratives, in graphic chronographs for each
patient, who died with all of the treatment
information redacted so they could assess the
likely cause of death.

Broadly, the deaths could be assessed by
the committee as either not related to the
gram-negative infection or not attributable, and if
not, either due to a co-morbidity, a different
infection, a drug-related adverse event, or an
iatrogenic death. Alternatively, the death could
be classified as due to the gram-negative infection
the patient was randomized into the study with or
attributable mortality.

These are the results of the adjudication committee assessment. Sixteen of the 34 deaths, or 47 percent of the deaths, in the cefiderocol group were considered to be unrelated to the gram-negative infection, and 4 out of the 9 BAT deaths, or 44 percent, were also considered unrelated to the gram-negative infection.

Eighteen of the 34 deaths were adjudicated as attributable to gram-negative infection, as were 5 out of 9 of the BAT deaths. No deaths in either group were considered to be due to a drug-related adverse event, that is, none were considered to be adverse drug reactions.

In an overall assessment of all-cause mortality, several observations were made. There were no toxicology or preclinical concerns to suggest a plausible explanation for cefiderocol contributing directly to mortality. The causes of death were various and followed no discernible pattern suggesting causality. Blinded adjudication confirmed that half the deaths in both arms were...
unrelated to the gram-negative infection.

An exploratory regression analysis gave inconsistent results with both groups having factors associated with a high mortality and showed no single factor impacts on the observed mortality difference. A PK/PD assessment with patient samples showed adequate exposure in plasma and calculated exposure in the lung.

All-cause mortality in a population with such severe illnesses is difficult to assess, and there was marked heterogeneity within each treatment group for underlying diagnoses and prognoses. The investigators, providing direct patient care, the independent DSMB, and the independent blinded adjudication committee did not identify any death as being due to an adverse drug reaction to cefiderocol, so the cause of the mortality differences is known, and it could be due to chance.

All-cause mortality was a secondary endpoint in this open-label study, and many patients in both groups had critical illnesses with
a poor prognosis. Half of the study population in the open-label study had nosocomial pneumonia, where all-cause mortality was a secondary endpoint. But we've recently completed a double-blind, randomized, clinical trial of cefiderocol in nosocomial pneumonia, where mortality was the primary endpoint. We considered it informative to assess the results from the two studies.

APEKS stands for acinetobacter, pseudomonas, E. coli, klebsiella, and stenotrophomonas. The study is called APEKS-NP and compared cefiderocol to high-dose extended infusion meropenem at 2 grams. This was a phase 3 global, double-blind, randomized non-inferiority study in 300 adult patients with nosocomial pneumonia caused by any gram-negative bacteria.

Randomization was 1 to 1 to either cefiderocol or 2 grams of meropenem infused 3 times a day over 3 hours, with linezolid additionally administered for at least 5 days to provide gram-positive cover in the cefiderocol arm and MRSA cover for both groups.
The study population included patients with hospital-acquired pneumonia, ventilator-associated pneumonia, and healthcare-associated pneumonia. The primary endpoints was all-cause mortality at day 14 for the mITT population, which is defined as all treated patients, except those who have only gram-positive pathogens identified at baseline.

The mean age was balanced at around 65, with more than a quarter of the patient population over 75 years of age. Approximately 40 percent in each group had ventilator-associated pneumonia and 40 percent hospital-acquired pneumonia. 61.5 percent of patients on cefiderocol were mechanically ventilated at baseline, and 58 percent of those on meropenem were mechanically ventilated. Around 49 percent in each group had an APACHE II score of 16 or above. Klebsiella was the commonest pathogen at 32.4 percent and 29.3 percent, respectively, for the cefiderocol and the meropenem groups. Pseudomonas was next at 16.2 percent and 16 percent, and acinetobacter was isolated at 15.5 percent and 16 percent,
respectively. E. coli was the next most frequently isolated pathogen followed by Enterobacter cloacae.

The study met the primary endpoint and demonstrated non-inferiority of cefiderocol to high-dose extended infusion meropenem for all-cause mortality at day 14. The all-cause mortality in the cefiderocol arm was 12.4 percent compared with 11.6 percent of patients in the meropenem arm, less than a 1 percent difference.

At day 49, the all-cause mortality in the cefiderocol arm was 27.5 percent and 25.3 percent for patients in the high-dose meropenem arm. So at all time points, the all-cause mortality was similar between the treatment groups.

In summary, in two double-blind studies, we've demonstrated the efficacy of cefiderocol with results consistent with superiority in the cUTI study compared with high-dose imipenem, and in non-inferiority, it's a high-dose extended infusion meropenem for all-cause mortality in nosocomial pneumonia. The 14 and 28-day all-cause mortality rates were similar between treatment groups, where
60 percent of patients were mechanically ventilated and on ICU care.

The open-label CREDIBLE-CR study demonstrated efficacy in a critically ill population with irreversible underlying co-morbidities. A difference was observed with a lower rate of mortality in the BAT arm. This difference has been extensively investigated and no definitive explanation has been identified. So thank you for your attention.

**Applicant Presentation – David Paterson**

DR. PATERSON: So I'd like to start by stating that I have been compensated for my time, but I've got no financial interest in the company, nor in the outcome of the meeting.

Hello. My name is David Paterson, and I hope to bring you a unique perspective on the benefits and the risks of cefiderocol. I currently work in Brisbane, Australia, but I spent 10 years working for the University of Pittsburgh Medical Center, including two years at their hospital in southern Italy.
In my time as an infectious disease physician over these three continents, I've observed the rise of multi-drug resistance in gram-negative bacilli, including the advent of multi-drug resistance, and then in pseudomonas, and then the advent of KPC producers in Pittsburgh, and then more rapidly emerging issues with NDM and other resistance mechanisms becoming a substantial problem in Asia and also in Mediterranean Europe.

In my clinical practice, complicated UTIs due to carbapenem-resistant organisms typically occur in patients with multiple co-morbidities. For example, I frequently see patients who have survived treatment for cancer or who have undergone organ transplantation, who, after receiving multiple courses of antibiotics for other treatable infections, end up with a carbapenem-resistant infection involving the urinary tract or another site.

In my experience, when these patients have CRE resistant to ceftazidime/avibactam, for example due to the presence of metallo beta-lactamases like
NDM, we really are close to an untreatable situation. So from a personal perspective, when I first heard about the in vitro activity of cefiderocol against NDM producers, I felt that I may now have an alternative to colistin, which is certainly not a wonderful drug to use in patients who are already at risk of renal injury.

This data from the CREDIBLE study shows, certainly within the limitations of very small numbers, that not only may cefiderocol be an option for KPC producers, but it could well be an option for NDM-producing enterobacteriaceae as well.

You heard earlier today from Dr. Karam that cefiderocol is also active in situations where there is porin loss. And again, there is data from the CREDIBLE study where cefiderocol does provide a new option for enterobacteriaceae that have porin channel loss.

Of course, it's not just the enterobacteriaceae, which can harbor metallo beta-lactamases. In this analysis from the CREDIBLE study, which includes enterobacteriaceae
but also non-fermenters, mainly pseudomonas, or
producing metallo beta-lactamases, you can see that
cefiderocol does appear to be active clinically
against MBL-producing organisms.

In our patients with carbapenem-resistant
pathogens, who have resistance to the new beta-
lactam/beta-lactamase inhibitor combinations, we
really do need alternatives to colistin because it
causes kidney injury. We also need alternatives to
the newer tetracyclines because they enter the
renal tract poorly, and they really don't have a
great track record for treatment of bloodstream
infection or sepsis.

In my opinion, patients with MDR pathogens
beyond KPC still do need affidavit treatment
options, especially when they're at risk of the
toxicity that comes with polymyxins.

Let's do a quick recap on what we've seen
today as to the potential benefits of cefiderocol
for complicated urinary tract infections. Although
designed as a non-inferiority study, the
complicated UTI study demonstrated that cefiderocol
was superior to imipenem.

The complicated UTI study was designed to include sicker, generally older patients, who presumably therefore would have a high rate of antibiotic-resistant pathogens, and the study population was limited to around 30 percent with uncomplicated acute pyelonephritis.

As we've already heard today, cefiderocol had a 72 percent response rate compared to 54 percent seen with imipenem, and this provided an 18 percent difference between the two therapies. As a clinician, this extent of difference certainly is a clinically meaningful difference.

The safety profile of cefiderocol appears quite similar to that of other cephalosporins. There were no new safety concerns raised and only a low rate of Clostridium difficile was observed. Overall, the adverse event profile was unremarkable, with the most common adverse events occurring at rates below 5 percent and all at rates similar to or lower than imipenem. Serious adverse events occurred at a lower rate than imipenem, and
were generally rare, and were unrelated to treatment.

This really now brings us to what could have been the possible reasons for the mortality observed with cefiderocol in the CREDIBLE study. Firstly, could it have been a safety or toxicology reason? But firstly, there were no preclinical concerns seen. Secondly, there did not appear to be a pattern of safety events suggesting toxicity, and thirdly, all of the cases had been reviewed by a DSMB and also an independent adjudication committee, neither of whom found evidence of a toxic effect.

Secondly, could it be a lack of efficacy? Clinical and microbiological outcomes appear to be comparable in the two groups. So clinical cure was 52 percent with cefiderocol and 50 percent with best available therapy. On the flip side, microbiological persistence was 20 percent in cefiderocol-treated patients versus 26 percent in best available therapy.

The third option was, is this a chance
finding? There were certainly methodological limitations with this open-label study with multiple infection types. The study had a small sample size, raising the potential for uncontrolled confounding or imperfect distribution of baseline differences.

The CREDIBLE data is also at odds with the mortality data seen in the other studies. In the complicated UTI study, just one out of the 300 patients treated with cefiderocol died. And as we've just heard, with the nosocomial pneumonia study, mortality outcomes were very similar.

So in my opinion, we do need cefiderocol, and we need it today. You've seen mentioned already the in vitro activity of cefiderocol against carbapenem-resistant organisms, regardless of whether that resistance is due to beta-lactamase production, porin loss, or efflux pumps.

Although data from the CDC indicates that only 10 percent of carbapenemase-producing enterobacteriaceae in the U.S. are currently due to metallo enzyme producers like NDM, my observations
in Asia and in southern Europe are that they are expected to become a much more dominant force in the United States.

Many of you might remember a JAMA editorial more than 20 years ago called Squeezing the Balloon. The late Jim Reinhold made observations in Queens, New York that an antibiotic stewardship intervention to reduce cephalosporins in response to an outbreak of ESBL producers led to more imipenem use and, in turn, more carbapenem-resistant pseudomonas.

As we used more of the beta-lactam/beta-lactamase inhibitor combinations like ceftazidime/avibactam, we can only really expect that more strains will become resistant to these agents via the production of metallo beta-lactamases in the near future.

I certainly do not feel that we can expect that our most vulnerable patients, like our transplant patients with complicated UTI, should be subject to the ongoing risks of polymyxins in this current era.
To sum up, how does this benefit-risk equation look like for cefiderocol for complicated UTI? Cefiderocol was highly effective in that study, with a superior outcome versus imipenem. For patients with complicated UTI caused by carbapenem-resistant organisms, including the NDM metallo enzymes, cefiderocol does provide a unique advantage over contemporary antibiotics. Importantly, given the complicated UTI population that we're discussing today, there is no renal toxicity observed with cefiderocol.

In my mind, the mortality risk in the CREDIBLE study is counterbalanced by the lack of mortality risk seen in the UTI study and, as we've just heard, in the nosocomial pneumonia study. I do feel that cefiderocol is a drug that we need, and I am very proud to support this submission. Thank you.

Clarifying Questions

DR. BADEN: Thank you, and I'd like to thank the applicant for covering a tremendous amount of data, complex data with many issues.
We will proceed to the clarifying questions for the applicant. To panel members, please indicate to myself or Dr. Hotaki if you have a question. If you have a follow-on question to a theme, I'm going to go to remove this from your card. Put your card this way. That way, we can have a thematic discussion versus totally random jumping around.

I implore my panel members to use the honor system; that you're not doing that to sneak in a different line of questioning. We will get to the different questions. I want to build on thought so we can try and get at the issues that have been raised, as these data raise some important issues, and we will go until 10:20.

I will start with the first question while other panel members indicate their questions to us. I will address this to Dr. Paterson, and I think it is, if we go to your slide, 130.

If the data had been the converse, where cefiderocol had showed a benefit, wouldn't we have titled the slide mortality benefit and not might be
due to chance? Why should I believe that this is
due to chance, is a more likely explanation, as it
does seem a bit convenient?

DR. PATERSON: I guess as a clinician, the
first thing that I really wanted to look at here
is, does cefiderocol cause a danger to my patients?
And I do feel assured that it is not an unsafe
drug. It doesn't have a toxic effect
I like to sort of bring parallels to other
all-cause mortality studies, and because I've done
one recently, the MERINO trial, where we did find
an unexpected difference in all-cause mortality,
but in that study, we found that the drug that was
associated with higher mortality was also
associated with worse clinical efficacy at a
defined time point.

So that's what is different about this
study, where when we look at the clinical cure or
microbiological persistence, we are not seeing
worse outcomes from that point of view. So that
leaves, well, what else could it be. Is it just
that it's a suboptimally designed small study?
So that's how I read it, and I have thought a lot about this because I don't want to be giving cefiderocol to my patients if it's going to be an unsafe toxic drug, and that, I am absolutely convinced it is not.

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

DR. GRIPSHOVER: Yes.

DR. BADEN: Not just Dr. Paterson, but other applicant commentators may join in, in the discussion, as I'm sure this is quite a central issue for the committee. Dr. Gripshover?

DR. GRIPSHOVER: So again, regarding that slide, when you had the clinical cure and microbiologic cure, if you died, do we have microbiologic persistence? Because the numbers go down, and I don't know that you would have the sample. So could that be skewing some of why it looks the same?

DR. ECHOLS: For microbiologic response, that might result in an indeterminate, but in terms of clinical response, if someone died with their
infection, they would be considered a failure. So there's no missing data in terms of mortality for the clinical response. It's from microbiologic response, if there's no specimen, they can't really specify.

DR. BADEN: Dr. Follmann?

DR. FOLLMANN: Yes. To amplify, on the chance hypothesis, I think you mentioned it could be due to chance due to baseline imbalances. I wonder how far you had drilled down into that. I know on page 113, you talked about a regression adjustment, which could identify whether the chance and balances, if there were any, were meaningful.

So could you give us a little more illumination about the chance and balance or baseline imbalance hypothesis?

DR. ECHOLS: Dr. Binkowitz, could you please discuss the regression analysis that was conducted for this study?

DR. BINKOWITZ: Good morning. I'm Bruce Binkowitz from Shionogi Biometrics. And yes, we conducted many regression analyses using many
different methods and different selection criteria to check for the robustness of the regression results.

Slide 1 up, please. As you can see, as we defined, we looked at 34 different variables that were explored based on demographics, infectious status at baseline, medical history overall, and medical history specifically within about a month of randomization.

In doing that, what we found going through all this is we did a series of univariate regressions, and I'll show now slide 2 up, please, a logistic regression model and a series of univariate regressions, meaning we kept treatment in the model, and then we adjusted for each of those covariates and separate models.

In doing that, what I've highlighted is, just as a rule of thumb, any time the adjusted odds ratio from this logistic regression deviated by more than 10 percent on the log scale from the unadjusted odds ratio, which was 1.98, so the overall unadjusted odds ratio, again, 1.98.
As you can see, I highlighted the 10 largest changes, and while those changes both go in both directions -- in fact, 5 of them show a decrease in the odds ratio; 5 show an increase in the odds ratio -- none of the changes, regardless of how large, brings you down to an odds ratio of 1.0, for example, where you would see no effect. The largest changes bring the odds ratio down into the 1.7 area.

DR. FOLLmann: Thank you.

DR. BADEN: Dr. Clark?

DR. CLARK: Yes. I had a similar question in looking at variables. I was just wondering if there was any attempt to look at time to appropriate therapy in the groups.

DR. ECHOLS: The protocol didn't really identify time to appropriate therapy. So patients could be enrolled if they had received up to 24 hours in the recent 48 hours of potentially effective therapy based on in vitro activity. But in terms of prior to that 24 hours and 48-hour time period, patients were receiving either ineffective
antibiotics, or if they had been on potentially effective antibiotics, they were excluded from the protocol.

So what I can say is that most of these patients had been treated with prior antibiotics. I think it was, like, 76 percent. But generally, those were not effective antibiotics. So trying to do a time to effective therapy is not possible.

The unique aspect of this study is that the patients had evidence of carbapenem resistance prior to randomization. So the physicians, when they did randomize the patient, knew they had an carbapenem-resistant organism, and they treated either with best available therapy or with cefiderocol, so basically time to effective therapy was the same between treatment arms.

DR. BADEN: Dr. Ofotokun?

DR. OFOTOKUN: Thank you very much for such a thorough presentation. I trusted in the process of the adjudication. I wanted to know how the committee that did the adjudication was constituted. Were they independent of the data
safety monitoring board? I just wanted to understand how that process went.

   DR. ECHOLS: Certainly, they were independent of the DSMB. It was a totally separate group. The DSMB was unblinded to the data as they reviewed it on an ongoing basis. So that was our reason for the blinded adjudication committee, because the DSMB, as well as Shionogi, as well as the investigator, were unblinded.

   We identified three experienced clinical experts. We did not tell them there was a mortality imbalance in the study. We did not show them any of the aggregate data. We only asked them to assess the cause of death, basically whether it was related to the gram-negative infection the patient was enrolled for or whether it was due to something else.

   DR. OFOTOKUN: Question to that; were there autopsy data on the deaths?

   DR. ECHOLS: I am unaware of any autopsy data from any of the patients who died.

   DR. BADEN: Part of the evidence that you
are putting forward, that it may be a chance finding, are the two RCTs, and then the two RCTs suggesting that there is not an imbalance in mortality.

Is the population in the CREDIBLE study really comparable to the population in either of the RCTs? And can we make that assessment that that's reassuring that the mortality is not observed in an RCT format, or in individuals in sepsis that are different and there might be an augmented risk?

DR. ECHOLS: I'd like Dr. Portsmouth to discuss the comparison with the APEKS-NP patient population and CREDIBLE.

DR. PORTSMOUTH: Thank you. Slide 1, up. I'll show you we've got a side-by-side demographic table here for CREDIBLE on the left and then APEKS-NP on the right.

CREDIBLE-CR, really the biggest difference, was that this included patients with carbapenem-resistant organisms, and so there was a high proportion of patients with acinetobacter. The
proportion who were ventilated in the APEKS-NP study was 60 percent.

So really, the major difference was the carbapenem resistance. The APACHE II scores, we didn't find these to be very helpful in the CREDIBLE study, but in the APACHE II scores for the CREDIBLE study, 56 percent had an APACHE II score greater than 16 compared with about half in the APEKS-NP study.

So it was a sick population in the APEKS-NP, but because of the carbapenem resistance and the organism, there were some differences, but still a sick population.

DR. ECHOLS: I think we would agree that the UTI study is not a comparable population in terms of severity of disease and stability. They were, however, an elderly population that was at risk for multi-drug-resistant infection, which some of them had, but the comparability was probably best made with the APEKS-NP study.

I'd just like to say that the APEKS-NP study, the data that we might show now and in a
moment is locked data. This is final data. It's just that the study report has not been submitted to the FDA, so they've not had an opportunity to review the data. But this is not preliminary data; this is locked database.

DR. BADEN: And I do hope that mortality findings won't easily change.

DR. ECHOLS: No.

DR. BADEN: On a new line of questioning, Dr. Follmann?

DR. FOLLMANN: Yes, thanks. In the APEKS cUTI study, you showed a nice significant benefit on the composite endpoint of cure and what you call microbiological eradication. They're very similar on clinical cure, actually, both very high.

So I'd like to understand a little more about the microbiological eradication endpoint, as you call it. How is it defined specifically? What does that mean in terms of downward consequences? If you're microbiologically eradicated, does that mean you're at much less risk of reinfection?

If you have data on the two arms in terms
of this endpoint, I think it's defined in terms of colony-forming units, if you could show the two different arms in terms of CFU to see how substantial and how meaningful this effect is on the CFU or biomarker endpoint.

DR. ECHOLS: Slide 1 up. The definition of the protocol required patients to have greater than 10 to the 5th colony-forming units at the time of study entry. And then for eradication, they had to have less than 10 to the 4th colony-forming units.

We also conducted an analysis using, at the time, the European, which required actually less than 10 to the 3rd colony-forming units, and there was really no difference. So you had to have a follow-up urine culture or the response was indeterminate, and it had to be less than a certain colony count to be considered eradication.

I would like Dr. Portsmouth, though, to address, I think, the question you had about how clinically relevant that might be in terms of persistence associated with relapse of symptoms.

DR. FOLLMANN: Right. Just a quick
question on this point; so not everyone had greater
than 10 to the 5 CFUs at baseline. Do you know
what percentage did?

DR. ECHOLS: That would be the difference
between the ITT safety population and the mITT
population, which had a qualifying urine culture.

DR. PORTSMOUTH: It was 83 percent of the
population in both arms at a qualifying colony
count of greater than 10 to the 5, 83 percent.

DR. BADEN: Of a gram-negative organism?

DR. PORTSMOUTH: Exactly.

So as far as what this means clinically, as
you notice, when you see the clinical response,
when patients are on antibiotic, they get a
clinical response because this is suppressing
growth, and later follow-up, there can be rebound
often because patients have stones or catheters
that have biofilms that contain antibiotic-tolerant
colonies that then can rebound later on.

We did see a lower rebound rate in
ceferocol-treated patients, and we saw later
follow-up, this did result in a difference
clinically of about 9 percent. So there was potentially a clinical benefit, although modest because antibiotics, even if they're not necessarily microbiologically effective, do seem to control symptoms.

DR. FOLLmann: So the rebound rate or the reinfection rate was 9 percent worse in the comparator arm?

DR. PORTSMOUTH: No, that was the clinical response. So actually, the symptomatic response of follow-up was 9 percent difference. The rebound rate, if we could --

DR. ECHOLS: Eighteen percent there.

DR. PORTSMOUTH: Yes, basically an 18 percent difference in rebound rate for the 10 to the 4 outcome and 16 percent for the 10 to the 3 outcome, a difference.

DR. FOLLmann: Thank you.

DR. BADEN: But it's also not really eradication. You're getting below a certain level. I know it's a linguistic issue, but eradication is a powerful term.
DR. FOLLMANN: Yes.

DR. BADEN: Dr. Clark?

DR. CLARK: Yes. I had a couple questions on the complicated UTI study. Was the response in bacteremic patients similar to the total groups? And the second question is on the number of immunocompromised patients, and were they evenly balanced in the groups?

DR. ECHOLS: Dr. Portsmouth, would you discuss first the response to patients with bacteremia, and then go back to the baseline characteristics to describe the patient population?

DR. PORTSMOUTH: Yes. So about 7 percent of patients in each group -- and it was a 2 to 1 randomization -- had a positive blood culture. Slide 1 shows post-baseline blood cultures. For 15 out of the 18 of the cefiderocol group, or 83 percent, this was negative. There were three missing samples, so these were considered indeterminate.

Of the 8 in the imipenem group, 6 of those were negative, and there were two that remain
positive. The lines below that are the clinical
and microbiological responses in the urine. The
microbiological response was, of those patients,
55 percent versus 37 percent. So even in that
subset, there was a treatment difference between
the two groups.

DR. ECHOLS: And the immunocompromised; if
you want to respond to that?

DR. PORTSMOUTH: Yes. Sorry. I forgot the
second question. So it's difficult, really, to
quantify immunosuppression. We only had one
patient in the end who had a kidney transplant, so
there were very few in each group.

DR. ECHOLS: I will say that
immunosuppression was not an exclusion criteria for
the study, so we did have one renal transplant, but
there may have been other patients that were
immunosuppressed for other reasons.

DR. BADEN: Thank you. Dr. Le?

DR. LE: I'm going to switch gears a little
bit and ask more about the pharmacology side.
You've indicated in here the drug was infused over
3 hours, really maximizing the pharmacodynamic property of beta-lactams. I'm curious, for all the trials, how did you infuse the imipenem and the meropenem? Was it over prolonged infusion as well?

DR. ECHOLS: So just to be clear, in the urinary tract study, the infusion time for both drugs, imipenem and cefiderocol, was 1 hour. We did not determine the 3-hour infusion benefit until after we'd initiated the UTI study. So both subsequent studies, both the CREDIBLE study and the APEKS-NP study, used a 3-hour infusion of cefiderocol.

In the BAT arm, they used whatever their normal process was for infusion time, depending on the drug. But in the APEKS-NP study, we used a high dose, 2-gram dose, of meropenem infused over 3 hours.

So in the APEKS-NP study, both drugs were given over 3 hours. In the UTI study, both drugs were given over 1 hour. And in the CREDIBLE study, it was mixed. But it was a 3-hour infusion for the cefiderocol in the CREDIBLE study.
DR. LE: That's great to hear that. As a follow-up to that, you mentioned that 75 percent of free drug above the MIC is what's needed for this drug. Now, for most cephalosporin, including carbapenems, we're looking at usually 50 to 60 percent.

Can you comment on why you need a higher percentage? The 75 is usually what I see more of a target attainment for neonates who have immature immune function. But can you comment on why the 75 percent?

DR. ECHOLS: Yes. Fifty percent time above MIC is the general ballpark for cephalosporins. I'd like Dr. Yamano to just describe the results. So we did these multiple animal thigh models that were using particularly problematic bugs, and we saw a higher variety or a higher range. So we took what we thought was a more conservative estimate for our target time above MIC.

Dr. Yamano?

DR. YAMANO: I'm Yoshinori Yamano, chief scientific officer for infectious disease, research...
division at Shionogi. What we have is a target to
time of MIC, which, as required, was one reduction,
the timing by the traditional model; that is mouse
thigh infection models.

Slide 3 up. This study shows the
correlation between the free time of MIC or
efficacy in neutropenic mouse thigh infection model
caused by Pseudomonas aeruginosa. In this study,
about 60 percent of free time MIC was a degradable
[indiscernible] reduction to [indiscernible]
reduction.

In part, we also conducted a study by using
[indiscernible]. [Indiscernible] shows one
reduction with about 70 percent to the time of MIC.
Next, we conducted a study with a [indiscernible]
isoalte by using the dose-ranging study.

Slide 1 up. With 75 percent of free time
MIC was [indiscernible] mouse thigh
[indiscernible], which is shown in the left here.
This [indiscernible] of enterobacteriaceae,
Escherichia coli, and Klebsiella pneumoniae, and
Pseudomonas aeruginosa. Also, the variation of the
free time MIC was observed with the
[indiscernible], and 75 percent free time MIC was
the target.

DR. BADEN: So do you have another?

DR. LE: Yes, one more question unrelated
to the previous two. I'm just curious. Since this
drug requires iron to bind to its effect, have you
studied at all -- because some of your patients had
CKD, and one patient, I think the one who died, was
on CKD. And some of the patients, you had on
hemodialysis, at least the pharmacology side.

Have you studied to see if the response is
in fact changes in patients with anemia?

DR. ECHOLS: So just to clarify,

cefiderocol binds to iron and uses that binding to
hitchhike, if you will, into the cell. So it
doesn't require iron. If anything, it wants an
iron-depleted environment where the bacteria
up-regulate their siderophores and their
siderophore transport mechanism. So it's not
requiring iron. But to get to your point, I would
like Dr. Ogura to discuss safety results, anything
related to anemia.

DR. OGURA: There is no clear evidence of an effect of cefiderocol on anemia. We evaluated anemia adverse events in the clinical trials.

Slide 3 up. In the cUTI study, the incidence of anemia adverse events were almost similar between groups, and also, in the CREDIBLE study, slightly higher incidence of anemia was reported in the cefiderocol arm, however, all cases are confounded by underlying disease.

Slide 3 up. In addition to this study, we also evaluated adverse events related to anemia in APEKS-NP study. There was no imbalance in the incidence between the groups. So based on this result, we didn't find any adverse events, clear evidence of anemia in the cefiderocol arm.

DR. BADEN: So I actually have a follow-on question to each of Dr. Le's themes. I'll deal with the second theme first since that's on the table.

She approached it from an iron deficiency state. What about an iron overload state such as
those patients who are heavily transfused? Might that have an impact on the targeting? Because, as you said, the hitchhiker; so if there's an iron overload state, might that impact the activity?

DR. ECHOLS: I'd like Dr. Skaar to address the potential confounding of an iron overload situation on the efficacy of a siderophore conjugate antibiotic.

DR. SKAAR: Good morning. My name's Eric Skaar. I'm a professor of microbiology at Vanderbilt University Medical Center, and I'm being compensated for my time today, but I do not have financial interest in the company or the outcome of this meeting.

Bacterial pathogens acquire siderophores under iron-starved conditions, where they up-regulate the receptors for the siderophores. And therefore, you would imagine that the MIC of these molecules would go up as a bacteria in higher iron conditions, and we see that in vitro. So when these bacteria are grown in high iron conditions, the MICs go up.
Interestingly, Dr. Nicolau has done some really nice animal work to show, in iron overload conditions in mice, the MICs are not affected in acinetobacter models, pseudomonas models, and enterobacteriaceae models.

Although the in vitro MICs are affected by higher iron, that does not seem to represent itself in an in vivo model. And therefore, by extension, we wouldn't expect iron overload to affect the efficacy in the clinical situation, but I think there's --

DR. ECHOLS: About binding.

DR. SKAAR: -- binding of --

DR. ECHOLS: Iron, even if there's an iron overload, how much free iron.

DR. SKAAR: So the thinking is that, even in a condition where an organism is in an iron overloaded state, as measured by typical clinical parameters, when you have the presence of immune cells at the site of infection, a large number of iron chelating molecules will be produced, which will keep the iron away from the organism in the
microenvironment. So these bacteria are probably always iron starved, regardless of the iron status of the host.

DR. BADEN: Do you know, in the three studies presented, the transfusion state or iron state of any of the failures?

DR. ECHOLS: We did analyze clinical response based on recent transfusions. Do we have a slide on that? Dr. Ogura, do you want to --

DR. OGURA: So we evaluated the effect of a transfusion on the efficacy. There is no evidence of an effect of transfusion on clinical outcome.

DR. ECHOLS: That's just iron. It's not transfusion.

DR. OGURA: Transfusion. So we can share after lunch.

DR. ECHOLS: Yes. That is something we've looked at. No. Excuse me. Slide 1 up. I think we finally got the slide.

DR. OGURA: Slide 1 up. This slide shows the all-cause mortality by the subgroups of transfusion. There is no clear effect of blood
transfusion or iron preparation on all-cause mortality. In addition, slide 1 up.

DR. BADEN: My question was -- sorry, yes, that's it.

DR. OGURA: Yes. This slide shows the clinical cure rate and the microbiological eradication rate occurred by blood transfusion. There was no clear difference with or without blood transfusion.

DR. BADEN: Dr. Moore, you have a follow-on for this line?

DR. MOORE: Yes. Just to clarify, I'm going to assume the patients who died were not included in the clinical cure table, which looks even, but those who died; did they receive more blood transfusions than others who did not?

DR. ECHOLS: So the patients that died probably had more blood transfusions. The mortality difference by transfusion reflects just the mortality difference in the study and is not causal. And clearly, the clinical and micro response was not related to whether they received
blood transfusions or not.

DR. BADEN: Dr. Green, a follow-on?

DR. GREEN: Yes. Can you please put the slide you just had on, that looked at outcome based on whether or not they received or did not receive a transfusion?

DR. ECHOLS: Slide 1 up, please.

DR. GREEN: So I'm not sure, when I look at that, if I look at the cefiderocol group, if they get a blood transfusion, they have a 32 percent clinical cure, but if they don't get a blood transfusion, they have a 65 percent cure. If you look at microbiologic, it's 19 versus 38.

So that might intimate to me that the presence of a transfusion impacted both clinical cure and eradication, in contrast to the laboratory-based study of the organism that Dr. Skaar told us.

Am I misinterpreting this slide?

DR. ECHOLS: Well, I would think that the control arm, which looked just exactly the same as the cefiderocol arm, and the control drugs are not
siderophore antibiotics. But I would like Dr. Nicolau to show you the data. This was a study he conducted, and it's fairly conclusive that iron --

DR. GREEN: Again, I would just look to microbiologic eradication. The control arm doesn't really change, 22, 25, and these are small numbers, but the cefiderocol goes from 19 to 38.

DR. ECHOLS: The N here; this is a 2 to 1 randomization in terms of the study.

DR. GREEN: Aren't those percents?

DR. ECHOLS: Okay. But the bottom numbers are actual numbers.

DR. GREEN: Right. I know. But I'm looking at the percents. So in the microbiologic eradication, I don't see an impact on eradication with the presence or absence of a transfusion for the comparator, but for the study drug, it looks like the absence of a transfusion results in --

DR. ECHOLS: Gives a better microbiologic response.

DR. GREEN: -- right, which if you're
worried about the question that Dr. Baden was
getting at, this is not reassuring.

DR. ECHOLS: Well, the observation is
there, but the sicker patients are the ones that
got the transfusions, and they're the ones that had
the worst clinical and microbiologic response.

Would you like to see the iron overload
data?

DR. GREEN: Sure.

DR. ECHOLS: Dr. Nicolau?

DR. NICOLAU: Good morning, Dave Nicolau
from Hartford Hospital, Hartford, Connecticut, the
director of the Center for Anti-Infective Research
and Development. I have been compensated for my
time here today and my travel. I have no equity
stake in the outcome of the meeting or the company,
but have conducted several other studies in
addition to the study that I'm about to share with
you.

Slide 1 up. If you look at these data,
what we did is use the classical pharmacologic
model, the thigh infection model, something that we
count on to assess efficacy in a new antibiotic role. What we did is we exposed these animals using iron dextran to supraphysiologic concentrations of iron, and you can see supraphysiologic concentrations of iron not only in blood or plasma, but certainly in the iron store organs of liver and spleen.

Slide 2 up. One of the first aspects of this study was to understand whether this excess iron would, in some way, affect the pharmacokinetic profile of this compound. So what we did was we reproduced the humanized exposures in normal animals, animals that weren't supplemented with iron, and we compared the pharmacokinetic profile to those hyper supplemented animals.

What one can see, I think very nicely, is that the pharmacokinetic curves, both supplemented and unsupplemented, fall right on top of one another and marry against the humanized profile, which is the dark solid line.

Slide 3 up. The last aspect of the study was to assess the efficacy against a broad range of
pathogens, as noted, the enterobacteriaceae, pseudomonas, and Acinetobacter baumannii. And what you'll see in the top bars, the darker bars that go north of the starting inoculums, is that in both the iron state and the normal state, these organisms grow very vigorously in the animal models of infection.

If you look at the blue bars, what you see is, between the light blue bar and the darker blue bar, that irrespective of this hyper iron state as compared to controls, the overall efficacy of cefiderocol is quite similar in both states.

So the hyper iron state that we produce, which, again, exceeds what we would expect to see in a human model, even with transfusion or no transfusion, doesn't appear to have a detrimental effect on the efficacy of this compound.

DR. BADEN: The time for a break has arrived. The questions that the committee has have not been exhausted. But what we will do is we'll take a 10-minute break, start at 10:35. The agency will present their presentations. We'll have a
discussion around their presentation, and then we will circle back to finish questioning the applicant, given the issues that have been raised; so a 10-minute break.

(Whereupon, at 10:24 a.m., a recess was taken.)

DR. BADEN: It is 10:35. We will resume in one to two minutes.

(Pause.)

DR. BADEN: Please take your seats. We shall resume. We will now proceed with the FDA presentations, if Dr. Suvarna will start the next session.

FDA Presentation – Kalavati Suvarna

DR. SUVARNA: Good morning. My name is Kalavati Suvarna. I'm the clinical microbiology reviewer for this application. I will present on the clinical microbiology considerations in assessment of cefiderocol.

As outlined here, I will go over the in vitro susceptibility test method, the in vitro activity against target pathogens, time kill
studies, and pharmacodynamic studies conducted in vitro and in vivo, followed by resistance development.

As already mentioned by the applicant, cefiderocol binds iron and uses the bacterial iron transport system to enter into the bacterial cell. The main mechanism of action is inhibition of peptidoglycan synthesis by binding to penicillin-binding proteins or PBPs for short.

Here, on this slide, I show you the cefiderocol IC50s, which is defined as a concentration of cefiderocol required for inhibition of binding of radio-labeled penicillin G to the penicillin-binding protein by 50 percent for each of the strains.

As you can see here, cefiderocol has high affinity to PBP3 in all four target pathogens. Of note, the A. baumannii PBP3 has a lower affinity as seen by the 10-fold higher cefiderocol IC50s.

During development of the in vitro susceptibility testing, the applicant measured cefiderocol MICs in the routine cation-adjusted
Mueller-Hinton Broth medium and in iron-depleted medium against the target pathogens.

The cefiderocol MICs and the cation-adjusted Mueller-Hinton Broth were two- to 4-fold higher than those observed in iron-depleted medium. Iron-depleted cation-adjusted Mueller-Hinton Broth was used for broth microdilution susceptibility test method based on the reproducibility observed in multiple labs and ability of the applicant to conduct PK/PD or target attainment analysis in animal models.

The total iron in the iron-depleted medium is 0.02 micrograms per mL, which is sufficient for bacterial growth and similar to concentrations of non-transferrin bound iron in healthy human serum.

Here, I show you the in vitro activity of cefiderocol against target bacteria. The cefiderocol MIC 90s or concentrations required to inhibit 90 percent of isolates in surveillance studies conducted between 2014 and 2016 are shown here.

I would like to point out that this table
is slightly updated from what was there in your briefing document because of some errors. The errors are shown as strike-out, and the correct number is shown in red.

The cefiderocol MIC 90s for enterobacteriaceae was 1 microgram per mL and those against a subset of meropenem non-susceptible isolates were 4-fold higher. For the non-fermenters, for Pseudomonas aeruginosa, the MIC 90s were 0.5. In the meropenem non-susceptible subset and in the multi-drug-resistant isolates, defined as isolates that are resistant to meropenem, ciprofloxacin, and amikacin, the MICs were quite similar.

In the case of Acinetobacter baumannii, the MIC 90 of cefiderocol was 2 micrograms per mL, and in the meropenem, non-susceptible was similar. However, in the MDR isolates, the MIC 90s were 4-fold higher. The cefiderocol MIC 90s for Stenotrophomonas maltophilia and the resistance subsets were 0.25 micrograms per mL.

One of the questions with the drug is to
understand whether it's degraded by beta-lactamases. One method of assessing degradation is to use purified beta-lactamases and look at the kinetics of hydrolysis of cefiderocol in vitro.

A second method, which I present here, is looking at the cefiderocol MICs in the presence of beta-lactamase inhibitors. The applicant used the beta-lactamase inhibitors avibactam, clavulanic acid, and dipicolinic acid, and measured the cefiderocol MICs in the presence of these inhibitors. Avibactam and clavulanic acid inhibit serine type beta-lactamases, while dipicolinic acid inhibits metallo type beta-lactamases.

The applicant tested over 74 isolates, which included enterobacteriaceae and non-fermenters, which had a range of cefiderocol MICs of 2 to greater than 32 micrograms per mL. Addition of avibactam lowered the cefiderocol MICs by greater than or equal to 8-fold in 63.5 percent of isolates, while addition of both avibactam and dipicolinic acid lowered the cefiderocol MICs by
greater than or equal to 8-fold in 86.5 percent isolates. This suggests that cefiderocol can be hydrolyzed by serine and metallo type beta-lactamases.

In addition to conducting MIC assessments, the applicant also conducted time kill studies and in vitro pharmacodynamic studies. In the time kill studies, the isolates are exposed to various concentrations of drugs, and at various time points, inhibition is measured through measurement of viable counts.

In these studies, regrowth was observed after initial 2 to 3 log kill at 8 hours at concentrations greater than or equal to the cefiderocol MICs. Cefiderocol concentrations, 2 to 16 times MICs, were required to achieve sustained killing over a 24-hour period for enterobacteriaceae. No sustained killing was observed for the non-fermenters at 16 times MICs, although the cefiderocol MICs for the strain tested were low.

The in vitro pharmacodynamic studies were
conducted using a chemostat, and this was used to assess the risk of resistance development using the simulated human dose of 2 grams every 8 hours, administered as a 3-hour infusion. Regrowth was observed after 8 hours for enterobacteriaceae and non-fermenters. The regrowth was sometimes to the same level as unexposed controls.

Here, I've tabulated the results from the chemostat study. It shows all the isolates that were tested. The last column shows you the log reduction at 24 hours and 72 hours. The rows highlighted in red show isolates where regrowth was observed, and a 3-log reduction was not observed at the end of 24 or 72 hours.

The isolates that were obtained post-exposure had an increase in MIC of greater than 8-fold. When avibactam was added to these post-exposure isolates, it reduced the MICs of cefiderocol, suggesting again that serine beta-lactamases were hydrolyzing cefiderocol.

Now, we go to the pharmacodynamic study conducted in the neutropenic thigh infection model.
This model used the simulated human dose of 2 grams every 8 hours as a 3-hour infusion. Around 95 different isolates, including enterobacteriaceae, A. baumannii, and Pseudomonas aeruginosa were tested in this model. It also included isolates where a range of MIC was tested.

The right-most column shows you the results of the study, represented as mean absolute growth, which is a positive number and shown in blue, or the mean reduction in bacterial counts, shown as a negative number in black, relative to the starting inoculum at 24 hours.

The activity was variable, however, reduction was observed for most isolates with cefiderocol MICs of less than or equal to 4 micrograms per mL.

Some of the isolates with low cefiderocol MICs showed growth in this experiment. These isolates were retested. For the retesting, the applicant picked 15 isolates with low cefiderocol MICs of less than or equal to 8, which showed growth at 24 hours in the neutropenic thigh.
infection model. The MICs of these isolates pre- and post-exposures were measured. As you can see in the table, several-fold increase in post-exposure MIC was observed in 3 of the 15 isolates tested.

The applicant also looked at resistance development. In vitro, the frequency of spontaneous resistance development to cefiderocol was measured at an MIC of 10x, and this ranged from 10 to minus 6 to 10 to minus 8. It should be noted that only 10x MIC was tested. The frequency of mutation will vary depending on the concentration that's used for selection.

Serial passage studies were also conducted. A 4- to 8-fold increase in cefiderocol MIC was observed in Pseudomonas aeruginosa, over 10 passages. As I mentioned previously, isolates with 4-fold increase in post-exposure MIC was observed in the neutropenic thigh infection model that used a simulated human dose.

In terms of mechanisms of resistance, the applicant looked at mutants that were obtained in
the resistance studies and isolates from surveillance studies that had high cefiderocol MICs. Whole genome sequencing was conducted, and two types of mechanisms were identified. One related specific to beta-lactams, and the other related to iron uptake and regulation that's listed here.

In summary, the in vitro activity of cefiderocol is impacted by iron concentrations in the test medium. Cefiderocol can be hydrolyzed by serine and metallo type beta-lactamases. In time kill experiments, regrowth was observed within 24 hours in gram-negative bacteria after initial kill, and sustained bactericidal activity was not attained in non-fermenters.

The regrowth pattern with increase in cefiderocol MICs was also observed in the in vitro pharmacodynamic model using simulated human dosing. In the neutropenic thigh infection model using simulated human dosing, isolates with high cefiderocol MICs were observed post-exposure.

All these suggest development of
resistance. The mechanism of resistance identified included mechanisms observed with beta-lactams and/or those impacting iron uptake or regulation.

Thank you for your attention.

DR. BADEN: Thank you. Dr. Rubin?

**FDA Presentation - Daniel Rubin**

DR. RUBIN: I will now present on the efficacy assessment of cefiderocol for complicated urinary tract infections. I will describe the study design of the cUTI trial, efficacy results, and provide an efficacy summary.

The cUTI trial was a randomized, double-blind, active-controlled, multi-national study. Intravenous cefiderocol was compared with intravenous imipenem/cilastatin, and both were given for 7 to 14 days. The protocol did not allow oral step-down therapy.

Adults were enrolled based on complications, signs and symptoms, and evidence of pyuria. The study included patients with and without pyelonephritis, but acute uncomplicated pyelonephritis was limited to no more than
30 percent of the study population. This was a study of carbapenem-susceptible infections.

The primary efficacy endpoint was a composite endpoint evaluated at the test-of-cure visit approximately 7 days after the end of treatment. Response required both microbiological eradication and investigator-judged clinical cure.

The primary analysis population was the micro ITT population of randomized patients who received study drug and had a positive baseline urine or blood culture. This was designed as a non-inferiority trial powered for a 20 percent margin, but with planned testing for a 15 percent margin, which was the non-inferiority margin FDA agreed could support an indication.

The baseline demographics table in this slide shows that over half of patients were over 65 years old. Patients were roughly evenly split between males and females. The study was mostly conducted in whites and largely enrolled in eastern Europe. Demographic factors appeared relatively well balanced between the treatment groups.
Approximately half of patients had a clinical diagnosis of cUTI without pyelonephritis. The remaining patients were evenly split between cUTI with pyelonephritis and acute uncomplicated pyelonephritis. Over half of patients had mild, moderate, or severe renal function. The predominant baseline pathogens were E. coli and Klebsiella pneumoniae.

This table displays results for the composite clinical and microbiological primary endpoint. No differences between the groups were seen at an early assessment visit on day 4 of therapy or at the end-of-treatment visit. The rows in red display the primary efficacy analysis at the test-of-cure visit 7 days after the end of treatment.

The cefiderocol group had a response rate of 72.6 percent and the imipenem/cilastatin had a response rate of 54.6 percent. The difference in response rates, which was adjusted for stratification factors, was 18.6 percent.

The confidence interval for the difference
went from 8.2 percent to 28.9 percent. Thus, the response rate was significantly higher in the cefiderocol group. The higher cefiderocol response rate was maintained at the follow-up visit 14 days after the end of treatment.

The superior composite response rates for cefiderocol were unexpected because imipenem/cilastatin was considered an effective anti-bacterial drug, and this was a trial of carbapenem-susceptible infections.

To further probe this issue, we examine results within subgroups to assess consistency of findings and whether results were driven by any particular subset. As shown on this slide, the composite clinical and microbiological response rate at the test-of-cure visit was consistently higher in the cefiderocol group than in the imipenem/cilastatin group in subgroups defined by demographic factors, clinical diagnosis, and baseline pathogens.

Because the primary endpoint was a composite, including both the microbiological
outcome and a clinical outcome, it was important to assess how results were affected by each of the two separate endpoint components.

Microbiological response rates were similar between cefiderocol and imipenem/cilastatin at an early assessment on treatment and at the end-of-treatment visit. Eradication rates were higher in the cefiderocol group by the test-of-cure visit 7 days after the end of treatment, as shown in red. Eradication rates for cefiderocol were also higher at the follow-up visit 14 days after the end of treatment.

In contrast, clinical cure rates were similar between cefiderocol and imipenem/cilastatin at the early assessment visit, the end-of-therapy visit, and the test-of-cure visit. For the test-of-cure visit results shown in red, slightly under 90 percent of patients in each treatment group were classified as having clinical cure. At the follow-up visit 14 days after the end of treatment, there was a numerically higher clinical cure rate in the cefiderocol group, although in principle
this may have been influenced by investigator
knowledge of earlier eradication results.

In addition to the investigator-judged
clinical outcome, the trial also measured
resolution of individual symptoms. These symptoms
included feeling feverish, chills, malaise, urinary
frequency, urgency, dysuria, incontinence, urine
color change, nausea, vomiting, pain above the
pubic bone, abdominal pain, flank pain, and back
pain. Each symptom was measured as none, mild,
moderate, or severe.

Resolution rates for each symptom are shown
in table 8-12 of your briefing book. Each symptom
was absent in over 90 percent of patients in each
treatment group by the test-of-cure visit, and
there were no differences observed between symptom
resolution rates.

These symptom results supported the
conclusion that the higher cefiderocol composite
response rate, seen in this trial, were driven by
microbiological findings rather than clinical
findings.
In summary, although this study was designed as a non-inferiority trial, cefiderocol met statistical criteria for superiority to imipenem/cilastatin for the primary efficacy analysis of composite clinical and microbiological response. Results were consistent across subgroups, and we were unable to explain the higher response rates by results in any particular subset of the patient population.

The primary efficacy results were driven by higher rates of microbiological eradication for cefiderocol. Clinical cure rates and symptoms were similar between the treatment groups through the test-of-cure visit.

FDA Presentation – Shabnam Naseer

DR. NASEER: Good morning. My name is Shabnam Naseer, and I will provide a clinical and safety assessment of cefiderocol for the treatment of cUTI. Here's an outline of my presentation. First, I will discuss the safety population and exposure to study drug, the safety results, and observed increases in MIC to study drugs, followed
This table shows the overall safety population in clinical trials with cefiderocol. The phase 1 trials included healthy subjects and subjects with impaired renal function exposed to single 100-milligram to 4-gram doses or multiple doses of up to 2 grams intravenously for up to 10 days.

The overall number of subjects exposed to cefiderocol from the phase 1 cUTI, CREDIBLE-CR, and APEKS-NP trials was 761. The number of subjects treated for the cUTI indication at the proposed dose of 2 grams IV every 8 hours was 326. 300 were treated in the cUTI trial and 26 subjects with cUTI were treated in the CREDIBLE-CR study.

The safety population was relatively small but considered adequate. This safety presentation will focus on the cUTI trial results. The CREDIBLE-CR trial will be discussed following this presentation, and for the APEKS-NP trial, safety findings were not available for review by the agency.
Over 90 percent of the safety population in each treatment group completed the study. There was a similar frequency of discontinuations from the study in both treatment groups. In the cefiderocol group, there was one discontinuation due to death and one due to an adverse event. Of the patients who discontinued due to other reasons in both treatment groups, the majority were lost to follow-up.

The mean and median exposure in days was similar between treatment groups. The median exposure was 9 days in both groups.

Next, I will discuss the safety results. This table shows a summary of adverse events in the cUTI trial. There were a greater number of TEAEs, SAEs, discontinuations due to adverse events, and severe TEAEs in the imipenem/cilastatin group. The death in the cefiderocol group will be discussed on the next slide.

There was one death in the cUTI trial, and this patient was in the cefiderocol group. This was a 76-year-old Croatian male with diabetes.
mellitus, hypertension, chronic kidney disease, cerebral infarction, dyslipidemia, and epilepsy, who was treated with cefiderocol for a cUTI with E. coli without pyelonephritis. He had concurrent bacteremia and azotemia. He had not been exposed to anti-bacterial drugs in the last 12 months. No TEAEs had been reported.

On day 7 of treatment, he had a sudden cardiorespiratory arrest, and the cause of death was unknown but was attributed to a possible vascular incident, given his underlying co-morbidities.

As the death discussed previously was due to a cardiorespiratory arrest, cardiac arrhythmias were further investigated. A standardized medical dictionary for regulatory activities query, or SMQ, for cardiac arrhythmias was conducted.

Three patients in the cefiderocol group as compared to none in the imipenem group had cardiac arrhythmias. Two patients had a TEAE of sinus bradycardia noted on routine EKG performed on day 4. These patients had not been receiving heart
rate lowering medications. No further complications related to bradycardia were reported.

One patient who was a 74-year-old male with no prior cardiac history and a clinical diagnosis of acute, uncomplicated pyelonephritis developed new onset atrial fibrillation and dyspnea on day 1. He required treatment with amiodarone.

On day 6, the patient developed a hospital-acquired pneumonia and cefiderocol was discontinued. He also had a TEAE of cardiac failure. In early clinical development, a thorough QT/QTc study had been performed, which did not show a clinically significant effect of cefiderocol on the QT interval.

This table shows the treatment discontinuations that occurred as a result of an adverse event. As discussed previously, treatment was discontinued due to a cardiorespiratory arrest in one patient. Three patients in the cefiderocol group had adverse events leading to discontinuation that were considered to be treatment related per the investigator.
One patient developed diarrhea on day 2, which resolved the same day after fluid and electrolyte repletion. One patient had drug hypersensitivity which manifested as pruritis without other signs and symptoms. The pruritus occurred after the first dose of cefiderocol and resolved the same day after treatment with IV steroids. No new medications had been given, and the patient did not have prior history of a beta-lactam allergy. The patient with hepatic enzyme increase will be discussed on the next slide.

The patient who discontinued treatment was a 32-year-old female with no pertinent medical history and normal liver laboratory tests at baseline. She was treated with cefiderocol for acute uncomplicated pyelonephritis. She had been taking concomitant medications, including oral contraceptives and newly administered acetaminophen, drotaverine, metamizole, and nasal spray, presumably for sinusitis and pain relief.

On day 4, the liver tests were moderately elevated as noted. The total bilirubin remained
within the normal range during the study. On day 8, cefiderocol was discontinued due to the protocol-defined liver event of AST or ALT greater than 5 times upper limit of normal. On day 9, the PT and INR were noted to be just above the upper limit of normal, but the other liver tests had started to decline. On day 17, the liver tests noted had resolved.

Next, we will discuss serious adverse events or SAEs. SAEs in 2 or more patients in any treatment group are shown in this table. Similar preferred terms were combined as noted. SAEs were reported in a higher frequency of patients in the imipenem/cilastatin group. All cases of C. difficile may have been related to the study drug, given that it is a known adverse reaction to beta-lactam drugs.

Two SAEs of anemia and hemorrhagic anemia in the cefiderocol group were explored further, given the potential effect of cefiderocol on iron transport or metabolism. Both patients in the cefiderocol group with anemia had gastrointestinal
bleeding from duodenal erosions and had received
confounding medications such as NSAIDs and blood
thinners. Thus, causality to study drug was
confounded.

The two patients in the cefiderocol group
who developed cardiac failure also had underlying
cardiac history. The SAEs shown above either
resolved or were resolving by the end of the study.

A subgroup analysis was performed to
evaluate certain parameters such as age over 65 and
in patients with varying degrees of renal
impairment. The frequency of SAEs in those
under 65 and with normal to mildly impaired renal
function was overall greater in the
imipenem/cilastatin group. However, SAEs occurred
at a slightly higher frequency in the cefiderocol
group in patients over 65 years of age and in those
with moderate to severely impaired renal function.

This table shows TEAEs with an incidence of
2 percent or greater in the cefiderocol group. The
overall incidence of TEAEs was numerically lower in
the cefiderocol group. Similar terms were
combined, and, thus, the exact percentages may differ slightly from the sponsor's analysis.

The incidence of rash, elevated liver laboratory tests, cough, and vomiting were greater in the cefiderocol group. The incidence of the other TEAEs listed -- diarrhea, hypertension, infusion site reactions, constipation, headache, nausea, candidiasis, and hypokalemia -- were slightly greater in the imipenem/cilastatin group.

In the cefiderocol group, cough and vomiting were mild in severity in most cases. In 3 out of 7 patients with cough, there were alternate explanations for cough such as underlying lung disease or confounding medications, and the remaining 4 patients appeared to have an unexplained cough.

Most rashes were mild in severity, except in one patient who had a moderate macular disseminated rash. In that patient, vancomycin was a confounding medication. All rashes resolved by the end of the study, except in one patient, and hepatic TEAEs will be discussed in the next few
This table shows the TEAEs by age group, gender, and creatinine clearance at baseline. As the sponsor previously noted, the frequency of TEAEs was lower in the cefiderocol group across these subgroups.

We will now take a look at adverse events of special interest, the incidence of TEAEs in the gall bladder-related SMQ, which contains the terms "cholecystitis", "cholelithiasis chronic", "cholelithiasis", and "gall bladder pain" was 1.7 or 5 out of 300 in the cefiderocol group, and 0 in the imipenem group.

Four out of 5 patients treated with cefiderocol had no prior history of gall bladder disorders. One of the patients who had history of cholelithiasis developed gall bladder pain, which was considered an SAE, as it caused prolonged hospitalization. Information regarding surgical management was not available in any of the cases. Although studies show minimal excretion of cefiderocol into bile, cholestasis from cefiderocol
could not be excluded given the temporal
association of this adverse event.

Four patients in the cefiderocol group and
one patient in the imipenem/cilastatin group had a
post-baseline increase in AST or ALT over 3 times
upper limit of normal. A post-baseline increase in
AST or ALT greater than 5 times upper limit of
normal occurred at a similar frequency of 0.7
percent in both groups. There were no cases of
Hy's law in the cUTI trial.

Other adverse events of special interest
included lowering of the seizure threshold. One
patient in the cefiderocol group and none in the
imipenem/cilastatin group had a seizure during
treatment.

The patient who developed seizure was a 51-
year-old female with a prior history of seizure
disorder who had not been receiving anti-seizure
medications in the two weeks prior to enrollment.
She had a seizure on day 7, which was treated with
diazepam and levetiracetam. Cefiderocol was
continued for another 3 days without further
seizure activity.

No significant worsening in post-baseline renal or hematological laboratory changes were noted with cefiderocol treatment.

Next, I will discuss increases in MIC to study drugs in the cUTI trial. A 4-fold increase in MIC is a change in MIC that may indicate that resistance has occurred or may be emerging.

2.3 percent of patients in the cefiderocol group and 2 percent in the imipenem/cilastatin group had 4-fold increases in MIC after starting the study drug. Most often, the MIC increase was noted in the enterobacteriaceae group. The composite outcome at follow-up was failure for 9 out of 10 of these patients.

This table shows the actual increases in MIC to study drugs. In one patient in the cefiderocol group, the MIC for Pseudomonas aeruginosa increased to 1 for the original strain and then increased to 8 at follow-up for a new Pseudomonas aeruginosa strain which was detected by gel electrophoresis.
Finally, I will summarize the safety results. The frequency of TEAEs, SAEs, and discontinuations due to adverse events was greater in the imipenem/cilastatin group. There was one death in the cefiderocol group which appeared unrelated to study drug.

The most common TEAEs in the cefiderocol group were diarrhea, infusion site reactions, elevated liver tests, and rash; 4-fold increases in MIC to study drugs were observed at a similar frequency in both treatment groups.

Overall, the safety findings from the cUTI trial were consistent with the cephalosporin class, which includes hypersensitivity reactions, hepatobiliary events, seizure, and C. difficile colitis. Thank you for your attention.

**FDA Presentation – Daniel Rubin**

DR. RUBIN: I will now begin our discussion of the CREDIBLE-CR trial. I will describe the trial design, efficacy results, and statistical considerations in the assessment of mortality.

The first patient was randomized in
September of 2016. In December of last year, the new drug application was submitted while this study was still ongoing. The application included an interim summary of the first 70 patients.

In March of this year, the last patient was enrolled and the final sample size was 150 randomized and treated patients. In August, we received a study summary and datasets for the completed trial, but did not yet have a full clinical study report or case report forms.

This was a randomized, open-label, active-controlled, multinational trial. Intravenous cefiderocol was compared with an investigator-chosen, best available therapy regimen with each given for 7 to 14 days. The study was designed for descriptive analysis and was not powered for formal statistical hypothesis testing.

Patients were enrolled based on suspected carbapenem-resistant, gram-negative infections. Patients could be diagnosed with pneumonia, meaning hospital-acquired, ventilator-associated, or healthcare-associated bacterial pneumonia. In
addition, patients could be enrolled when diagnosed with bloodstream infections or sepsis. Finally, patients could be enrolled with a complicated urinary tract infection, which is the indication under review.

Potentially effective prior anti-bacterial therapy was allowed for up to 36 hours, except for cUTI, where it was allowed for up to 24 hours.

Although not designed for statistical hypothesis testing, the protocol did prespecify primary efficacy endpoints. The primary endpoint depended on the body site of infection. For pneumonia or bloodstream infections, the primary efficacy endpoint was investigator-judged clinical outcome at the test-of-cure visit 7 days after the end of therapy.

For complicated urinary tract infections, the primary efficacy endpoint was based on microbiological eradication at the test-of-cure visit. The primary analysis population for efficacy was the carbapenem-resistant microbiological intent-to-treat population of
patients with baseline carbapenem-resistant gram-negative pathogens. The primary analysis population for safety was the safety population, comprised of all 150 randomized and treated patients.

At the design stage, the applicant and FDA did not reach agreement that this trial was an adequate and well-controlled study capable of supporting an indication. Limitations included the relatively small sample size; descriptive analysis; combining of cUTI with different, more serious infection types; the open-label assessment of a subjective primary clinical outcome endpoint without adjudication; and the applicant's continuous monitoring of unblinded results.

While the study was ongoing, the applicant first alerted FDA to a mortality imbalance of 6 out of 25 versus 0 out of 13 deaths disfavoring cefiderocol. An independent data safety monitoring board was convened, and at all meetings, recommended study continuation, and the study enrolled to the originally planned sample size.
This slide displays the patient disposition. Of the 152 patients randomized, 150 were treated and included in the safety population. There were 118 patients in the carbapenem-resistant microbiological intent-to-treat primary efficacy analysis population. This represented over three-quarters of enrolled patients having carbapenem-resistant infections.

This slide displays demographic factors in the safety population. The cefiderocol group had a higher proportion of patients 65 years or older, although the age distributions were actually similar when looking at other cutoffs. The majority of patients were male. Most enrollment took place in Europe and in Asia.

In terms of clinical diagnoses, slightly under half of patients had pneumonia. Approximately 30 percent had bloodstream infections or sepsis, and approximately one-quarter of patients had complicated urinary tract infections.

Approximately half of patients had an APACHE II score of 16 or higher, which represented
a study population at a high underlying risk of
death. Each pathogen row in this table includes
patients with monomicrobial or mixed infections.
The predominant baseline pathogens were
Acinetobacter baumannii, Klebsiella pneumoniae, and
Pseudomonas aeruginosa. By chance, all 5 patients
with Stenotrophomonas maltophilia were randomized
to the cefiderocol group. Over half of patients in
this trial had mild, moderate, or severe renal
function.

In the cefiderocol group, the majority of
patients were initially treated with gram-negative
monotherapy. In the best available therapy control
group, over half of patients were treated with
colistin-based regimens.

This table displays results for efficacy
outcomes in the carbapenem-resistant
microbiological intent-to-treat population at the
test-of-cure visit. Results for the clinical cure
and microbiological eradication endpoints did not
raise concerns related to the efficacy of
cefiderocol.
Success rates were numerically higher in the cefiderocol group than in the control group for both endpoints and in most disease-type subgroups. Note that the microbiological eradication results include cases with presumed eradication.

I will now discuss statistical issues in the evaluation of mortality. Before displaying results, I will briefly discuss time points of assessment. I will subsequently show day 14 and day 28 all-cause mortality because secondary objectives of the trial included assessing these endpoints.

There were no censored mortality data through day 28. Mortality was captured for each patient through the end of study visit 28 days after the end of therapy, and thus, the window for data collection could differ between patients. However, all recorded deaths through the end-of-study visit occurred by day 49. In subsequent slides, I will therefore also discuss day 49 all-cause mortality.

This table shows the proportion of patients
with censored mortality status by time point. As previously noted, all patients had complete data for day 28 all-cause mortality. By day 49, one-half of patients had unknown mortality status. Consequently, statistical assessments at later times may be less reliable because they cannot necessarily correct for all patterns of censoring, although censoring did not appear to greatly differ between treatment groups.

We asked the applicant if it would be possible to retrospectively obtain mortality status for all patients at later times beyond the end-of-study visit, but the applicant noted that this would present logistical challenges due to the possible need for reconsenting patients or reobtaining IRB approvals.

Here are mortality results over time for the two treatment groups in the safety population. From the Kaplan-Meier curves, you can see that the cefiderocol mortality numerically exceeded the best available therapy group mortality through day 49. The estimated hazard ratio from a time-to-death
analysis was 1.77 on a scale where values greater
than 1 represented higher cefiderocol mortality.
The confidence interval for the hazard ratio went
from 0.87 to 3.57, and the two-sided p-value was
0.11.

Thus, based on this time-to-death analysis,
there was a numerical trend of higher mortality in
the cefiderocol group, but this did not reach the
level of a nominally statistically significant
difference.

This table displays all-cause mortality
results at day 14, day 28, and day 49. At day 14
and day 28, the mortality rate was approximately
6.5 percent higher in the cefiderocol group than
the best available therapy control group. However,
the confidence intervals did not exclude zero
mortality effect.

At the day 49 time point, when all deaths
through the end-of-study visit were recorded, the
mortality rates were 33.7 percent in the
cefiderocol group and 20.4 percent in the control
group. This yielded a difference in mortality
rates of 13.3 percent and a lower confidence limit for the difference that was near zero. However, as previously noted, one-half of patients had censored mortality status at this time point, and these patients are not counted as deaths in this table.

This slide shows day 28 all-cause mortality results by clinical diagnosis. The cefiderocol group had a numerically higher mortality rate than the best available therapy group in patients with pneumonia or bloodstream infections. In complicated urinary tract infections, there was no signal for increased cefiderocol mortality, but the sample size was quite small, with only 10 patients in the control group.

The next table displays day 28 all-cause mortality by demographic subgroups. The subgroups had very small sample sizes, and thus, there is a high degree of uncertainty. But within demographic subgroups, the mortality rates were generally higher in the cefiderocol group than in the control group.

This slide shows day 28 all-cause mortality
in additional baseline subgroups. Cefiderocol had a numerically higher mortality rate than the control group in patients with higher APACHE II scores. In addition, cefiderocol had a higher mortality rate than the best available therapy group in patients with Acinetobacter baumannii.

The mortality effect was not possible to assess for Stenotrophomonas maltophilia because all 5 patients were randomized to the cefiderocol group, but 4 of these 5 patients died.

In summary, there were numerical trends toward higher mortality in the cefiderocol group than in the best available therapy control group. Overall, while the difference in mortality rates was not large enough to provide statistically conclusive evidence of increased cefiderocol mortality, it did prompt additional clinical evaluation. This will now be discussed by my colleague, Dr. Shabnam Naseer.

**FDA Presentation – Shabnam Naseer**

DR. NASEER: Hello again. I will now provide a clinical assessment of the CREDIBLE—CR
study. Here's an outline of my presentation.

First, we will discuss exposure to the study drug, followed by an overview of safety results, a mortality analysis, a discussion about observed increases in MIC to study drugs, and lastly, other safety events.

All of the analysis contained in this presentation are based on the safety population of the CREDIBLE study unless otherwise specified.

Per protocol, the treatment duration was 7 to 14 days. This may have been extended to 21 days based on the investigator's clinical assessment. For cUTI, a minimum of 5 days was recommended. The overall mean and median exposure to study drug was similar in both treatment groups. The mean duration of exposure to study drug was similar for HAP/VAP/HCAP, bloodstream, or sepsis subgroups.

For the cUTI subgroup of 36 total patients, the mean and median duration of exposure were higher in the cefiderocol group by about 4 days. This may have been skewed due to 7 patients in the
cefiderocol group and none in the BAT group who received greater than 14 days of treatment. One of these patients in the cefiderocol group received 29 days of treatment for Pseudomonas aeruginosa cUTI with orchiepididymitis.

Next, I will discuss an overview of the safety results. This table shows a summary of TEAEs or treatment-emergent adverse events. These were adverse events that occurred after the first dose of study drug up to the end of the study or 28 days after the end of treatment, plus or minus 3 days.

Over 90 percent of patients in both treatment groups had at least one TEAE. There was a slightly greater number of TEAEs and severe TEAEs in the BAT group. There were more SAEs in the cefiderocol group. The number of fatal SAEs or TEAEs leading to death was greater by about 15 percent in the cefiderocol group than in the BAT group. The percentage of TEAEs leading to discontinuation was greater by about 4 percent in the cefiderocol group as compared to the BAT group.
Next, I will discuss mortality in the CREDIBLE-CR study. This table shows the number of deaths based on the study day that the death occurred. Most deaths occurred within 15 days of the start of study treatment in both groups. About 6 percent of deaths occurred between 15 and 30 days in both treatment groups.

Nine deaths occurred beyond 30 days in the cefiderocol group, and one occurred beyond 30 days in the BAT group. This death was not captured in the datasets, as the death occurred post-end of study, and the sponsor was notified of the death in a safety report. The cause of this death was also unknown. Thus, this death will not be included in further analyses throughout this presentation.

The most common TEAEs leading to death were represented in the infections and infestations system organ class. The frequency of infection-related death was higher in the cefiderocol group at 20.8 percent as compared to 6.1 percent in the BAT group. This difference represents worsening or the progression of infections.
In the cefiderocol group, 11.9 percent of infection-related deaths occurred before day 15, 3 percent occurred from day 15 to 30, and 5.9 percent occurred after day 30. There were no large differences in other system organ classes, including cardiac, respiratory, or renal disorders.

This figure shows a closer look at the specific TEAEs represented in the infections and infestations system organ class. The blue bars represent the cefiderocol group, and the maroon bars represent the BAT group. On the Y-axis is the percentage of patients with a TEAE associated with death on the X-axis.

A patient may have had more than one TEAE associated with death. Septic shock occurred at a frequency of 10.9 percent as compared to 6.1 percent in the BAT group. The next three TEAEs only occurred in the cefiderocol group. These were pneumonia or bacterial pneumonia in 5.9 percent, sepsis in 3 percent, and bacteremia in 2 percent. One patient in the BAT group had both septic shock and a device-related infection, which was a central
line-associated bloodstream infection.

These were the other TEAEs leading to death. Similar terms were combined. Patients may have had more than one TEAE associated with death. For example, one patient in the BAT group had 3 TEAEs associated with death, including metabolic acidosis, acute kidney injury, and respiratory arrest. One patient in the cefiderocol group had 4 TEAEs associated with death, such as oliguria, hypotension, multi-organ failure, and shock. The frequency of cardiac arrest, respiratory and renal-related TEAEs was similar between the treatment groups.

The TEAEs in the hepatobiliary system organ class leading to death were observed in 2 percent of patients in the cefiderocol arm, both of whom had underlying liver disease.

The sponsor appointed three external experts in medicine, infectious diseases, and intensive care to adjudicate the fatal cases. This included reviewing the results of the cUTI trial, the CREDIBLE protocol, and the death narratives.
They classified the cause of death with blinding to the treatment assignment in 43 fatal cases, 34 in the cefiderocol group and 9 in the BAT group.

First, the death was categorized as directly related or unrelated to the original gram-negative infection for which the patient was randomized into the study. Next, they voted on subcategories.

For death directly related to the original gram-negative infection, was there a failure of the study drug treatment, yes or no? For death unrelated to the original gram-negative infection, was death likely due to the patient's underlying co-morbidity, a different infection, or a drug-related adverse event?

This table shows the results of the adjudication committee. Overall, there were more deaths considered to be directly related rather than unrelated to the original gram-negative infection. Of the patients treated with cefiderocol in the CREDIBLE-CR study, 15.8 percent of the deaths were attributed to treatment failure.
Of patients treated with BAT, 8.2 percent of deaths were attributed to treatment failure. There is a difference of 7.7 percent between the two treatment groups in terms of deaths adjudicated to failure of study drug treatment.

9.9 percent of cefiderocol-treated patients and 4.1 percent of BAT-treated patients had a death, which was attributed to their underlying co-morbidities, with a difference of 5.8 between groups. There was a similar frequency of deaths attributed to other causes.

There were 3 patients in the cefiderocol group in which there was no unanimous vote on the subcategory. No deaths in either treatment group were attributable to a drug-related adverse event.

Here is a summary of treatment failures in both groups. Among the treatment failures in the cefiderocol group, 11 deaths occurred before day 15, 3 occurred between day 15 and 30, and 2 occurred on or after day 30. Most of the deaths related to treatment failure in the cefiderocol group involved acinetobacter species. In about
9 percent of treatment failures in the cefiderocol group, the primary pathogen was A. baumannii or A. nosocomialis.

In 4 patients who had 2 or more baseline pathogens, all 4 had Acinetobacter baumannii as a co-pathogen. More deaths due to treatment failure in the best available therapy group involved Klebsiella pneumoniae as a baseline pathogen.

Most of the deaths in both treatment groups occurred in critically ill patients, those with an APACHE II score greater than or equal to 16. About 11 percent of patients in the cefiderocol group and 6 percent of patients in the BAT group had an APACHE II score of over 16. The mean APACHE score of those with treatment failure was 19, and this was the same in both treatment groups.

In the cefiderocol group, the majority of deaths due to treatment failure occurred in patients who had a baseline clinical diagnosis of HABP and VABP. There were 2 deaths due to treatment failures in patients with a bloodstream infection and one death due to treatment failure in
a patient with a cUTI. I will discuss deaths in the cUTI subgroup on the next slide.

There were 6 deaths out of 36 patients in the cUTI subgroup. The incidence of death was 4 percent in either treatment group. One death in the cefiderocol group was adjudicated as infection related with treatment failure. This was a 92-year-old male with chronic obstructive pulmonary disease, an APACHE score of 11, and a SOFA score of 1.

On day 1, the urine culture showed Klebsiella pneumoniae resistant to carbapenem, ceftolozane/tazobactam, cefepime, and amikacin, and susceptible to colistin and ceftazidime/avibactam.

He received 8 doses of cefiderocol, 2 grams every 8 hours from day 1 to 3. On day 3, he developed nausea and vomiting with subsequent SAEs of hypotension, oliguria, and indeterminate refractory shock. He did not respond to fluids or vasopressors. A CT scan did not reveal an abdominal source for shock. The family withdrew consent for treatment, and the patient died on
day 4. In the BAT group, the 2 deaths that occurred were not adjudicated as treatment failures.

Next, I will discuss increases in MIC to study drugs. As previously discussed for the cUTI trial, a 4-fold increase in MIC to a study drug may indicate that resistance has occurred or may be emerging. In carbapenem-resistant mITT population of patients treated with cefiderocol, 15 out of 80, or about 19 percent of patients, had evidence of a 4-fold increase in MIC to cefiderocol. Of these 15 patients, 9 had a fatal outcome and 6 survived, of which 2 had clinical failure and 4 had cure.

In the BAT group, 5 out of 38 patients, or about 13 percent, had a 4-fold increase in MIC to any component of the study regimen. Of the 5 patients, 2 died and 3 survived, all of whom had clinical failure. The patients who had a 4-fold MIC increase to study drugs and an eventual fatal outcome will be shown on the next two slides.

This table shows cefiderocol-treated patients who had both a 4-fold MIC increase to
cefiderocol and an eventual fatal outcome. All 9 had a clinical diagnosis of HABP/VABP or sepsis due to VABP. Eight of the deaths involved an increase in MIC for a non-fermenting pathogen such as A. baumannii, Stenotrophomonas maltophilia, and Pseudomonas aeruginosa, and one involved Klebsiella pneumoniae.

There were a few instances where more than one pathogen was present at baseline, but only pathogens with a 4-fold MIC increase are shown in the table.

The MIC increase was observed anywhere from study day 3 to 23. The TEAEs leading to death suggested a non-resolving infection or progression of infection in most cases. Also, the patient number highlighted in red on the left indicates that the death was considered directly related to the original infection with treatment failure per the adjudication committee.

In the BAT group, there were 2 patients who had an MIC increase to the components of BAT and an eventual death. Both of these patients had
Klebsiella pneumoniae at baseline, and one had a bloodstream infection, and the other had VABP as the baseline diagnosis. The 4-fold MIC increase to any component of BAT was observed at day 13 for both patients. Both deaths were considered to be directly related to the original infection with treatment failure per the adjudication committee.

Next, we'll discuss other important safety events. This table shows treatment discontinuations due to adverse events in both treatment groups. Overall, there were a greater number of discontinuations in the cefiderocol group.

In the cefiderocol group, 3 patients were considered to have treatment-related adverse events, one with transaminase increased, one with drug eruption, and one with pyrexia. In the BAT group, 2 patients were considered to have had treatment-related adverse events, one with an anaphylactic reaction and the other with status epilepticus.

This table shows the TEAEs that occurred in
10 percent of subjects in either treatment group. The TEAEs noted to be greater in incidence in the cefiderocol group were diarrhea, elevated liver tests, and pyrexia. The TEAEs noted to be greater in incidence in the BAT group were septic shock, vomiting, acute kidney injury, hypokalemia, and hyperkalemia, as well as thrombocytopenia.

One patient in the cefiderocol group met the biochemical criteria for Hy's law. This patient was a 46-year-old male with diabetes, Down syndrome, asthma, and chronic hepatitis B diagnosed 12 years prior to enrollment into the study.

No information was available about prior treatment for hepatitis B, and he was not receiving concomitant antiviral treatments. No recent hepatitis B serology or PCRs were available. He was receiving concomitant medications such as propofol, metamizole, metoclopramide, and several others.

Admission had been for an asthmatic crisis requiring mechanical ventilation. He developed a carbapenem-resistant Klebsiella oxytoca HABP and
was given cefiderocol. Baseline AST, ALT, and total bilirubin were between 2 and 2 and a half times the upper limit of normal.

The time course of elevated liver tests is noted in the figure above. On day 4, the biochemical criteria for Hy's law was met. After cefiderocol was discontinued, the AST and ALT improved, however, the total bilirubin remained elevated, and a fatal SAE of refractory hepatic failure was reported on day 34.

Next, I will summarize the clinical assessment. The mortality analysis shows an imbalance of death disfavoring cefiderocol. The cause of mortality imbalance is uncertain, but does not appear to be related to any particular organ-related drug toxicity. There was a greater number of deaths in the cefiderocol group related to treatment failure and 4-fold increases in MIC, which often involved acinetobacter species with underlying HABP/VABP. Thank you.

FDA Presentation – Edward Weinstein

DR. WEINSTEIN: So at this point, I'd like
to provide some summary comments and points for consideration. The data presented so far has included nonclinical data, including in vitro anti-
microbial data and animal models of infection.

The clinical data package included a randomized active-controlled non-inferior trial in cUTI, comparing cefiderocol to imipenem/cilastatin. There was also a descriptive study, the CREDIBLE study, comparing cefiderocol to best available therapy in patients with infections due to carbapenem-resistant organisms. A clinical trial in patients with nosocomial pneumonia was completed during the NDA review. The trial results have not been reviewed by the agency.

In terms of the cUTI trial, clinical and microbiologic success rates at the test-of-cure visit were 72.6 percent in the cefiderocol group and 54.6 percent in the imipenem group. The difference in the success rate was 18.6 percent.

The clinical response rates were similar between the treatment groups. The difference in overall response was driven by the microbiologic
success component of the composite endpoint.

The safety profile was consistent with the cephalosporin class anti-bacterial drug. The safety database was relatively small, consisting of 300 subjects. Adverse events included hypersensitivity reactions, C. diff colitis, seizure, hepatobiliary, or adverse events. There was one death in the cefiderocol group that appeared to be unrelated to the drug. No deaths occurred in the imipenem group.

For CREDIBLE-CR, the trial enrolled patients with infections across body sites with carbapenem-resistant gram-negative organisms. The BAT regimens were 1 to 3 drugs. The majority were colistin based. This was a descriptive study with no prespecified hypothesis testing.

All-cause mortality was higher in the cefiderocol group compared to the BAT group. The mortality imbalance disfavoring cefiderocol occurred in the pneumonia and BSI/sepsis subgroups, but not in cUTI. An independent adjudication committee determined that infection-related death
with treatment failure was more frequent in the cefiderocol group than the BAT group, but also noted imbalance in deaths due to underlying co-morbidities.

Pharmacokinetic exposure-response analysis did not show an association between cefiderocol exposure and the risk of mortality. The most frequent treatment-emergent adverse events that led to death in the cefiderocol group were generally infection related, such as septic shock, pneumonia, sepsis, and bacteremia. Hepatic adverse events occurred more frequently in the cefiderocol-treated patients than the BAT-treated patients.

This brings us to some points for consideration. First, the cUTI trial indicated statistical superiority of cefiderocol compared to imipenem, primarily due to differences in microbiologic success rates. Clinical cure rates were comparable, so the clinical relevance of the microbiologic superiority is uncertain. Microbiological failures generally do not require re-treatment or rescue therapy.
There was no specific reason identified for the observed mortality imbalance in the CREDIBLE study. Some of the deaths were related to progression of infection and/or a lack of a clinical response. Some deaths were associated with infections due to non-fermenting gram-negative organisms such as acinetobacter, stenotrophomonas, and pseudomonas.

MIC increases to cefiderocol were observed both in vitro and within the clinical data. There was at least a 4-fold increase in cefiderocol MIC, including 8 deaths that included carbapenem-resistant non-fermenters. It's unclear whether the difference in mortality truly reflects a deficit in the activity of cefiderocol in critically ill patients or is a chance finding.

A mortality imbalance was not observed in the cUTI subgroup of the trial, but the subgroup was less severely ill than subjects with pneumonia or BSI/sepsis.

At this point, thank you for your attention, and the review team would be happy to
take your questions.

**Clarifying Questions**

DR. BADEN: So as before, please get myself or Dr. Hotaki's attention so we can add you to the list to ask questions of the agency. I know there are residual questions for the applicant. We'll come back to that afterwards. Now is the time to clarify with the agency. So we will start with Dr. Moore.

DR. MOORE: I think I'm going to hold off and ask the sponsor. Thanks, though.

DR. BADEN: Dr. May?

DR. MAY: Yes. I have two questions, one of them regards to the comment that was made, that the applicant said that it would be difficult with regard to getting IRB approval and re-consenting to obtain deaths for about half of the study, where records were missing. Right?

I understand the concerns with regard to IRB approval, but at least in the United States, it's usually possible to get death ascertainment from registries, and the fact that somebody has
died is public knowledge after the death, as far as
I know.

Since the study closed in March, wouldn't
there be an opportunity to ascertain the remaining
deaths through registries? That was one question.

The other one is, I was a little bit
surprised that the study, the CR study, was not
stopped prior to full enrollment because of the
difference in mortalities, which was about doubling
in mortality.

Is there any additional information with
regard to the monitoring of it with regard -- I
know that there was no primary hypothesis specified
and no sequential monitoring boundaries, but
nevertheless, I think such a big difference in
mortality, I was surprised to see that they didn't
stop enrollment early in that study.

DR. RUBIN: So for the follow-up of death,
the way that the study was originally set up, it
was to be followed through the end-of-study visit,
28 days after the end of therapy. So it wasn't
necessarily a protocol violation that not all
patients had mortality status out to longer, like day 49. I just want to make that clear up front.

As far as steps to possibly retrospectively obtain that, that might be a question that the applicant would be better prepared to answer.

As far as registries, one comment I'll make here is that it was largely an international study with, I think, only 9 patients in North America, which may complicate some of the abilities to look at that. But obviously, we're not on the ground in these studies and don't know how to find those data, but that may be a question that the applicant could follow up on.

As far as why the study wasn't stopped, this was a study that originally was not set up with a DSMB. It was added after there was an observed mortality imbalance.

We do have the minutes, and from our perspective, we tend to give a fair amount of deference to independent DSMBs in making those decisions. It just appeared from their review of cases that they considered deaths more to be due to
underlying co-morbidities, but we do give a fair amount of deference to independent DSMBs for why studies are stopped midstream.

DR. BADEN: I know that the applicant may have some comments. If you can keep a list, then after we clarify things with the agency, we'll come back and have you fill in some of these thoughts.

Just on the DSMB issue, it's analogous to this committee. It's a very anxiety-producing way to provide service, and they do spend a lot of time agonizing over the issues in great detail, so the deference makes sense.

Dr. Clark?

DR. CLARK: I had a question for Dr. Suvarna. It's a little bit hard for me to interpret the regrowth studies and the spontaneous development of mutations with cefiderocol. Are those data similar to what would be seen with other beta-lactams?

Also, other than the iron conditions, are there any technical issues with determining MICs for cefiderocol, and do you know, for the CREDIBLE
study, whether all the isolates were sent to a reference lab?

DR. SUVARNA: Yes. So to the first question, in terms of -- okay, let me just talk about the method first. They tested various conditions. That's part of establishing an in vitro susceptibility test method, so they looked at the effects of pH, inoculum effects, and serum effects. Serum effects were mostly seen for the non-fermenters, and you saw an increase in MICs.

In the CREDIBLE study, all the data that was there was from the central laboratory, and I forget the first question. Sorry.

DR. CLARK: With the regrowth and spontaneous mutations, is that any different than you would expect with other beta-lactams?

DR. SUVARNA: No, that's quite similar for the beta-lactams because the mechanism of action is basically binding to penicillin-binding proteins, so you would see that with other beta-lactams also.

DR. CLARK: Thank you.

DR. BADEN: Dr. Green? And if anyone has
follow-on questions, we're following the same system. Dr. Green?

DR. GREEN: Thank you. I note a rather dramatic difference in focus and resistance between the agency's presentation and the sponsor, so I have a question for either Dr. Rubin or Dr. Naseer.

We certainly saw some inferences between an association of the 4-fold rise in MICs, regardless of whether it exceeded what would be potentially MIC for the organism against this new drug and increased associated mortality.

I wonder if a formal statistical analysis was done comparing those patients who experienced a 4-fold increased MIC death in that cohort compared to death in the, I think it is, 65 individuals that did not experience the 4-fold increase, that met the criteria for the microbiology intention to treat.

DR. RUBIN: So we don't have formal statistical inference with anything like a p-value for that analysis, partly because MIC increase is a post-baseline variable, so stratifying on that
subset can complicate causal interpretations of comparisons between treatment groups. But some of our slide summaries did have raw comparisons of deaths in MIC increases.

DR. GREEN: So ignoring causality, just looking for association, because you provided us with inferences of association, it would be interesting to see, if just in a 2-by-2 table, what those show, because I think we're being asked the question or we're being presented the inference that a rising MIC is associated with death.

I use the word "associated" intentionally and would recognize that a p-value would be an association, not a causality inference.

DR. RUBIN: Thank you. At this time, we don't have the display in a 2-by-2 table, in exactly the format I think you're requesting.

DR. BADEN: So along the lines of Dr. Green's question -- and this was the other side of my question for Dr. Le's first question -- the dosing. If there may be a relationship between dosing and baseline susceptibility of the organism,
do they have the correct dosing, and should they be using a higher dosing?

Is 2Q8 versus 3Q8 a better dosing format given the background susceptibility of the organism, which may be unknown until sometime into treatment? Obviously, I will bring this to the applicant later on, but from the agency's perspective.

DR. WEI: My name is Tracey Wei. I'm the clinical pharmacology reviewer. Regarding the dosing for cefiderocol, according to the protocol for the CREDIBLE study, the dose only adjusted based on the renal function, so we didn't see if they also adjusted or take account of the baseline susceptibility.

DR. BADEN: But would it make sense that if it was less susceptible at baseline, perhaps a higher dose might be beneficial?

DR. WEI: Yes, I agree. We were also thinking the probability of target immune analysis to look at a higher MIC may be helpful.

DR. BADEN: Dr. Siberry?
DR. SIBERRY: I realize that the sponsor may have some thoughts on this later, too, but I think that the presentations from the agency at least raise the possibility, for me, of a disconnect between the sort of in vitro basic findings and outcomes, specifically for acinetobacter.

So are you concerned that there is specifically clinical failure of acinetobacter serious infections with this drug? And I just briefly would say there's no acinetobacter infections in this complicated UTI study, so the good efficacy there gives us no information about acinetobacter.

Acinetobacter makes up about half the infections in the CREDIBLE-CR study, where serious pneumonias were dominant and where the mortality difference was a concern. In the APEKS study, there were only 15 percent acinetobacter infections, so the lack of a difference in mortality in that other randomized serious infection study may be less reassuring if the real
weakness here is acinetobacter.

We heard that, at baseline, the MICs for acinetobacter are higher than the others. We also heard that it had many-fold higher than the MIC. Sustained killing doesn't happen for non-lactose fermenters for acinetobacter.

So I guess I'm just asking the agency, when you put your presentations together, are you coming up with the fact that perhaps serious infections like pneumonia, where killing may matter and where MIC may not tell the whole story, are you concerned that this drug does not work against acinetobacter?

DR. NASEER: Yes, we do agree with your concern that the mortality imbalance seems to be greater in patients with Acinetobacter infections and in underlying HABP/VABP as well.

DR. RUBIN: Could you go to backup slide 69, please? Here are some subgroup results for day 49, all-cause mortality by pathogen and also by clinical diagnosis within the CREDIBLE study.

I don't think we had shown these before,
but you can see that it's really in HABP/VABP, where you have the death rates of 4 out of 11 for cefiderocol versus 0 out of 6 for the control group, which was the predominant source of the acinetobacter. For cUTI within CREDIBLE, there just were very few patients with only 6 subjects between the two treatment groups.

DR. BADEN: For the VABP study that they have not submitted to you, are you able to comment on that, or that is absent from your analysis?

DR. RUBIN: At this time, that is absent from our analysis. All we have really reviewed in detail from that study are the top-line mortality results.

The only additional thing I'll say from that is that if the non-inferiority pans out, that may address some of the issues. It might show that what was going on in CREDIBLE in the HABP/VABP subgroup wasn't due to, say, lung penetration. It wouldn't necessarily address all of the issues about overcoming carbapenem resistance.

DR. BADEN: Thank you.
Dr. Siberry, I share your concern, but the numbers are so small, it's hard to know what to make of it, although a pattern it might be.

DR. SIBERRY: I think when we look at these mortality differences, we're thinking, is it illness severity and location of an infection, or is it the combination? And I think with the APEKS trial, if the sponsor can tell us what the mortality rate was by pathogen, again, numbers are small, it just may help us get an idea.

DR. BADEN: Dr. Ofotokun?

DR. OFOTOKUN: To follow up on this same line of questioning, if we have any, either human or animal, data of how stable this product is in the lung, and if we have any PK data of this drug in the lung; because it does appear that a majority of the mortality and also the resistance that we see have occurred in this setting of pneumonia, either hospital-acquired or ventilator-acquired pneumonia.

I don't know if the agency has any sense of those data.
DR. WEI: Tracey Wei, clinical pharmacology reviewer. So based on our review on the data submitted from the applicant, we know that they conducted the lung penetration study in healthy subjects. The result shows that the AUC ratio of the drug cefiderocol in the epithelial lung and fluid to the plasma is around 0.1. So it's a relatively low lung penetration drug.

DR. BADEN: Dr. Le?

DR. LE: Back to VABP acinetobacter, I'm just curious. Did you do a subgroup analysis, like a Kaplan-Meier that you had previously, excluding the VABP acinetobacter, to see if the curve is not as pronounced?

DR. RUBIN: Right. We actually don't have a time-to-death analysis with exclusion of acinetobacter to display for you.

DR. BADEN: Dr. DeLeo?

DR. DELEO: So I'm curious about the molecular epi and whether having that information could in fact explain a little bit of the all-cause mortality, at least some of the results for the
CREDIBLE study. You don't know whether it is a
clonal outbreak that may perhaps have a certain
strain that is more resistant, as we were talking
about to cefiderocol, versus the BAT.

Are those data available or do you know is
there any way to ascertain? I know, for example,
if you look in the U.S. -- and I know the table
that we had here, for example, with Klebsiella
pneumoniae, it says "KPC", but there are a number
of KPC types, and some may be more or less
hydrolyzed by the antibiotic versus another type.
So having the molecular epi could be an important
aspect.

DR. SUVARNA: The applicant did submit
something more recently, and I think they provided
a summary table in their presentation, which shows
the number of KPCs, NDMs, and porin mutants that
they saw.

DR. DELEO: But for acinetobacter, I mean,
it's something similar by analogy, I guess is what
I'm getting at.

DR. SUVARNA: No, we don't have that
information. We just received recently a dataset which has the complete information.

DR. BADEN: But if I understand your question, Dr. DeLeo, which the applicant will be able to address subsequently, do they have molecular epi of the infecting pathogen and then the relapsing pathogen. And even if it is KPC with the same mechanism, it could be a different organism.

DR. DELEO: Yes.

DR. BADEN: So do they have the molecular epi --

DR. DELEO: That's right.

DR. BADEN: -- to understand the before and after organism for failure?

DR. DELEO: That's right; absolutely

DR. BADEN: And that's something that they can address subsequently.

So then, I guess at this point, we're down to the last question to the agency unless others have questions.

In the cUTI study, I think there were
252 individuals who received active compound, and the mortality issue bothers all of us. If there were to be, let's say, a 1 percent increased rate of mortality in treatment A versus treatment B, how many deaths would you expect to see in a study with 250 people, increased compared to the comparator?

DR. RUBIN: Right. So the number you would expect to see would then also depend on the comparator rate. If the comparator group had a rate near zero and there was a 1 percent increase, you might still only expect to see 1 or 2 deaths in the treatment group for the cUTI study.

So it doesn't necessarily rule out very small but maybe still clinically important differences if applied to a large but low-risk population.

DR. BADEN: And that's just a fundamental challenge, which is small numbers mean differences are hard to detect, because I think it's about a 1 in 3 detection rate. So you need about 300 to detect 1 or 2 events. So we don't know that that one death may not be a signal of increased rate or
may be background noise.

DR. RUBIN: Well, from 1 versus 0 deaths in that study, I would say that, statistically, certainly that gives no statistical evidence of a problem. What it doesn't do is rule out that there's a potential problem just because the sample size is not large enough to do that.

DR. BADEN: Then I want to just get back to asking you the first question I asked the applicant, but the opposite side, which is, for the CREDIBLE study, they make the argument that it is perhaps chance. On the other hand, there is what looks like a numerically increased difference in mortality in the CREDIBLE study.

Do you believe that chance explains it, or what is the level of concern that it might be a substantive finding, and how do we weigh that?

Well, let me rephrase that. How do you weigh that?

DR. RUBIN: I hate to take a pass on this, but I think that's sort of what we're asking you all here today.

(Laughter.)
DR. BADEN: I know.

DR. RUBIN: Right.

DR. BADEN: But, no. I think that both the applicant and the agency have thoughts on this, and ultimately, all of us will have our own thoughts. But they provide several lines of evidence saying that there's no safety signal and they don't see a toxicity signal. Therefore, it must be chance.

Do you accept that or will you continue to bob and weave as we will try to do?

(Laughter.)

DR. RUBIN: So I'll try to bob and weave less --

(Laughter.)

DR. RUBIN: -- but I think, from a statistical perspective, there were trends that identified a signal. It was a small enough study where, at that point because we couldn't get a conclusive statistical answer, it depended on clinical assessments. But I don't think we're here today to say it definitely was chance or wasn't chance. But I'll just address one of the points
that you and the applicant brought up, which was
that if it wasn't chance, there would have been a
difference in efficacy results.

Could you go to my backup slide 63? This
is showing in CREDIBLE the joint distribution of
the clinical outcome on day 49, all-cause
mortality. Similar to what we saw before, if you
look at the top row, there's a similarity between
the groups in patients who survived and then had a
clinical cure. There's a handful of indeterminates
in both groups.

But then, if you look at the bottom two
rows, you do see sort of a numerical difference,
where there's a greater failure rate in the control
group, but a greater mortality rate in the
treatment group. If there is an efficacy
decrement, it could be possible that there's a
similar number of cures between the two groups, but
that patients who normally would fail could
succumb.

So I don't think that the clinical outcome,
which also for these complicated patients is
measured with a fair amount of noise -- I don't
think that the similarity in clinical cure rates
necessarily addresses all of our concerns.

DR. BADEN: Dr. Weinstein?

DR. WEINSTEIN: So I'd like to thank you
for asking the question, both of the applicant and
also the agency. One of the challenges is that
calling a chance is an answer of exclusion, so you
have to feel fairly confident that the alternatives
have been sufficiently ruled out, that you feel
confident that the safety profile is not different
than the comparator and also that the efficacy is
the same.

So once those alternate possibilities have
been exhausted, it's at that point that perhaps
there's a level of comfort with settling on chance.

DR. BADEN: I appreciate the diagnosis of
exclusion as many of our specialties. So we
appreciate the opportunity to continue to
contribute in that vein.

Dr. May?

DR. MAY: A very quick follow-up question;
on your slide, the backup slide that you had just shown, am I correct in that it implicitly assumes that the missing data for deaths at day 49 are represented or assumed to be alive in both groups equally?

DR. RUBIN: Yes. On this slide, the missing data are imputed as survival.

DR. MAY: Thanks.

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

DR. FOLLmann: No, it's a separate --

DR. BADEN: Separate; that's fine.

DR. FOLLmann: Yes. This is really a question about the discussion point. You ask us to discuss the mortality imbalance in CREDIBLE-CR with respect to the overall risk-benefit.

Is that risk-benefit for cefiderocol for cUTI or is it a more general comment? Because you earlier just mentioned we have to think of benefit and risk in reference to the CREDIBLE study, but we're not evaluating cefiderocol for that indication in HABP, VABP, BSI, and so on; so just a
little clarification about the discussion point.

DR. NAMBIAR: Thank you for the question. The reason we included the question on discussion first and then the voting question second was because I think you need to take the entire picture into consideration before you vote. So I think this discussion will have relevance to how you decide to vote on the second question.

We didn't want to separate them completely because you cannot really discuss the benefit-risk for UTI alone, having this piece of information at hand. So we wanted to give you the opportunity to provide your assessment of the study. We're not asking you to vote on it, but how you would take the data that you have at hand from this study in your overall benefit-risk considerations for this cUTI indication.

DR. FOLLMANN: Thank you.

DR. BADEN: I think the question that I asked the applicant and then the agency, they're asking us.

Are there any other questions for the
agency?

(No response.)

DR. BADEN: If not, then we have about 15 minutes to resume, or 20 minutes to resume some clarifications with the applicant. I think I will start by asking the applicant, if there were questions raised with the agency in the last 20 minutes that I know you would like to respond to, please do. And if you can do them individually so that if panel members want to do further questioning to understand the issue, please allow us.

DR. ECHOLS: Thank you very much for this opportunity to provide some clarification. I'm not sure exactly where to start because there were many, but I would like to start with the discussion of resistance and change in MIC. I'd like to have the core slide showing the SIDERO wild type study.

Cefiderocol is a siderophore cephalosporin, and that's different from other cephalosporins. Slide 1 up. It's got a much broader range of MICs than a normal cephalosporin, and that's because it
has multiple differences, both in terms of how quickly it gets into the cell and what happens when it's in the cell. It's a biological phenomenon of the siderophore antibiotic. It's been seen with other siderophore beta-lactam antibiotics.

So you can have a 4-fold change in MIC and starting at 0.003. You can have an 8-fold change in MIC, and it's still incredibly susceptible.

When we looked at the -- and I can go through a lot of the data, but what I would prefer to do is show the clinical data. So we have looked, routinely, as all clinical trials do, for a change in MIC from baseline to subsequent cultures. And I'd just like to point out you have to have a subsequent culture to have a retest of the MIC.

So if either the patient was cured, and there was no bug to culture; in other words, it was eradicated; you can't look for a change in MIC; or if there's missing data, you can't look for a change in MIC.

But Dr. Portsmouth, would you just run through the clinical trials and look at both the
patients that had a 4-fold change, but those that might be considered resistance in comparison with the control arm?

DR. PORTSMOUTH: Thank you, yes. Slide 2 up. This briefly has been discussed, really, a couple of times today, is the changes in MIC in the cUTI study, where there were 6 subjects where the MIC changed, but it didn't reach -- well, the highest was 1, so it didn't reach the threshold for what we would consider resistance, whereas in the imipenem arm, there were 3. Slide 1 up. In the CREDIBLE study, the CR study, there were 15 subjects where the MIC changed 4-fold; that was 19 percent and there were 5 in the BAT arm. In only 4 of those did it reach the breakpoint for cefiderocol, so 5 percent of those. So otherwise, they would be considered susceptible.

I'm just going to show you the APEKS-NP studies for comparison, compared to high-dose meropenem. Slide 3 up. In this study, there was an equivalent number of patients who had a change in MIC, but only one of those in the cefiderocol
arm reached the threshold that we would consider to
be resistant.

There's a bit more detail from CREDIBLE in
slide 1. This is, again, looking at the MIC, the
changes in each of the patients, so there were 3
acinetobacter that went to a resistant threshold
and one pseudomonas, whereas on the right there,
the BAT arm, most of those or all of them became
resistant.

DR. ECHOLS: The point is that a 4-fold
change in MIC, particularly for a drug that has a
very broad range in MICs, does not necessarily
constitute resistance. So it's perhaps a marker of
potential, but when you look at the clinical trial
data, there's no difference. And if anything,
there's less frank resistance in cefiderocol-
treated patients than there are in control
patients.

DR. BADEN: So follow-on questions,
Dr. Gripshover?

DR. GRIPSHOVER: Do you have data on the
clinical outcomes? Because I thought that the
agency said, in the cUTI trial, that the patients who had the increase in MICs, even though they might not have gone to Europe, what you would call resistant had worse outcomes.

Maybe I -- is that correct?

DR. ECHOLS: In the UTI study, outcome is not mortality. In the UTI study, outcome, it's a composite of clinical response and persistence, but any outcome is driven by the microbiologic component, so you have to have a culture that's positive to then compare any difference or change in MIC.

So again, the UTI study, you can have clinical response, and patients do perfectly well even though the follow-up urine is -- do you want to? Yes.

DR. PORTSMOUTH: Yes, sure. I just want to show you the data, so slide 1 up. This is the 6 patients in the cUTI trial. As Roger was mentioning, they do have a post-baseline culture, so they tended to be persistent, so that would be a composite failure. But in fact, all of them had a
clinical response.

DR. ECHOLS: Meaning what? Clinical what?

DR. PORTSMOUTH: A clinical success.

DR. ECHOLS: Yes. So there's no correlation between an increase in MIC and clinical response.

DR. BADEN: Please keep the slide up. To Dr. DeLeo's previous question, were the failures molecularly the same as the infecting isolate; or is it presumed that they're the same because it's E. coli, for this and for any of the failures across the studies?

DR. ECHOLS: I'm sorry. Can you repeat that?

DR. BADEN: Were the failures, the relapsing isolate, the same as the infecting isolate? This was Dr. DeLeo's previous question.

DR. ECHOLS: In terms of that type of molecular analysis, we do have resistance genes analysis, but really getting into either pulse-field electrophoresis or whole genome sequencing, the one case from the UTI study -- and
I think we may have a separate slide on it -- that actually had a post-culture MIC of 8, that indeed by pulse-field electrophoresis -- slide 3 up -- was a different organism. It was not the baseline organism.

You actually had 2 pseudomonas at this time point. One of them was the baseline, but it did not develop resistance. There was one strain that was a different strain.

DR. BADEN: But this wasn't systematically done for all failures? I'm just trying to know what information is available.

DR. ECHOLS: So that was the UTI study. The CREDIBLE study, there's still molecular analysis going on for those isolates that developed a 4-fold change, and similarly for the APEKS-NP study. So we have the phenotypic data. We don't have the molecular data.

DR. BADEN: But that's in process?

DR. ECHOLS: Yes.

DR. BADEN: It will be evaluated in due course.
DR. ECHOLS: Yes.

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

DR. GREEN: I want to keep in the tradition of our chairperson of flipping questions to both sides. We have these increases in MIC causing fatal -- or associated, not causing; let me strike causing -- associated with patients in the CREDIBLE study who are having only 10 percent of serum level of your drug get into the ELF fluid.

In particular, acinetobacter with a potentially augmented signal and a background piece of data that was shared with us is that the PBP affinity of your drug for the PBP of interest here was less good, resulting in a background higher sort of natural MIC, I guess, for that organism.

So what can you do to assure us -- to assure me; I've got one vote -- that this is chance, as opposed to all the circumstantial data is pointing us to at least a level of concern, using it for one bug and one site?

After you answer the question, I'd like to call on an old friend who's on your panel,
Dr. Paterson, who's put forth that chance theory to independently, or at least to us, share his thoughts in light of all these points that have been made by the agency. But I'm happy to hear you and then Dr. Paterson since the other people have done it both ways as well.

DR. ECHOLS: I certainly welcome the chance to address the question because I think we do have sufficient answers.

Slide 1 up. Just to orient, this is a fairly traditional, what we call ELF bowel study. So healthy subjects, not pneumonia patients, have been given a single dose of a drug, and you simultaneously measure the plasma, and through bronchoscopy and bronchial alveolar lavage, you measure ELF concentrations.

Even though the absolute ratio is 0.1, you always correct for free drug in the plasma. So since the protein binding is 60 percent, the actual penetration ratio is the ratio between free drug in plasma and the actual measured concentration in ELF, and that penetration is 24 percent of the free
drug.

So that 24 percent, based on healthy subject data, is what we use to estimate, based on actual plasma concentrations, in patients with pneumonia from CREDIBLE, as well as the APEKS-NP study.

So it's not just for acinetobacter; we'll get to that. But if we look at slide 1, I believe, this is the CREDIBLE study. We're only interested in patients that have pneumonia, because that's where you'd be concerned about ELF concentrations.

Looking at the patient's actual bug, including acinetobacter, and the patient's actual plasma concentrations, 25 out of the 30 patients using that 24 percent estimated penetration, 25 out of 24 had ELF concentrations exceeding the MIC of that patient's organisms 100 percent of the dosing interval. You can't do better than 100 percent.

So it is not a matter of inadequate penetration into ELF to explain why the patients did well or did not do well. What we see here is both clinical cure and survival. The vast majority
of the patients with pneumonia had more than
sufficient, more than the 75 percent target,
100 percent, and there was really no correlation
between mortality and even estimated ELF
concentrations.

Slide 3 up, is a much larger population
from the APEKS-NP study, so it's the same kind of
analysis. And even those patients, again, that did
not have a hundred percent time above MIC that
might have had 75 percent time above MIC, there was
no correlation between ELF concentrations and
outcome for either survival or clinical response.

I'll just add one other factor before
turning it over to Dr. Paterson. We do have a
patient ELF bowel study ongoing. It's ongoing. We
have, I think, sufficient results so far to say
that the penetration in actual patients with
pneumonia is consistent with the data that we saw
in the healthy subjects.

So there's plenty of drug in ELF in
patients with pneumonia to treat organisms with
MICs of 4 or less.
DR. BADEN: David?

DR. PATERSON: So I guess the very first thing to say is today is predominantly about complicated UTI, and I'm not sure I've ever treated acinetobacter in the urine before. So a lot of the talk about acinetobacter has really got to be captioned in terms of what are the results in the pneumonia or RCT, which was done as a rigorous trial.

I guess two other things just briefly about a personal experience of treating acinetobacter; first of all, treatment at the current time is a mess. We really don't know what to do; colistin, nebulized therapy, tigecycline, combination therapy.

I just want to highlight that it is really a marker of sick people, difficult conditions, so there is that level of difficulty with assessing outcomes with Acinetobacter pneumonia.

But I think the most pertinent issue is the company has done a trial on pneumonia. Thirteen percent or so had acinetobacter. They've got some
data on how patients went with Acinetobacter pneumonia, and maybe we should see that, if that's possible.

DR. ECHOLS: Are you passing the baton?

DR. PATERSOON: I am. I think Dr. Portsmouth, I guess, is the one who's the --

DR. ECHOLS: So you're absolutely right. Acinetobacter was the third most common organism, but in terms of absolute numbers, there were, if anything, more patients with acinetobacter in the lung in the APEKS-NP study than there was in the CREDIBLE study.

So I'd like Dr. Portsmouth to illustrate -- I would just do the APEKS-NP, and the acinetobacter, and then the forest plot with higher MICs.

DR. PORTSMOUTH: Thank you. Slide 2 is the all-cause mortality in patients with acinetobacter in the APEKS-NP study and really showing the day 14, day 28, and at end of study, the results were very similar.

We have a forest plot as well, looking at
the carbapenem-resistant meropenem in this study, again, which does show that there is efficacy in acinetobacter. So overall, slide 1 up, this is patients with acinetobacter in the APEKS-NP study; to the left is favoring cefiderocol for mortality.

These are very small subgroups, but we see, with an increasing MIC to meropenem, greater than 8, greater than 16, and greater than 32, there is a trend towards a high mortality in the meropenem group.

DR. ECHOLS: Again, it's not a matter of apologizing. It's a matter of timing. The FDA has not had the opportunity to review all these data, but these are locked, final data. The drug has equivalent efficacy to very high-dose, extended infusion meropenem for all organisms, including pseudomonas, including acinetobacter. And for those acinetobacter that are less susceptible to meropenem, there's actually a mortality advantage or trend favoring cefiderocol.

So I'd like to reassure you that when you look at the APEKS-NP data, it certainly is not
consistent with what was seen in the CREDIBLE data with regards to acinetobacter.

DR. BADEN: We have follow-on questions that several of the panel members have. However, it is 12:30, so I think we should break for lunch. We'll resume at 1:30 with the open public hearing session. After the open public hearing session, we will come back to further clarifying questions with the applicant. Thank you.

We'll now break for lunch. We will reconvene again in this room at 1:30. Please take any personal belongings you may want with you at this time. Committee members, please remember that there should be no discussion of the meeting during lunch, amongst yourselves, with the press, or with any member of the audience. Thank you. See you all at 1:30.

(Whereupon, at 12:30 p.m., a lunch recess was taken.)
AFTERNOON SESSION
(1:30 p.m.)

Open Public Hearing

DR. BADEN: It is now 1:30, and we shall resume. We'll now begin the open public hearing session of the meeting.

Both the FDA and the 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 that 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 of any financial relationships that you may have related to the topics of this meeting.

Likewise, FDA encourages you, at the beginning of your statement, 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 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 the issues before them.

That said, in many instances and for many topics, there are a variety of opinions. One of our goals today is for the 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 any organization you're representing for the record.

DR. FOX-RAWLINGS: Thank you for the opportunity to speak today on behalf of the
National Center for Health Research. I am Dr. Stephanie Fox-Rawlings, the center's research manager.

Our center analyzes scientific and medical data to provide objective health information to patients, health professionals, and policymakers. We do not accept funding from drug or medical device companies, so I have no conflicts of interest. There is a need for new antibiotics, and the --

DR. HOTAKI: Can you get closer to the mic, please?

DR. RAWLINGS: There is a need for new antibiotics, and the cUTI trial provides encouraging evidence that this drug could improve the symptoms of complicated UTI and reduce bacterial colony counts. However, the safety and efficacy for this indication is based on only a single pivotal trial.

As you know, replication is the key to scientific evidence. Independent trials could result in different rates of symptom improvement or
adverse events due to differences in demographics, treatment profiles of patients, or other factors, or even due to chance.

Unfortunately, this trial has several limitations that raise concerns about how generalizable it is for patients in the U.S. Less than 2 percent of the patients in the trial were from the U.S., and medical practices can differ between other countries and here. In addition, about 96 percent of the patients were white, and almost all of the rest were Asian.

The sponsor considered treatment a success if the patients had just had a reduction in complicated UTI symptoms and at least a temporary reduction in bacterial colony counts. Patients were not necessarily cured by the treatment.

Using colony counts as part of the primary endpoints is not meaningful to patients. They're also not relevant to clinical practice, nor are they a validated surrogate endpoint. While the 2018 FDA guidance on developing drugs to treat complicated UTI was finalized after the study was
started, it is useful to note that it recommended
the primary endpoint evaluated resolution of
symptoms instead of just improvement.

The second study, CREDIBLE-CR, was an
open-label descriptive study included to provide
additional information. It doesn't provide
adequate support for efficacy and instead raises
major concerns about the drug's safety. Most
concerningly, the number of patients that died were
much higher for this drug compared to the best
available treatment, an estimated hazard ratio of
1.77.

While many of these deaths were in patients
with bacterial pneumonia, or blood infections, or
sepsis, this may suggest that there is a set of
patients for whom the risks greatly outweigh the
benefits.

Another option is that the much higher
number of deaths and other adverse events were
caused by differences in baseline characteristics
in the treatment arms just due to chance, and
that's still a problem. In that case, the trial
still cannot provide adequate evidence that the drug is effective.

In summary, there's a single study that provides some evidence for safety and efficacy and another which raises serious concerns. Another study is needed, treating patients representative of those that would be treated using this drug here in the U.S.

While there is a need for new antibiotics, those products need to have sufficient evidence for efficacy and safety. To continue to be the gold standard for approval, FDA needs to maintain high standards of evidence for approval. Thank you.

DR. BADEN: Thank you.

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. BYRNE: Good afternoon. My name is Dana Byrne. I'm an infectious disease physician at an academic hospital in New Jersey. I'm here voluntarily of my own accord. I did get
compensated from Shionogi for travel, but I am not an employee of Shionogi. Thank you for hearing my testimony today.

As you know, one of CDC's serious threats for healthcare is carbapenem-resistant acinetobacter. It's a difficult healthcare infection to manage and is intrinsically resistant to certain antibiotics, is very hardy, and can survive traditional disinfection, which makes it prone to cause outbreaks.

Outbreaks have been described across the United States over the last decade, and particularly in the intensive care units of tertiary care hospitals.

Our hospital began experiencing an outbreak of multi-drug-resistant, specifically carbapenem resistant, acinetobacter, in late 2017. At first, the cases were sporadic, but over time, they multiplied. This outbreak strain was resistant to most available antibiotics, including ampicillin sulbactam, cefepime, ciprofloxacin, aminoglycosides, and carbapenems.
Generally, the outbreak isolates were only sensitive to polymyxin and intermediate tigecycline. Often, these patients were already sick and in the intensive care unit. The most common sites of infection were bloodstream infections as bacteremia and lung infections as pneumonia. Neither polymyxin or tigecycline are extremely effective drugs for these types of infections, but these were the only options we had at the time.

I spent the week of 9/22/18 on call in the hospital for infectious diseases. That particular week, I watched 4 patients die and suffer with carbapenem-resistant acinetobacter infections. These were ICU patients already fighting for their lives, who often had overcome the odds of surviving their initially potentially fatal illness, only to get another one. These patients had already survived such insults as aneurysm rupture, lymphoma treatment, heart attack, and cardiac arrest, and a motor vehicle accident with multiple fractures.

I was treating the patients with drugs like
polymyxin and tigecycline, which are not very
effective for blood infections or severe pneumonia,
and caused more side effects and toxicities. I had
to tell these suffering patients' families that we
had no other options to fight their infections.
Often, the families had already been on a roller
coaster ride of having a critically ill loved one
for weeks or months, only to now hear that their
hope for their loved one returning to their
baseline life was destroyed by infection with a
nearly impossible-to-treat superbug.

That week, we decided to reach out to
Shionogi about compassionate use of their
investigational drug, cefiderocol. We had seen
information presented at the Infectious Disease
Society of America annual meeting about this drug,
as it's one of the few novel agents in the
relatively dry antibiotic pipeline and has good
activity against MDR pathogens, including
carbapenem-resistant acinetobacter.

Cefiderocol, derived from the widely used
beta-lactam class of antibiotics, and beta-lactams
generally treat most infections more efficiently
than non-beta-lactam drugs and are well tolerated,
this was a much more attractive option for treating
these infections in our patients.

At first, we utilized the individual
emergency investigational drug use process for each
compassionate-use patient. Three began the
process, but died before getting any drug. Two
more died within 48 hours of receiving their first
dose of cefiderocol by EIND.

Fearing the process was taking too long to
be helpful in critically ill patients, and with the
encouragement of Shionogi and the FDA, we created
an expanded access protocol for cefiderocol access
for patients in my hospital.

After approval by Shionogi and my
institution’s IRB, we began initiating cefiderocol
an average of 3 days sooner, and out of the
7 patients with carbapenem-resistant acinetobacter
infections who received cefiderocol at our
hospital, 5 patients survived at 28 days
post-treatment.
The 28 percent mortality rate seen in these patients is less than described in the literature for serious carbapenem-resistant acinetobacter infections, which has been shown to range from 35 to 81 percent.

As an infectious disease physician and a director of antimicrobial stewardship at our hospital, I recognize that multi-drug-resistant pathogens are a rapidly emerging threat to human health. I work to combat it every day, and I've seen the havoc antimicrobial resistance wreaks with my own eyes.

In addition to stewardship and other strategies to prevent emergence and spread of antibiotic resistant pathogens, we also desperately need agents like cefiderocol that are novel in mechanism of action and effective against multi-drug-resistant organisms to combat bacterial resistance, and this is why I came to present to you today. Thank you.

DR. BADEN: Thank you.

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

DR. ZERVOS: I'm Marcus Zervos. I've received no compensation from Shionogi, either as a consultant or for grants. I did receive compensation for my plane ticket here from Detroit. I'm a professor of medicine and assistant dean of global health at Wayne State University School of Medicine in Detroit. I'm also chief of infectious diseases at Henry Ford Health System in Detroit.

Henry Ford Health System is a large, integrated health system in Detroit. We see about 3 million people annually within our health system. Everyone here knows how important, of course, antimicrobial resistance is and how new agents are needed. As an infectious disease physician who hears and sees about these patients fairly regularly, the need is very pressing, and I'll start with a case.

This is a patient that I saw that illustrates a number of very important points.
He's an 82-year-old male with cholangiocarcinoma that was metastatic towards end stage. He developed cholangitis with pseudomonas and pseudomonas sepsis. He was treated with colistin. He went into renal failure with colistin, and cefiderocol was used in compassionate use of that patient.

He illustrates several important points, the first being that these are patients that have multiple co-morbidities, was very sick in and out of the hospital. The second is the illustration of the limitation of options, including the need for beta-lactams to be able to treat these patients.

The third is that, despite the treatment, the pseudomonas infection, bacteremia, resolved, but towards the end of therapy, because of multiple complications, the family decided to make the patient hospice, and he died.

That point, I think, is important, looking at some of the earlier information that was presented because it is very difficult to evaluate cause of mortality in these patients. These are
patients that are terribly ill. They have multiple morbidities, mortality. And attributing sepsis as a cause of mortality or infection as a cause of mortality is very difficult with all these co-morbidities.

What I saw earlier today and from my knowledge, I have devoted my career to antibiotic resistance, including prevention and stewardship. This is an effort that's being done now worldwide, including looking at new agents.

What I saw today was an agent that has a novel mechanism of action, has excellent in vitro activity, and has both experimental and clinical trials that support its use. What I'll finish with is just a statement that this is an agent that is urgently needed, and I hope it's made available to us. Thank you very much for your attention.

DR. BADEN: Thank you.

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. ALEXANDER: Hi. My name is Jose Alexander. I am the medical microbiology director for AdventHealth in central Florida division, in Orlando, Florida. I haven’t received any compensation, or my facility has not received any compensation from Shionogi, but just getting support for the trip here from Florida.

We have a major challenge, and this major challenge is actually non-fermenter organisms. This is an example of what we face almost weekly. We have a cystic fibrosis clinic, but we also have a transplant unit.

This was the first patient that received cefiderocol in our facility. This is an example of what this patient actually has to face during multiple years of colonization with non-fermenter organisms, and this particular example, this organism was susceptible to cefiderocol if we use a breakpoint for pseudomonas. That was one of the points of the decision to access to compassionate use.

The other critical case, especially with
those patients, is they receive multiple courses of treatment with different classes of antimicrobials, making this particular organism expressing into a resistant mechanism. Most of them have acquired a resistance mechanism, but we know that most of them are already there from day 1.

These are the 3 patients that we successfully treat with cefiderocol. When we mention successfully, we're not talking about eradication. We're not talking about cure. We know that these patients have to live with this organism almost their entire life, but we probably are improving the quality of life of this patient and actually allow those patients to have access to lung transplant.

Our first patient was the previous slide. The patient had extended drug-resistant Achromobacter xylosoxidans and multi-drug-resistant pseudomonas. The treatment was cefiderocol and eravacycline, and the patient received 21 days pre- and post-transplant.

The patient was being evaluated for a liver
and lung transplant, and the patient was
successfully transplanted a few months ago. The
patient is currently at home. We haven't seen the
pseudomonas coming back in her culture, although
the achromobacter does show always in a low amount
in some of the culture.

The second case was a lung transplant of
almost 20 years ago. This patient has an extended
drug-resistant Stenotrophomonas maltophilia. The
only antimicrobial that this patient actually has a
low MIC was colistin, and this patient also was
susceptible to cefiderocol. After 21 days of
treatment, the patient was successfully discharged.

The last case is a patient that currently
is waiting for a lung transplant. The patient came
for exacerbation for cystic fibrosis with
Achromobacter xylosoxidans, multi-drug-resistant
pseudomonas, and Mycobacterium abscessus. The
patient was treated also with combination,
cefiderocol and eravacycline, and the patient is
currently waiting for transplant. All these
patients, we didn't see any adverse effects, and

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the three of them were susceptible in vitro for cefiderocol.

This is our major challenge, and this is the biggest concern that we have as microbiologists. We know that we have a good inhibitor in the markets, but when we are dealing with non-fermenter organisms, especially those list of organisms on the right, these are the mechanisms that we don't have any current drug able to overcome those mechanisms, and cefiderocol seems to show one unique mechanism that we can use against this organism.

When this organism, especially pseudomonas, acquire other carbapenemase genes, we actually have nothing else to do with any of the beta-lactam inhibitor on the market because we know that they cannot overcome these particular resistant mechanisms.

When we evaluated the use of cefiderocol, our first point of discussion was what is the mechanism behind those organisms, and what kind of drugs are we trying to bring on board for treating
those patients. The decision was based on an evaluation of microbiology data that was available for cefiderocol and the unique mechanism of action, and the decision was based at that level.

When we face this organism every single day and every week, cases like this, the final decision comes to in vitro testing. Most of those patients are drug resistant, and no matter how clinical an outcome we have for many of those drugs that we currently have on the market, the final decision is based on in vitro testing.

So in the name of AdventHealth and myself, we actually ask to consider an extended indication based on microbiology data, especially against multi-drug-resistant and extended drug-resistant gram-negative when there's limited or no treatment option available, especially for non-fermenter and when susceptibility data is available for local susceptibility data for different facilities.

Thank you.

DR. BADEN: Thank you.

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

DR. DZINTARS: Good afternoon. My name is Kate Dzintars, and I'm the clinical pharmacy specialist at the Johns Hopkins Hospital, practicing in the areas of infectious diseases and antimicrobial stewardship. The comments I'm making today reflect my own personal point of view and not necessarily the views of the institution for which I practice.

I am not a consultant for any pharmaceutical companies with antibiotics in development, including Shionogi, and other than nominal travel support, I am not receiving any compensation for my appearance here today.

Antibiotic stewards such as myself would argue that antibiotic resistance is one of the biggest public health crises to emerge, with over 2 million people developing an antibiotic-resistant infection annually.

The CDC has identified several notorious
gram-negative organisms that are of particular concern to the public welfare, including multi-drug-resistant pseudomonas and acinetobacter, as well as carbapenem-resistant enterobacteriaceae, which had been labeled as serious and urgent threats respectively.

Patients likely to develop these infections are the sickest of the sick and often have prolonged hospitalizations, gross antibiotic exposures, and are immunosuppressed in some way, whether it be through solid organ transplantation, hematologic malignancy, or are receiving other immune-devastating therapies. Additionally, patients suffering from cystic fibrosis and/or burn victims may also have significant risks.

I do have the opportunity to care for patients with cystic fibrosis. One such patient I've recently encountered underwent bilateral orthotopic lung transplant just under two years ago. This individual was colonized with Burkholderia cepacia complex prior to the transplant, and any attempts to eradicate
colonization was a failure in the setting of complete drug resistance. Despite this, this patient accepted the post-operative risk of infection and underwent a successful procedure.

Within just 2 weeks post-op, the burkholderia once again reared its ugly head, and efforts to combine multiple therapies ensued with the hopes of getting the patient out of the immediate post-transplant period until immunosuppression could be scaled back to any degree.

As bronchoscopy cultures continue to remain positive, we continued to look for alternative therapies, including new beta-lactam/beta-lactamase inhibitors that had come to the market. With one such exacerbation, we investigated the use of dual beta-lactam therapy with novel inhibitors. And while treatment was successful, we exposed the patient to unnecessarily large amounts of beta-lactams with the potential for antibiotic-associated toxicity.

Since that time, she continues to grow
burkholderia at low levels, which we continue to
monitor and hope another exacerbation does not push
this individual over the edge, as we have no
optimal treatment options left at our disposal.

Infectious diseases have been my chosen
discipline for the last 15 years. In that time, we
have witnessed the rise of extended spectrum
beta-lactamase or ESBL-producing organisms. We
could, however, reach into our antibiotic reserves
and pull out carbapenems to successfully treat
these patients.

Bacteria won out, though, quickly adapting
and giving rise to carbapenemase-producing
organisms, most specifically in the form of KPC
producers in the U.S. We then had a resurgence of
the, quote, "old school" antibiotics, including the
polymyxins to be used for therapy. When those
failed, we look to alternative administration
techniques such as extending infusions and adding
aminoglycosides, and once again, patients were
exposed to multiple antibiotics, some of which were
highly toxic.
Practitioners were able to bide their time with the management options until new agents prevailed, such as improved cephalosporins and novel beta-lactamase inhibitors, yet with these, we still see unacceptable rates of baseline resistance or the rapid development of resistance after exposure to therapy.

We still don't have an answer for some of the more problematic bacteria, including acinetobacter, stenotrophomonas, and burkholderia species. There is a desperate need for agents that possess activity against these bad bugs. The reserves are empty, and it is critical that we have antimicrobial agents to meet the unmet needs of these patients we serve.

I hope that one day soon, I'm able to reach into these reserves and pull out something new to give the patient I just informed you of, should they need it in the future.

I'd like to thank the committee for the opportunity to speak today. I do appreciate your time and attention.
Clarifying Questions (continued)

DR. BADEN: Thank you.

The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. The subcommittee 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. And before we go back to the applicant providing further clarification, I just have one clarification for the agency.

The data presented to us by the applicant and the agency included the cUTI study and the CREDIBLE study. The APEKS study, the applicant has provided us information, but we don't have that fuller picture that we get from a more complete analysis.

How should we weigh or evaluate the APEKS data?

DR. NAMBIAR: So that's correct. As part of this new drug application, we have results from the cUTI study, and the CREDIBLE study, and what
was also provided towards the end of the review, what was the review towards the end. During the review was the top-line results from the APEKS-NP study. I think, as has been noted by the applicant, the agency has not reviewed any detailed information from the APEKS-NP study, so we really cannot provide our thoughts on the data.

So really, what we are looking for from the committee is for their input based on the information that was included in the briefing package, which really focuses on the cUTI trial and the CREDIBLE study. And as such, the questions were frames based on the information available to the agency as part of the new drug application review.

DR. BADEN: Based on those two studies, and the APEKS-NP study and the compassionate-release data are in the applicant's briefing document to us and allow us to have a better understanding of the data that are out there. But in terms of the formal review, it's on the two studies that you noted.
DR. NAMBIAR: Right, because the agency, we have not received or reviewed the data from the APEKS-NP study, so I just want to make that clear.

DR. BADEN: Thank you.

So I would like to go back to the applicant to continue providing clarifications from the many issues raised this morning. And actually, before you begin, there were several follow-on questions that we didn't get to with the question we were addressing at the end of the morning.

I don't know if Dr. Le, Gripshover, or Weina remember their follow-on questions from an hour ago, or an hour and a half ago, If so, I will go back to the follow-on before we go on to the new.

Dr. Weina?

DR. WEINA: Thank you. This goes back to an earlier question when we were slicing and dicing, and had all the discussion regarding regardless of MIC, and other microdata, and everything else. There was a statement that was made that people did better clinically with the
I just wanted to be absolutely clear that I'm interpreting the data correctly, but in the cUTI data, the results of better is driven by the micro outcome, and in reality, when we talk about clinical outcomes, just what the patient experienced, it's actually the study drug and comparator that are essentially equivalent. And there is no better or worse; they're just basically the same for the majority of the data that we're looking at.

Is that correct?

DR. ECHOLS: Yes, that's correct.

DR. WEINA: Okay.

DR. ECHOLS: But this was a non-inferiority study, not intended to show superiority.

DR. WEINA: No, I understand that, but there's an awful lot of discussion about -- in the answers, there were a number of discussions about how MIC didn't matter, and clinically they did better than the micro might have shown us.

DR. ECHOLS: The composite results were
driven by the microbiologic results.

DR. WEINA: Right. Thank you.

DR. BADEN: Dr. Le?

DR. LE: Just a clarification here. I know we discussed earlier that there wasn't a correlation, in the complicated UTI trials, between the MIC and the response, and I don't think that's atypical to see with drugs that are highly concentrated in the urine. Even if it's reported resistance, you may see a response.

DR. ECHOLS: Exactly.

DR. LE: So it goes both ways for the comparator and the study drugs. But I think what the committee was concerned mostly with is the CREDIBLE C2 studies, where you saw MIC increased among acinetobacter from 1 to 8, from 1 to 4, 2 to greater than 64. I think that's where the concern lies, and this is in the clinical isolates that was reported by the agency.

So I just wanted to point that out, that our concern lies in that rather than the complicated UTI.
One question here, I'm trying to wrap my head around all of this. So far, if we're looking at complicated UTI, we have about 252 plus 27 subjects who received the study drug in total, so that's about 280 subjects that we're looking into whether or not this should go forward with approval. And of these, about 70 percent were carbapenem resistant, complicated UTIs.

I'm just trying to figure out, with that knowledge, what's the standard for defining eradication, I think is where I'm stuck at. Because here, we define as a response as eradication, I think, less than 10 to the 4th CFU per mL.

Is that the standard for defining response?

DR. NAMBIAR: I can comment on what's in our complicated UTI guidance. For micro eradication, as was stated earlier in the draft guidance, that was available when the study was designed, it was defined as in 10 to the power of 4. But subsequently, the guidance was revised, and the current guidance is 10 to the power of 3.
But the applicant, I think, has mentioned it, and we've looked at the data as well. Whether you look at it using a 10 to the 4 cutoff or 10 to the 3 cutoff, the results don't change substantially.

Also to correct, I think the numbers are a little different. The UTI trial had 300 patients exposed to cefiderocol and 26 might have been from the CREDIBLE study. And they were not carbapenem-resistant organisms; that study was carbapenem susceptible. So I just wanted to make that clear.

DR. BADEN: Dr. Gripshover?

DR. GRIPSHOVER: Mine was pretty much actually what Dr. Le just said. But you had showed us the table of the organisms that had the increased MIC in the urinary tract. And I think, actually, the agency does have a table of the increased MICs in the CREDIBLE 2 associated with outcomes, because I think 9 out of the 15 who had an increased MIC 4-fold ended up having a fatal outcome.

DR. ECHOLS: With your study, you're
talking now about the CREDIBLE study.

DR. GRIPSHOVER: Now I'm talking about

CREDIBLE, yes.

DR. ECHOLS: So can Dr. Portsmouth show you

those cases? I think it'll provide some

clarification on the patients themselves and what

happened.

DR. PORTSMOUTH: Yes. Thank you. I think

these cases really do illustrate Dr. Green's point,

that this really is an association and certainly

not causation. These patients were incredibly

sick, and so looking at their outcome is very

confounded.

These are patients, and because, of course,

the test was available later with the

susceptibility available later on, it's a very

biased sample as well because these are patients

who perhaps don't get source control of their

infection, and so continue to have infections.

Slide 1 up. This is going to go through

each of the cases one by one. There are 9 of these

cases where there was a change in MIC, and the
The first patient was a patient who had a ruptured aortic aneurysm. This aneurysm then progressed, and the patient then lost his renal arteries. He came into the hospital, had a long stay in the hospital, and was ventilated, and then came off the ventilator, but got Acinetobacter baumannii. Then later, the patient got an ischemic bowel, which perforated. The patient had all of his bowel removed. He then later on had more perforations of whatever bowel was left and died of septic shock.

So the change in MIC here was from 0.2 to 2. And really, I think, when you see a clinical case like this, you can clearly say that this was not related to a failure of antibiotic treatment.

The next patient we discussed earlier. This was a patient who had hepatic cirrhosis and had a major GI bleed 4 days before coming into the study with spontaneous bacterial peritonitis and clotting abnormalities again, and had a pulseless cardiac arrest. He came into the study, and then
died later on, after a palliative extubation, and his change in MIC was from .06 to .25.

The next patient, if we could put slide 2 up, these are the chronographs that explain the clinical course of the patients that come into the study. So this was a patient, again, an acinetobacter patient, who came into the study and had a very long course of treatment, and was put on cefiderocol. The patient has leukemia, was post having chemotherapy.

At the end of the treatment, they then went on to rescue therapy with imipenem/cilastatin and colistin. And then towards the end of the study, over to the right, you can see that they were transferred to hospice and then died later.

If we could have those 4 cases up again; so slide 2 up. The fourth patient was a patient who had a change from 2 to greater than 64. This was a patient with gangrenous infective cholecystitis, where it was inoperable. It was impossible to get source control. The patient was treated with -- could we put slide 1 up -- cefiderocol at 3
different doses because their renal function was changed. They had a clinical cure, and a sustained clinical cure, but then died later on of massive hemoptysis towards the end of the study.

Slide 1 up again. These are further 5 cases where there was a change in MIC and the patient died. The patient at the top was an aortagenic pulmonary hemorrhage who later on in the study died of sepsis and had Candida tropicalis, candidemia, and then developed multi-organ failure.

The next patient was a VABP patient who had a locally invasive lung cancer in his chest. He had a perforated esophagus, which could not be operated on, so there was absolutely nowhere of getting source control in this patient.

Then if we could show the 1 up, which is the chronograph, the patient was treated with cefiderocol and then died due to an upper gastric hemorrhage and eventually mechanical ventilation was refused by his family.

Slide 1 up again. If we go to the patients second from the bottom, this was a patient who had
ventilator-associated pneumonia. This was a patient who had 56 percent total thickness burns and smoke inhalation. This patient, again, was a very late death with a bloodstream infection with Candida glabrata.

The final patient at the bottom, again, had a change in MIC and died. This was an 84-year-old patient who had a new stroke before coming into the study, was ventilated, and then eventually died of septic shock in a cardiac arrest. But really, those very small changes in MIC, you would not expect those to be related to the very complicated cause of death for these very tragic cases.

DR. ECHOLS: Thanks, Simon.

DR. BADEN: Thank you. I turn it back over to you?

I'm sorry. Dr. Clark?

DR. CLARK: Yes. I had a question on what was just presented, when you're saying that it's confounding to interpret the cases with the increase in MICs, the pneumonia patients, the test of cure didn't necessarily always include a repeat wipe?
culture. So you wouldn't know if somebody was persistently colonized and had an MIC that was increased and was a success.

Is that what you're saying or is that true?

DR. ECHOLS: If patients remained intubated, they often had persistence of the organism that was independent of their clinical response. So particularly, basically, the endotracheal tube is a foreign body. You have biofilm formed by these gram-negatives, particularly the non-fermenters. So you can't really eradicate the organism from an endotracheal tube. You can change an endotracheal tube, which happens sometimes. And in UTI studies, we always change the urinary catheter because you can't really rely on a contaminated catheter culture.

So I'm obviously not answering your question.

DR. CLARK: No, that's kind of what I'm getting at, just if you had data to say these patients survived, there were clinical cures, but they had persistent acinetobacter, or whatever, and
their MICs increased, that would make it a little bit more helpful to understand this.

DR. ECHOLS: Okay. Again, if the patient survived, they were able to have a follow-up culture, and they may have been off-study, and they may have had a clinical relapse, but they still responded to the initial treatment, and that 4-fold increase in MIC was not what was driving the clinical failure.

We could only show you these -- again, this is the study design. It was to be a descriptive study, not a comparative study of X versus Y in a subset of something. It was a descriptive study, so we both, for purposes of evaluating the deaths, but also the successes -- we went into great detail and provided the whole clinical course of those patients to assess does the drug work or does it not work.

The people that have had, fortunately, that amount of time, including DSMB members, to look at these cases in depth, they feel that the drug works, as do we.
DR. BADEN: Thank you.

Dr. Echols, back to your further clarifications from the morning.

DR. ECHOLS: So I would like to come back to the whole issue of beta-lactamase stability. The data that was presented by the agency is correct, but it's highly selective, and I think there's some additional information that might be helpful, and really to clarify where some of the bugs came from.

So I'd like Dr. Yamano to first describe the in vitro data on the stability of cefiderocol to various purified beta-lactamase carbapenemase enzymes, and then to describe the identification of these acinetobacter, which represent a very small percentage of the surveillance data, and why adding a beta-lactam inhibitor helped reduce the MICs.

DR. YAMANO: So cefiderocol is stable to various kinds of carbapenemase, which are evaluated [indiscernible] by the kinetic studies using highly purified enzymes.

Slide 1 up. This slide shows a summary of
the stability to various beta-lactamases. The
upper part, on the upper side, the stability to
various serine type of carbapenemases, serine type
of beta-lactamases, including carbapenemase, was
shown against the KPC, OXA-23, OXA-24 -- 48. These
are carbapenemases.

In addition, the ESBL [indiscernible] and
the chromosomal enzyme [indiscernible], we use the
same type of beta-lactamase enzymes. In this case,
no hazards were observed for cefiderocol, which
shows more stability as compared with other
beta-lactams.

The lower part, though, shows us
[indiscernible] data, using the various metallo
types of beta-lactamases, like IMP-1, VIM-2, L1,
and NDM-1. The kinetic studies shows that the
[indiscernible] was observed, but the highest
potential was very small compared with meropenem.
In the case of IMP, VIM, and L1, the potential was
less than 1 percent. That's why NDM-1, we have not
obtained the highly purified enzymes, so only the
high dosage rate was compared with meropenem, which
was about 20 percent lower.

Next, we would like to show the profile of the cefiderocol resistant isolates. So by using the profile and by evaluating the profile of cefiderocol resistant isolates, we have found that some beta-lactamases could be related with cefiderocol high MIC.

Slide 2 up. This slide shows you the list of the cefiderocol recent isolates from our three-year global surveillance studies. In total, 30,000 isolates were observed, and 0.6 percent of the isolates show cefiderocol resistance.

You can see that many of the cefiderocol was resistant to Acinetobacter baumannii, followed by enterobacteriaceae, and other non-fermenters. We have conducted the detailed observation by using the EL-1 [ph] isolate.

Slide 2 up. This slide shows the geographic information and the molecular information for the cefiderocol high MIC isolates. In the case of enterobacteriaceae, 9 isolates were observed to cefiderocol resistance. Among them,
5 isolates were NDM producers, all from Turkey, and
other 4 isolates was non-NDM producing good
isolates, and we could not identify beta-
lactamases. Of the non-fermenters, 28 isolates
were A. baumannii, and among the 28, 25 isolates
were PER [ph] producing isolates, which are mainly
from Russia and Turkey, and only 4 [indiscernible]
have identified non-PER producing Acinetobacter
baumannii.

In addition, we also observed non-PER
producing Pseudomonas aeruginosa and burkholderia.
By using [indiscernible], we evaluated the effect
of avibactam and beta-lactamase inhibitor.
Avibactam is a certain type of beta-lactamase
inhibitor, and it uses [indiscernible], which is a
major beta-lactamase inhibitor. Those are shown by
the agency.

Slide 1 up. This slide shows the
[indiscernible] of the beta-lactamase inhibitors.
As shown on the left side, against the non-metallo
beta-lactamase producers, including PER 1-producing
Acinetobacter baumannii and non-PER producing
isolates, on the MIC, [indiscernible] in the presence of avibactam. The green bars shows the MIC [indiscernible], and the pink bars shows MIC in the presence of avibactam. So this shows us that some setting types of beta-lactamases could be related to high MIC to cefiderocol.

For many, [indiscernible], is a contributor for high MIC, however, we also have additional information that cefiderocol is active for many PER producers [indiscernible]. It shows that this factor was cefiderocol high MIC, but only PER does not cause high MIC to cefiderocol. The right figure shows us the result was MBL producer, not the NDM producing [indiscernible].

In these cases, the blue bars shows the original MIC, and when we did the [indiscernible], which is a metallo beta-lactamase inhibitor, the MIC did not decrease, as shown by the part blue bars. Also, meropenem MIC was decreased significantly in these conditions.

Avibactam and metallo beta-lactamase inhibitors, the MIC decreased. This shows that
much beta-lactamase could be related with cefiderocol high MIC, but at the same, it shows that only NDM does not cause high MIC. For example, PER 1 [ph] or NDM could have a high [indiscernible] to cefiderocol, but it does not have a big impact on the cefiderocol high MIC, and some beta-lactamases plus additional factors could be related with cefiderocol high MIC.

So from these results, we concluded that cefiderocol is very stable to various kinds of beta-lactamases compared with other comparators.

DR. ECHOLS: Thank you, Yamano.

So you've heard a lot of experimental data. I'm going to try to bring it down to a clinical level for a second.

There are actually two fundamental questions. One is preexisting resistance to cefiderocol, and that's what you were just listening to. So these were surveillance studies not exposed to cefiderocol, less than 1 percent have high MICs to cefiderocol. Those are almost all either acinetobacter or some metallo-containing
enterobacteriaceae. They're from Turkey and Russia.

If you do add a beta-lactamase inhibitor to those strains that have preexisting resistance, you can lower the MICs. But this is a highly selected, 39 isolates out of 30,000 or something like that. That's preexisting.

Now, the acquisition, in other words, the change in MIC on therapy, I'm going to stick my neck out as a clinician and pretend I'm a microbiologist, but you can't acquire a new gene for a beta-lactamase that doesn't exist in the baseline organism.

So the change in MIC is not related to preexisting resistance. These are two different things. Change in MIC is not the same thing as resistance, whether it's preexisting or after exposure to the drug. And we've tried to show that even when you have a change in MIC, the organism can still be highly susceptible. And based on all of our drug exposure information, whether it's ELF, or plasma, or otherwise, there's plenty of drug
exposure to inhibit the growth of the organism.

DR. BADEN: Dr. Gripshover?

DR. GRIPSHOVER: Just one quick question when we're talking about beta-lactamases; I notice, on your first slides, 35 and 36, when you just show, in general, your activity against clinical isolates, if you look on -- when you switch to the ones that are carbapenem non-susceptible, your MICs, especially for the enterobacteriaceae, really move up.

If you flip to the next slide --

DR. ECHOLS: So slide 1 up.

DR. GRIPSHOVER: Yes, the purple, and move over.

DR. ECHOLS: So you're actually correct.

DR. GRIPSHOVER: Yes. So do you know what the mechanism of that?

DR. ECHOLS: This contains -- so now we're sort of selecting out carbapenem-resistant organisms, which is selecting out the ones that contain NDM, and some of the other carbapenemase enzymes, KPCs, as well as other mechanisms of
resistance. So there's no question that, at least with the enterobacteriaceae, the presence of carbapenem resistance does move the MICs of cefiderocol to the right. But still, the point that we're trying to make is that still 97.7 percent are susceptible -- of all the organisms are susceptible to cefiderocol at 4 micrograms.

So we're agreeing with you that there is a shift to the right with enterobacteriaceae.

Do you know the mechanism of resistance in those? You have something you wanted to say.

DR. YAMANO: Maybe you're asking about the mechanism of the cefiderocol high MIC to 1 or 2 micrograms per mL of enterobacteriaceae. Correct?

As Dr. Echols said, we have no information on the reason for the cefiderocol reductive high MIC. However, concerning [indiscernible] with cefiderocol, the recent isolate was an MIC of 4 micrograms per mL. Some beta-lactamase could be related with high MIC, such as NDM or another identified beta-lactamase. However, we could not
have identified the molecular of those enzymes.

DR. ECHOLS: And I would like to just come back to both the in vivo efficacy data that Dr. Nicolau has provided with human drug exposure, that even with these strains that have higher MICs up to 4, the efficacy is apparent.

Then from the clinical trials, Dr. Paterson and Dr. Portsmouth showed actual clinical patients that had these NDM, and VIM, and IMPs, and KPCs actually did better than the control group with the cefiderocol treatment. So we have clinical evidence now from real patients that when they're infected with these bad carbapenemase enzymes, they actually respond to cefiderocol treatment.

DR. BADEN: Dr. Ofotokun?

DR. OFOTOKUN: So I understand that a vast majority of patients that were enrolled in all the clinical studies that you presented are from outside of the U.S., mostly Asia, eastern European countries. And I was also thinking about all the isolates that you have been looking at, and whether -- it seems like there's at least 1 percent
pre-exposure resistance in the general population, people that have not seen the product before but have some kind of baseline resistance.

DR. ECHOLS: Yes.

DR. OFOTOKUN: Yes. I was wondering if you have looked at geographical variation in this baseline resistance, whether the pattern, varies from different parts of the world.

DR. ECHOLS: I won't ask Dr. Yamano to present again, but in that presentation of the less than 1 percent of resistant isolates, there were 39 and there are 28 acinetobacter, and all but one came from Russia and Turkey, even in the bad NDM isolates, 4 out of 5 or so, 5 out of the 9 enterobacteriaceae came from Turkey.

So it's clear, I won't say they're global studies. They're basically Europe headed, moving as far east as Turkey, and they're North America. These surveillance studies did not involve the southern hemisphere, but they clearly show there is geographic difference, if that's your question.

Does it represent what we see now in the
United States? No.

DR. OFOTOKUN: That is what I'm trying to get at.

DR. ECHOLS: Now, in the United States, the enterobacteriaceae, 90 percent are KPC, 10 percent are NDM, whereas in Europe, it's about 50/50 KPC and other enzymes. But it's changing. It's what happens in some parts of the world, and there is certainly abilities to change geographically the organism. We need to be prepared, if nothing else, in the United States.

We just had a case a week ago of someone who came from India with an NDM pan-resistant pseudomonas, and it was the first one the state of Connecticut has seen. That's a patient that came from India, subcontinent, in the United States.

DR. BADEN: So better understanding the clinical data, where you have some patients treated and they have persistent organism or relapsed organism with an increased MIC, in that subgroup of patients, do you know the mechanism of that increased MIC in the human cases that failed?
DR. ECHOLS: From the CREDIBLE study, we don't have that molecular follow-up at this time.

DR. BADEN: Thank you.

Dr. Moore, did you have a follow-on?

DR. MOORE: Yes, I did. A lot of times, when you come to this advisory panel, the data that are provided indicate, where relative, a contribution of various countries or places around the globe where the patients are recruited. I didn't see that here.

Do we have any preliminary information as to where?

DR. ECHOLS: We do have it by region. So which study are you interested in?

DR. MOORE: Show me what you got.

(Laughter.)

DR. ECHOLS: Simon? I think we have it for all three studies; the distribution of patients by region for each of the three studies.

DR. PORTSMOUTH: First of all, the cUTI study was mostly performed in eastern Europe.

Slide 1 up. This is actually in alphabetical
order, and the highest enrolled was Romania. We had two sites in the U.S. that enrolled 7 patients. But really, it was mostly eastern European countries.

Do we have the breakdown for all of the studies together in one slide? I think we do somewhere. The CREDIBLE study was done in southeast Asia.

DR. ECHOLS: No, not clinical, just the demographics. The demographics, we can do it by study. That's APEKS-NP.

DR. PORTSMOUTH: Just the geographic location of all the sites for each of the studies.

DR. ECHOLS: So slide 2 up.

DR. PORTSMOUTH: That's CREDIBLE.

DR. ECHOLS: Do you want country level or region?

DR. MOORE: Country would be great, but I'll take region. It's not that critical. I'm very curious as to -- for example, when ceftaroline came to the advisory panel, a full 40 percent of the patients that were enrolled came from Romania.
There were significant concerns about application of the results globally. So I wanted to reassure myself, as best as I could, that the geographic distribution was not so highly focused.

DR. ECHOLS: It's not highly focused in any one region, but it's highly focused outside of the United States.

DR. MOORE: I understand.

DR. ECHOLS: And particularly for the CREDIBLE study -- his is the APEKS-NP study --

DR. PORTSMOUTH: Slide 3 up. Europe includes Israel, Korea, Turkey, Taiwan, Spain, Greece, some sites in the U.S.A., and then Brazil.

DR. ECHOLS: So with the CREDIBLE study, we wanted to go where we could find carbapenem-resistant organisms, and that's going to be more likely outside the United States. But the other ones, the geographic distribution for APEKS-NP and UTI, were not selected for resistance. It was really selected for reasons that the studies could be conducted. A major problem with the UTI study is that we did not allow oral step-down therapy,
and most hospitals, and even ethics committees in the United States, would not accept that type of study.

So there were different reasons for different things, except for the CREDIBLE study, where we wanted to go where the highest resistance rates were.

DR. MOORE: Thank you.

DR. BADEN: Dr. Siberry?

DR. SIBERRY: I just wanted to come back a little to understanding possible reasons to see different results for the UTI study versus the study that included sicker patients. And I appreciated that the non-lactose fermenters, this drug does not appear to be cidal, even at very high concentrations relative to the MIC, even when that MIC is low.

Do you think that's contributing to the observation of double the mortality risk among people with pneumonia who have got non-lactose fermenter infections in your randomized study, or if not, can you talk about what else you think
might be it?

DR. ECHOLS: Alright. So I'm going to answer that two ways. One, the definition of cidal activity depends on what experiments you're looking at, and you can look at the ratio between MIC and MPC. You can look at time kill curves, and look at X amount of log. You can look in vivo like Dr. Nicolau has done. And he's clearly shown cidal activity; in other words, drop in CFU relative and absolute.

So I would not agree with the statement that the drug is not bactericidal. It depends on what experiments you're looking at. And even in the MIC/MBC study, it may not have reached 99.9 percent, 3 log drop, but it was 99.5 percent. That's still not static. That's still cidal, but it doesn't reach that cutoff.

So I would really place my faith more in the in vivo studies, which have colony counts from, as I say, in vivo experiments.

DR. SIBERRY: With the chair's permission, maybe I misinterpreted Dr. Suvarna's presentation.
Maybe you could comment on what you talked about in terms of the ability for sustained killing by this drug specifically for non-lactose fermenters.

DR. SUVARNA: So basically, they did the pharmacodynamic studies, where they used the simulated human dosing as exposure. And in those studies, within 8 hours, you saw a regrowth of the bacterial strain, and in some of the cases where you saw the regrowth, you also saw an increase in MIC.

DR. ECHOLS: That's the chemostat study you're referring to specifically.

DR. SUVARNA: Yes.

DR. ECHOLS: I can have Dr. Yamano describe it in more detail, but when we discussed it beforehand, these were isolates, which were the selected that had high MICs to cefiderocol to begin with. So they were highly selected.

DR. SIBERRY: This says, "No sustained killing observed for non-fermenters at 16 times MIC, although cefiderocol MICs for the strains tested were low."
DR. ECHOLS: But these would represent less than 2 percent of the overall acinetobacter organisms. The MIC 90 of acinetobacter is either 1 or 2, depending on what study you look at. So if we're picking an MIC that's already 2 or 4 --

DR. SIBERRY: No, 0.015 to 0.06, so again, I'm looking --

DR. ECHOLS: Well, that's one; that's one isolate out of the 10 listed here.

DR. SIBERRY: Again -- so what I'm trying to get at, Chair, with permission, is I feel like the urinary studies for organisms susceptible to both this drug and the comparator, there was evidence of good outcomes.

For the serious illness studies, we have a real question here about why there's an impossible difference in the most important outcome of all, mortality, and there's a real disproportionate representation of non-lactose fermenters; acinetobacter with a mortality of 36 percent compared to 18 percent, comparator. We can't even compare stenotrophomomas, but 80 percent mortality
among the 5 isolates in that group.

So I'm trying to see if we can learn from
the in vitro information, a possible explanation,
and if not, something else, because quite frankly,
even though we're focused on an indication for
UTIs, as we've heard from our public testimony,
there's enormous interest in using this drug for
these bugs when they're causing infections other
than UTIs, and especially very serious ones.

DR. ECHOLS: So I'd like Dr. Portsmouth to
present the data from APEKS-NP in seriously ill
patients with acinetobacter, with APACHE scores
greater than 20 in the ICU, so I hope we can bring
that slide up.

DR. PORTSMOUTH: Yes. First of all, I'll
just show -- slide 3 up -- the mortality of
patients with acinetobacter in the study. And
acinetobacter was the most frequently isolated
organism in the study, and the mortality was
50 percent compared to 23 percent, so a 50 percent
difference, as has been pointed out.

When we look at Acinetobacter baumannii,
then the difference is 48.7 percent compared to
23.5 percent. For pseudomonas, it's 35.3 percent
versus 16.7 percent. But when we look at
pseudomonas without acinetobacter, then the
difference is actually equal. There were 2 out of
11 deaths.

Klebsiella, the mortality was balanced at
23 versus 25 percent, but then, when we look at
klebsiella without acinetobacter, then the
mortality actually was higher in the BAT group.

Slide 2 up. This is the all-cause
mortality at day 28 in patients in the APEKS-NP
study, and we've really isolated out the patients
here who were the most severely sick, so patients
who were ventilated, patients who had an APACHE II
score of 20 or above, patients in ICU, and patients
with a SOFA score of 7 or above, and showing that
there's no mortality difference between the
cefiderocol and meropenem arm.

When we look at the acinetobacter
subset -- slide 1 up -- as shown before at day 28,
again, the mortality tends to favor cefiderocol at
the higher MICs for meropenem as well.

So what we're seeing in the APEKS-NP study, it does not correlate with what we saw in the CREDIBLE study, where we think this is really confounded by the co-morbidities, the very sick patients, and the potential heterogeneity even within the patient groups that make it very difficult to assess. And we didn't see it repeated in a similarly sick population in the APEKS-NP study.

DR. BADEN: What's tricky is the APEKS-NP study has not been reviewed, so we're in a tricky position of how to evaluate these data, since they've not had a chance for full vetting.

DR. SIBERRY: Thanks very much.

DR. BADEN: Dr. Echols, if you have more in the clarification phase?

DR. ECHOLS: I don't have any more on the clarification per se, although I will just -- since you gave me an opportunity, regarding the DSMB, all I would say is that the DSMB was notified of each fatal case within days, and within a week or so,
had a full narrative to review.

So they weren't just meeting periodically, which they did do, but they were reviewing every fatal case as fast as it came in, and they did a marvelous job. We were also in communication with the FDA, with each one of these meetings, with each one of these updates.

We had a very formal statistical analysis conducted at each DSMB meeting, and the decision at each time point was to continue the study. And that's just the way it worked.

DR. BADEN: Thank you.

Dr. Clark, do you have a question?

DR. CLARK: I had a question going back to the regional differences. I remember reading, and I don't know if it was presented, that it looked like a significantly higher rate of the deaths were in Asia and the Pacific. And I was wondering if that was looked at any further or if it was just that there were more acinetobacter infections from that area.

DR. ECHOLS: So I'm just going to
summarize. That was one of the first things we looked at, is by region, because many of the first patients were enrolled in Asia, they were pneumonia patients, and they died. But overall, from the whole study, it did not come out as being a statistically relevant factor that influenced it.

We looked at region. We looked at type of infection. We looked at all those various factors. So although you could get into the granular details and say that's an imbalance, none of them rose to the level of providing an explanation.

So we think that there are multiple things going on, and I think, again, the APEKS-NP study -- I shouldn't be saying, "I think." The APEKS-NP study, the agency has not had a chance to review in detail, but it does provide a counterbalance to what was observed in the CREDIBLE study.

DR. BADEN: Dr. Naseer, do you have a question or clarification?

DR. NASEER: We would like to just display slide 18 again from the CREDIBLE study; the other
While the slide is being pulled up, we just wanted to clarify that in the cefiderocol arm, 18.8 percent of patients had an MIC increase, 4-fold, and we considered a 4-fold increase as a potential development of resistance, whereas the BAT arm had a 13.1 percent. So even with the 2 to 1 randomization, the frequency was higher in the cefiderocol arm.

Then on slide 18, that was the table where it showed the 4-fold increases to cefiderocol and eventual death. As you can see, the MIC rose as early as day 3 in the first patient, and the day of death was 9, so some of the MIC rises were early and somewhat correlated with the day of death.

Five patients actually had an outcome of death by the test of cure, and then a fatal outcome soon after that MIC increase was seen.

In all five of those patients, the TEAE leading to death seemed to reflect failure of treatment for the original infection to which the patient was randomized into the study. And again,
highlighted in red, you can see that 7 out of 9 of those patients were adjudicated as study drug treatment failure as well.

This is not to provide a causality of deaths, but to provide correlation with increasing MICs and subsequent fatal outcomes.

DR. ECHOLS: I think what Dr. Portsmouth was trying to show with the previous slides is not that there wasn't an association, but these were highly confounded cases. And even if they died of their infection, there were a lot of other things going on that contributed to the death.

DR. NASEER: Yes, and I can appreciate that, but we did look at a lot of baseline characteristics between the two treatment arms, and there were not many significant differences. We looked at age groups, bacteremia, and several other medical histories, and they were pretty much similar.

DR. BADEN: Dr. Ofotokun, you had a question?

DR. OFOTOKUN: Just a question of
clarification on how this process goes. I understand why a lot of the participants were recruited from either Asia or eastern European countries for the CREDIBLE study and the other study.

I was wondering about the cUTI trial, which the inclusion criteria, the target population could easily have been found in the United States, why many more participants were recruited from the United States in that study.

DR. ECHOLS: The main reason is we did not allow oral step-down therapy. So there are seven recent complicated UTI studies, and many of them did allow oral step-down therapies. Some of them actually encouraged it. The type of patient that you get into those studies tend to be younger, more female, more acute, uncomplicated pyelonephritis.

Our task was to identify a patient population at risk for MDR infection. That was discussions we had with the agency, and that's how we approached the protocol. And to do that, we did two things. We would not allow oral step-down
therapy because we wanted to have more drug exposure because this was a safety study in a way, definitely a safety study. And we also limited the number of acute uncomplicated pyelonephritis cases, and that just was not attractive in the United States.

As I say, I don't know what the number is, but I'm sure we contacted more than 50 sites in the U.S., and we ended up with a handful.

DR. BADEN: Thank you. Dr. Kartsonis?

DR. KARTSONIS: I just want to remind the committee, as we've looked at a number of these gram-negatives over the last few years, that what you're seeing in terms of the regional differences are really on par with all the other clinical studies that have taken place, especially the UTI studies and the HABP/VABP studies, and I think the sponsor has nicely articulated that.

Some of this is related to the oral use, but even in those studies where they've allowed oral use, the U.S. participation has been poor, and there's a lot of reasons for that. And I would
tell you that it's not for lack of trying on their part or for pharma's part in terms of that.

On the HABP/VABP side, I would also remind folks that the limited amount of prior antibiotic therapy is a problem in this particular country if you're trying to do clinical studies for pneumonia; so just some small gentle reminders about the consistency of this data relative to others.

DR. BADEN: These studies are very hard to do. Your point is well taken.

So if no further clarifications from the morning's comments, we still have further clarifications from the committee. I know Dr. Green --

(Dr. Green gestures no.)

DR. BADEN: -- and we may have addressed questions from this morning. Dr. Siberry?

DR. SIBERRY: Just one question; have you done any preclinical reproductive toxicity fetal safety studies if this drug is coming to licensure?

DR. ECHOLS: Yes.

DR. SIBERRY: Were any pregnant women
included in your compassionate use protocol?

DR. ECHOLS: Not until a week ago. So the answer is, yes, one patient a week ago. But the preclinical data, all the reproductive toxicology data did not have any significant findings.

DR. BADEN: Dr. Moore?

DR. MOORE: I'm going to pass. It's far afield.

DR. BADEN: Dr. May, did you have a clarification from earlier?

DR. MAY: No. I think it has been resolved. Thanks.

DR. BADEN: I have another clarification. Are you satisfied with the dosing?

DR. ECHOLS: Absolutely.

DR. BADEN: And do you think that a higher dosing might have added efficacy for organisms with a higher baseline MIC or is that a non-issue?

DR. ECHOLS: Based on our clinical data from the CREDIBLE study, from the APEKS-NP study -- and again, everybody got the same dose when adjusted for renal failure. The dose was very
consistent across all types of renal failure. The exposure was actually somewhat higher in the CREDIBLE patients, so not lower. Ventilation didn't change the drug exposure.

So we've thoroughly evaluated, I think, the adequacy of the drug exposure. If there were to be an adjustment, it wouldn't be to dose so much as maybe change the breakpoint. The breakpoint that we've been suggesting is one we've got provisional recognition by CLSI, but it's certainly not final.

So if you felt that you needed more drug, that's a consideration, but I think, overall, since there seems to be a very poor correlation, if any, between drug exposure and response, that more drug is not going to change the outcome.

DR. BADEN: I guess, on the breakpoint, I wish it would be based more on in vivo than in vitro data, but that is a conversation for another committee.

Dr. Siberry?

DR. SIBERRY: Just on the dosing, I note that, for the complicated UTI study, which had good
results, it was a 1-hour infusion, not a 3-hour. Is that adequate? It might be easier for ICUs to do infusions over 1 hour instead of 3. I just want your opinion on that.

DR. ECHOLS: So if you had a highly susceptible organism, a 1-hour infusion is not going to increase your safety concerns; in other words, we extended the infusion not because of a safety concern at Cmax, but to optimize the anti-bacterial activity. But besides just treating the organism that you started with, extending the infusion, at least theoretically, should also help inhibit any change in MIC.

So it's really what we refer to as optimizing the dose, not maximizing the dose. The only reason -- I mean, with UTI, there's probably not a reason to use a 3-hour infusion, but that wasn't the reason. We weren't thinking 3-hour infusion when we started the UTI study. And it was only subsequent data, and then we went to the 3-hour infusion because, based on the animal models, it seemed to make a difference if you had a high
MIC to cefiderocol.

DR. BADEN: Dr. Le?

DR. LE: I have a question related to pediatrics, more for my own knowledge. You started at pediatric and included neonates, too. What were the doses that you used?

DR. ECHOLS: If we could have slide 3 or 4, just showing the clinical development? The pediatric studies are approved. They've been designed and approved by both the FDA and the EMA. They have not really started yet; they're about to start. It's broken into several components and it's by age.

So basically, first we're doing a single-dose study to confirm the drug exposure, which is modeled. So we've modeled using all of modern science to come up with a proposed dose that, then, we verify with a single-dose study, and then we do a safety study with multiple-dose treatment of infections.

So to answer your question, it's not started yet. There is a single-dose component and
a multiple-dose component, and there's a neonatal component and a greater-than-3-month component. So we're doing the youngest kids last, I think out of we want to learn as we go along and not make any bad mistakes. But the dosing is based on modeling. We've seen it work before, but it will be verified and then studied in all age groups.

DR. BADEN: Any other questions from the committee for clarifications?

(No response.)

DR. BADEN: Any other rebuttal or clarifications from the applicant?

DR. ECHOLS: I'd just like to ask Dr. Paterson to come back and I think try to provide, again, focusing on acinetobacter in severely ill patients, considering both options, what are available options versus what cefiderocol might contribute to the benefit.

DR. PATERSON: I might even go back a step, I guess, and just think, as an antibiotic steward, complicated UTI, if there are organisms resistant to what we have at the moment, and that's probably
going to be metallo beta-lactamase or some of our pseudomonas isolates, that would certainly be a place we're going to use the drug.

Secondly, some of the difficult non-fermenters, as we have seen, there's never going to be trial data, unfortunately, for those. And then thirdly, this whole question about whether or not it could be used for acinetobacter, I might just put slide two up.

So there have been a number of randomized trials in recent years. Three of them have all been investigated or initiated, one from Israel, which compared colistin versus colistin plus meropenem; one from Italy that looked at the combination with rifampin; and one from Thailand, looking at colistin plus fosfomycin.

I just wanted to show, where does mortality sit normally in these acinetobacter-focused studies, and normally about 50 percent of patients die by day 28. That is pretty much consistent with what was seen in the CREDIBLE study with acinetobacter treated with cefiderocol; 38 percent
died.

But what was unanswered to me was why best available therapy in the CREDIBLE study had such a low mortality rate. And that, to me, is another one of the factors that came into my head as to, could this just be by chance that there were issues at baseline; that meant whether it's lacking the hypervirulent acinetobacters by chance, or was it baseline variables, things that we just can't explain. But that to me looks way out of whack compared to the other acinetobacter data that has come out in the literature in the last few years.

DR. ECHOLS: Thanks, David.

The size of the boxes there are the number of the patients, so there are over 600 patients treated recently in prospective, randomized, intervention clinical trials, either exclusively or predominantly due to acinetobacter. Regardless of the treatment arm, the mortality is always greater than 40 percent. These are not retrospective studies.

These are not cohort observational. These
are prospective randomized studies, just like CREDIBLE, except they were focused exclusively on acinetobacter. We have 17 patients in the BAT arm with a less than 20 percent mortality rate, and that's what we're being judged by here. We're not being judged by the acinetobacter that's in APEKS-NP. We're being solely judged by the acinetobacter in CREDIBLE, which is highly confounded, and the BAT arm is just not consistent with not just expectations, but what every other study has shown.

DR. BADEN: You're not being judged.

DR. ECHOLS: Pardon?

DR. BADEN: You're not being judged.

DR. ECHOLS: Okay.

DR. BADEN: We are evaluating the data as you have evaluated the data to best inform the community of how this potential therapy fits in. And I apologize if you feel judged, but that is not the intent.

DR. ECHOLS: Okay. Slide off.

DR. BADEN: But I will say, as I said
earlier, if you switched which treatment arm, you would be here saying superiority for mortality. So I do have some issue with it's unfair to say that it's the result you didn't want, but if it was the result you did want, that slide would be leading mortality benefit.

The data are the data, and we understand the unevenness and the complexity, but we have to look at the data in totality across the studies and the information provided. We are very grateful for the amount of information that the agency has shared and that you have shared.

And I do accept Dr. Kartsonis' comment. These studies are incredibly difficult to do, and the amount of analysis going on both by you all and by us, where we're looking at this study, with this organism, in this tissue space, with this MIC, and then it's 3 or 4 organisms or patients, very tricky.

So you are to be incredibly commended for the amount of work that you have done to complete these studies and to provide these data as
completely as you have, and I am very grateful for that. But I am not judging.

   DR. ECHOLS: Okay. Thank you.

   DR. BADEN: I am appreciating the amount of information being shared to inform the community because we all want to solve the issue of how do we treat difficult-to-treat pathogens that our patients face. And you've brought forward a potential modality for that, and we are very grateful for your efforts in doing that and for sharing the information. So thank you.

   DR. ECHOLS: Thank you.

   DR. BADEN: Is there another question?

Dr. Follmann?

   DR. FOLLmann: Just a comment on that slide; to me, the main comparison is the randomized groups, which showed lower mortality rate with BAT, and the other ones are not randomized; they're other concurrent studies. I would focus on the randomized comparison.

   In other situations, people say it's not that the treatment had too high of a mortality
rate; it's the other arm that was the problem.
That argument doesn't resonate with me, that the
mortality rate is too low in the BAT arm. I would
focus on the randomized comparison.

DR. BADEN: The data are complex, and we
have RCTs for a reason.

It's now 3:00. We will actually go to
break a few minutes early, and we'll have a
10-minute break until 3:10. Then we will go to the
agency's questions to us; so a 12-minute break.
Thank you.

(Whereupon, at 2:58 p.m., a recess was
taken.)

Questions to the Committee and Discussion

DR. BADEN: We shall resume the meeting.
And again, I want to thank both the agency and the
applicant for very extensive presentations of
complex data.

We'll now proceed with the questions to the
committee and panel discussion. I'd like to remind
public observers that while this meeting is open
for public observation, public attendees may not
participate, except at the specific request of the panel.

We have two questions from the agency. The first question is a discussion question, and to address that, we shall do what the agency asks, have a discussion. In that discussion, what I would like is for panel members to share their thoughts about how -- well, let's read the discussion question, and then we can have the discussion.

Please discuss your evaluation of the mortality imbalance observed in the CREDIBLE-CR study with respect to the overall risk-benefit assessment for cefiderocol and provide recommendations for labeling and/or the need for additional studies.

I don't know if the agency has any other clarification they want for us. Then, I think the best way to have this discussion is I would like to start with where we ended, right before the break, with Dr. Follmann, who was commenting about how to interpret the BAT group versus the active
treatment, if I can frame it that way, and how you weigh the interpretation of the better than expected mortality in the BAT group, therefore that's the aberrancy.

Because I think we need to have a discussion, and I would like all of the committee to participate and raise issues that haven't been raised in the discussion so the agency can hear all of our thoughts. But I think that was a nice place to open, and how do we weigh the activity of cefiderocol, which either increases the mortality or actually gives you average mortality for this condition; and the placebo group, with only 3 of 17, if there were 2 more deaths, it would have been 30 percent, and 2 more deaths, and you'd say it's no different, and that was artificially low?

How do you view those types of data since this becomes a critical evaluation element?

DR. FOLLemann: Well, I guess I want to make two points. One is, for me, the only thing that matters -- the main thing that matters is the randomized comparisons between BAT and the
sponsor's drug.

DR. BADEN: When you say "randomized", in the cUTI study, or randomized --

DR. FOLLMANNN: No. I'm talking about the CREDIBLE-CR study. To me, that was I think the main reason we were brought together today, because of the CREDIBLE-CR study and the mortality imbalance. And the issue that I wrestle with, is it real or not, is it a fluke or not?

There are different aspects of that, that I've thought about. One is that, overall, Dan did an analysis where he looked at the hazard ratio, which was, I think, 1.77 or so, with a p-value of 0.11, so it's not definitive. As Dan pointed out, it's maybe suggestive.

Another thing that I've pondered about with this is, is this causal or not? It's borderline, perhaps, if that. And if you look at the death rate for infections, it's twice as much, and if you look at the death rate for non-infections, it's twice as much in the CREDIBLE-CR study.

So to me, it would be stronger for
causality if all of the signal was, say, in infections, and then maybe the drug isn't working well against infections, or if all of the signal was in non-infections, then maybe the drug has some toxic effect that we're not aware of, or it pushes these sick people over the edge. But the fact that we see sort of the same doubling in both of these disparate kind of causes, if you want to think that, makes it more puzzling to me and less definitive.

To me, the big issue really is that all of the signal is in non-cUTI, and we're discussing cUTI today, and the CREDIBLE study is rather different from the cUTI study.

DR. BADEN: But I think we'll get to the cUTI study.

DR. FOLLMANN: Okay.

DR. BADEN: The mortality imbalance in CREDIBLE raises a signal that is hard to ignore. And if we look at --

DR. FOLLMANN: To me, that signal is focused on non-cUTI. So that's a fair question,
but maybe that's a question for a HABP/VABP or BSI licensure setting.

Do I want to make the leap that this applies to cUTI when it's sort of a different population? They're sicker, different pathogens, different site of infections. That's a lot of differences in my mind.

DR. BADEN: So then you see this as, in severe infection, there is a concern, but in severe --

DR. FOLLMANN: In severe infection and outside the urinary tract.

DR. BADEN: The cUTI setting.

DR. FOLLMANN: Yes, and I know that that's -- to me, today, we're looking at cUTI, for the most part. It would be a lot more troubling, I'd worry a lot more, think a lot more, if we were discussing HABP/VABP and bloodstream infections, if we were talking the licensure for that.

DR. BADEN: I heard comments over here.

Dr. Weina?

DR. WEINA: But the study was never
designed to be statistically analyzed, and that's the problem. It was a descriptive study, and we're post hoc applying all of these statistics to it.

I mean, clearly, there was something. There was an imbalance in mortality, but I mean, I've heard a whole mess of times, this is a descriptive study; this is a descriptive study. And it was never designed to be looking at the differences between the groups. They were so small. We keep dancing around and trying to explain, well, this is by chance, but it was never designed to be looking at it by chance.

We're doing all of these post hoc kind of analyses on this thing, trying to say, well, maybe this explains it, maybe this explains it, maybe this explains it; and maybe what we need to do is just go back and redesign another trial that actually looks at specific data.

I mean, if we're going to be having that discussion, the reality is, to paraphrase M.A.S.H., really sick people die, and rule number 2 is doctors or new drugs can't change rule number 1.
So maybe what we need to do is go back and redesign the study so that it actually tries to answer a question rather than just be a descriptive study that we hope is going to turn out to our favor when we analyze the data.

DR. BADEN: So then are you arguing that the CREDIBLE study is uninterpretable?

DR. WEINA: I think you can interpret it any way you want, dependent upon what you want the results to be. If you didn't design it so that you can analyze the data before you went ahead and did the study, prospectively, you can analyze it -- if I were the sponsor, I'd be trying like hell to explain away that mortality difference. And if I were a risk-adverse population, I'd be explaining like crazy, oh, my god, I can't do this. There's a risk here, and we're a zero-risk population.

DR. OFOTOKUN: I have a question for Dr. Follmann [inaudible - off mic].

DR. BADEN: Well, we have a series of folks. We will get to everyone's comment and having discussion across to each other, I would
like to encourage. So we will add you to that, but I want to make sure the voice on the phone, Dr. Smith, has a chance to chime in, and he's indicated that he has some thoughts.

Dr. Smith?

(No response.)

DR. BADEN: We cannot hear you if you are talking.

DR. SMITH: Yes.

DR. BADEN: You're live.

DR. SMITH: I'm live. I guess my question is if the antibiotic is given approval for UTIs, then it's very likely to be used for other hard-to-treat infections like nosocomial and bacterial pneumonia -- this is supported by our public comment statement -- especially like acinetobacter. But the mortality imbalance between cefiderocol and BAT in the CREDIBLE study is concerning, but the baseline differences in study participants, the small numbers make it difficult for definitive conclusions.

In my read, perhaps the mortality rate in
the CR study would have been similar if they used imipenem versus colistin, and there wasn't as many acinetobacter that are there. And this is supported by the APEKS-NP study.

In other words, the antibiotic seems to be better than imipenem, but not as good as colistin, especially for acinetobacter, but that trial needs to be done. And it also is going to be dependent on complications of the infection type.

So my suggestion is that additional large-scale, double-blinded, randomized-controlled studies versus these observational studies need to be done to sort that out. But if the question is about labeling, then it needs to be really focused on the UTI study and versus this other CREDIBLE-CR study. That does have an interesting and scary signal for mortality, but that needs to be sorted out in a different study. That's all.

DR. BADEN: So Dr. Smith, if I can push you a little bit, you said an RCT should be done. What RCT were you suggesting?

DR. SMITH: I think that it needs to be
powered based on mortality for comparing -- if the
sponsor wants to go after an indication for
invasive gram-negative infections that include
acinetobacter and others, then that needs to be a
double-blind, randomized-controlled study, and
powered based on seeing no difference in mortality
to BAT.

DR. BADEN: Thank you. Dr. Green?

DR. GREEN: Actually, my comments are a
follow-on on the last two speakers and also address
the latter half of the question posed to us for
discussion.

So everybody knows that if this drug is
approved for complicated UTI, its use is going to
go beyond that. The only potential limitation to
its use is a concern that third-party payers won't
reimburse, which won't limit any of us from
prescribing it if we have a pan-resistant organism
in a sick patient.

All the discussion we've had so far today
does not make the concern that this signal for
mortality is not chance alone. And I agree with
Dr. Smith that one should do a trial better than CREDIBLE, but at a minimum repeating CREDIBLE, because if it's chance alone, then it should flip as likely to the other way as the same way, but why not do a formal study that answers the question?

Having said that, I think that this product has a need, and it might get approved. But if it gets approved, then I think its label needs to identify some of the concerns that we see. The mortality imbalance is not attributable, and yet it seems. So I think the label could provide some information about the mortality imbalance there.

I think the risk of acquired resistance appears to be real, and I think the label should identify the fact that organisms may have increased MIC and could become resistant on therapy so that the providers know about this.

I think that an educational strategy beyond the label might be in order. A lot of providers just read a study, and they don't read a label, and they might not read the study on CREDIBLE; they might read the cUTI study. So I think that we
would ask the sponsor perhaps to specifically provide that information.

I think that the label might identify a concern for the lactose non-fermenters or at least acinetobacter because everybody should be aware that that's where our concern seems to be. And argued away or not, there's a concern; although, as Dr. Paterson has said, that might be the organism for which the need is absolutely greatest.

Then, as I said, I think that we should repeat a study that either confirms the mortality signal or refutes the mortality signal, and then we're not guessing, we're not doubting, and we're not comparing to studies that are historical or observational, and that can answer the question.

Having said that, we do need to try to make sure that the prescribing physicians, if they get access to this drug, understand the potential limitations of our knowledge and potential risks they might give to their patient when using it off label.

DR. BADEN: While the study you propose is
ongoing, which may take several years, if this were
to be approved, this will then be used. And your
concern about the mortality imbalance in CREDIBLE,
you don't find credible enough.

DR. GREEN: I don't think it's definitive
enough. Actually, what I should say to you,
Dr. Baden, is you're asking me to cast my vote for
question 2 in advance of the vote. And so --

DR. BADEN: No, I am not. I would never do
that.

(Laughter.)

DR. GREEN: -- I'm not supposed to reveal
my answer to question 2 while we're having this
discussion.

DR. BADEN: Right. I am probing your
thinking because I value the thinking of all in
this room.

DR. GREEN: Let me just say that I assure
you I will answer your question, eventually.

DR. BADEN: Dr. Gripshover?

DR. GRIPSHOVER: I think that, obviously,
the mortality is disconcerting, this difference. I
do think it's reassuring that it doesn't appear to be that it's a toxicity of the drug, and also, the APEKS makes it look like it's at least it's not a lung effect, either.

But I am concerned that there could be an efficacy problem, especially in multi-drug-resistant organisms, because that's what's different about this particular study. They've been selected already to be carbapenem resistant to get into the study, and we know, at baseline, those are organisms that already have a higher MIC.

Maybe when you add the drug pressure, that makes them more prone to get resistance faster. They also use 80 percent monotherapy. I don't know if dual therapy might have made a difference, too, in terms of thinking of future studies and how to use it. But I think that would be interesting to think, if that would have better outcomes. So those are my thoughts.

DR. BADEN: Thank you.

Dr. Weina, did you have a follow-on to Dr. Green's?
DR. WEINA: Actually, I did, and it was triggered by a comment that Michael made. And that was being very specific in the label that it said X, Y, and Z.

When is the last time you actually read a label completely for a new drug?

DR. BADEN: Before I give a talk.

(Laughter.)

DR. WEINA: But very few of us actually do that.

DR. BADEN: We'll do that, but there has to be extenuating reasons.

DR. WEINA: Yes, I know. I'm not going to try and get you in trouble with your lawyers. But the point I was trying to make is that when you're talking about recommendations for labeling, I mean, few of us completely read the labels unless it's in a black box that says, "You better pay attention to this or else you're going to get your butt sued."

So I just wanted to make that point because there are a lot of recommendations that we make sometimes about the labels, but they get buried in
there, and nobody ever reads it. It's kind of like
the fine print that you read before you accept
anything on your laptop or anything like that. So
I just wanted to make that clear.

DR. BADEN: Thank you. Dr. Clark?

DR. CLARK: Yes. I do worry about the
design of CREDIBLE and the heterogeneous
population, and agree with comments earlier that
it's very difficult to sometimes even diagnose
infections in these patients versus colonization,
and certainly to evaluate attributable mortality.

The proposed indication, as stated I guess,
by the applicant, didn't include, or doesn't
include, acinetobacter, and I kind of agree with
what they've laid out here in terms of
restrictions. I don't have other comments beyond
that right now.

DR. BADEN: Thank you. Dr. Ofotokun?

DR. OFOTOKUN: The concern I have has been
expressed. The point I wanted to make, just to add
to what everybody has said, I'm concerned about the
mortality signal. I'm concerned about the
I also just wanted to highlight the fact that the CREDIBLE study that we're talking about is a randomized trial. At what time do you really -- I mean, there is this discussion whether this is due to chance or is there a true signal.

The question I wanted to ask the statistician, at what point, at what critical sample size, do you have that confidence that whatever you're saying is not due to chance in a randomized trial? So randomization was supposed to take care of this issue of balance between the two arms of the study.

DR. BADEN: We'll give Dr. May the first shot, Dr. Follmann?

DR. MAY: Thank you. I think I have two different ways of looking at it. For a benefit, I want to see a well-powered study, and then we have a standard of 1 in 20 of making a mistake on that one.

One of the other comments that I wanted to make was that, for safety, I don't care about
statistical significance. I might be concerned about safety regardless of whether it's statistically significant or not because we usually don't power a study for safety, and I would be concerned. Also, the p-values, the 0.11, I think actually the doubling of the effect, the doubling of the mortality rate, was very concerning to me regardless of statistical significance.

DR. BADEN: Dr. Follmann, did you also want to answer the query?

DR. FOLLMAN: I'd prefer to bob and weave, if I might. I think it's difficult in this particular instance because this was a descriptive trial. There was a DSMB monitoring it. They didn't see a reason to stop. It's very heterogeneous. It's just very difficult to interpret. So it's still puzzling to me about what's going on there, and I don't think it's definitive. So it's a tough one.

DR. BADEN: I want to go back to Dr. May. For safety, you don't care about the p-value.

DR. MAY: Can I revise that? If it were
statistically significant, I would be worried. So there are two components: is it of clinical importance and is it of statistical significance?

DR. BADEN: I know you care.

(Laughter.)

DR. BADEN: We'll use mortality and a p of 0.11, so that has been referred to. It's a p of 0.11. It's not statistically significant, yet it's mortality.

DR. FOLLmann: Yes.

DR. BADEN: And that, in part, is what is being proffered to us to weigh, and I am highly skeptical of the alter of 0.05, in my own view, because I don't think 0.04 and 0.06 are different, and with safety, it becomes very complicated how to assess.

So the 0.11, how do you weigh that as seen in this case?

DR. MAY: So if I'm consistent from what I said before, I'm not looking at the 0.11. I'm looking at the doubling of the risk of rate of mortality in this case. Sometimes we switch it
around. Right? We ask what effect size would you want to see to change practice, and say, okay, now, I'm going to prescribe this; I'm going to give this to everybody with this indication. What would be the clinically important difference in that direction?

So the counter question would be, what would hinder you from giving it if you see an effect that is of a certain size. A doubling in risk, from my perspective, is a strong one.

Does that answer your question?

DR. BADEN: It wasn't meant to have an easy answer, but the perspective is appreciated.

I think we have, then, Dr. Le? Oh, Dr. Follmann. Sorry.

DR. FOLLMANN: I'll just add there's more evidence than the p 0.11 and the doubling of mortality. Two important things, I think, are the APEKS-NP study, where we don't see the mortality signal; admittedly, it's in people with non-resistant pathogens. Then also the fact, as I mentioned earlier, we see this doubling both for
infections and both for non-infections, which I am puzzled about and makes me think it's more curious than a stronger signal.

So we look at more than just that one thing.

DR. BADEN: Sure. So I guess now I'll go to my turn with comments. I have a couple of comments on that; that the infection versus non-infections by an adjudication committee, how accurate is that adjudication? And this is a very complex arena, so I'm not as persuaded that I truly understand that adjudication that was done and done in an independent fashion.

I also, in looking at these data, think back to both the safety and the efficacy issue, and cefepime and its ceftaz story; and daptomycin and its pulmonary story; and Trovan and its liver story.

So I think, as Dr. Weina said, this is a Rorschach. We can see what we want in the data. I think that it's very hard to know, in my view, what truth is because there are examples, in the last
decade or two, where both safety and efficacy emerged in a way we didn't anticipate, and we're left with this obtuse finding in a very difficult-to-interpret study. I think it's hard to ignore, but it's hard to sort of bet the farm on it in terms of it being definitive because it's nuanced for all the reasons that have been discussed.

So I just raise that, both on the safety and efficacy side, the complexity, at least from my view, of interpreting the data.

I think we have Dr. Le. You have a comment?

DR. LE: Yes. I think it's very clear to me that additional studies are needed, a robust one, obviously, particularly looking into resistant development, whatever CLSI approves as the breakpoint at that time, from that angle, rather than 4 times increase in MIC.

I do agree with Peter in the sense of having labeling that includes maybe -- because we're talking about mortality here. Whether or not it's real or not, we see something here that we
have to be able to provide the information for; either it be a black box to say this is what we're seeing, there's an occurrence of mortality imbalance for pneumonia, BSI subgroups, encompassing mortality, and all-cause infection related; potentially arising from HABP/VABP and acinetobacter. That means further investigation.

DR. BADEN: Thank you.

Dr. Moore, did you have another comment?

DR. MOORE: Well, just a quick question. I assume we're not going around the table to discuss question 1; we're just weighing in.

DR. BADEN: Correct. I didn't want to go around the table.

DR. MOORE: That's cool.

DR. BADEN: I wanted to sort of develop the themes --

DR. MOORE: That's fine.

DR. BADEN: -- and make sure that we add things that haven't been discussed already.

DR. MOORE: That's fine. So I didn't want to jump in if it wasn't my turn.
I think that the difficulty is we're being asked to discuss a product regarding a trial about which we don't have all the information. The trial hasn't been vetted by the FDA, so we're trying to infer something about a drug where we don't have all the information.

DR. BADEN: You're talking about the APEKS, because we have the information on CREDIBLE.

DR. MOORE: Yes, that's right. I'm talking about the APEKS, because that's really the issue, is the mortality associated with APEKS comes out of the blue. If we're talking about the drug for a complicated UTI, I think, sure, no problem, but the mortality with the APEKS trial really gives everybody pause.

DR. MAY: The CREDIBLE.

DR. MOORE: I'm sorry, CREDIBLE. Sorry, the CREDIBLE study. Thank you. I have been paying attention --

(Laughter.)

DR. MOORE: -- despite all evidence to the contrary.
So I concur with Dr. Paterson's observation about the relatively low mortality in the BAT arm in the clinical trials. That's very puzzling and has not been my understanding of the review of the literature on acinetobacter. I can't quite explain that, and perhaps maybe it's because of the low numbers of enrolled patients, and maybe the mortality will pick up later -- were to pick up later if more people had been included.

The low mortality in the BAT arm notwithstanding, I would like to make a comment that I think they're going to have to parse out the data on blood transfusions. I really think that's, honestly, the biggest concern regarding the mortality in the CREDIBLE trial.

I mean, obviously the drug is brought into the bacteria through siderophores. The fact that you can't analyze MIC data on the organism unless you use iron-depleted media really says a lot. If you're giving blood transfusions to patients in a hospital, there's a lot of free iron. There's a significant amount of free iron you're giving with
those patients.

I really think that may be the ticket. Now, maybe I'm sure there are other things as well, but that's something that's going to have to be looked at very closely when the data are submitted for the APEKS to the FDA.

DR. BADEN: Thank you. Dr. Siberry?

DR. SIBERRY: Just to highlight, my concern is not about safety, but rather potential reduced efficacy in these serious infections, so that if we end up recommending that it be approved for use in complicated UTIs, I think, it's extremely important to have a caution about a potential increased mortality for use of this drug for treatment of other serious infections other than UTIs.

Then we've sort of talked around it, but I think the FDA and others should fully evaluate the APEKS results before deciding what additional trials should be done, because I think we should maximize our understanding of the available data before designing the next potential trial to be more definitive about our concern.
DR. BADEN: Thank you. Dr. May?

DR. MAY: Initially, I had thought just like Dr. Follmann, that we have in front of us the cUTI approval. But then the sponsors have done a beautiful job in describing how the drug would work on all three different ways and in three different mechanisms, and I did not see any arguments why that should be different for the different indications.

So I am more concerned with the CREDIBLE study just because there is no other way that the mechanism could work just for cUTI, but not for the others and be of concern.

The other thing that I want to say is, amplifying on something that was said before, when we have positive results, we tend to believe them, whether we understand the mechanism or not, because that's what we want to see and want to believe. Then if we have negative results and don't have a good argument for it, then we say it's by chance. So that's an easy way out, so to speak, for people.

Then the other component, I have seen often
in clinical trials that the background failure rate is lower than what you anticipated. So then it's truly -- and I agree with Dr. Follmann completely that the priority is to look at the trial. And it was randomized, and if it was randomized well, then that's really the comparison rather than to other historical cohorts.

DR. BADEN: Any other comments in this discussion from the committee? Dr. Gripshover?

DR. GRIPSHOVER: Just one more thing that we might want to look at, if we can learn what the mechanism of the increase in MIC is. I know you said you don't know now, but that might be helpful if they can figure it out.

DR. BADEN: So if I may summarize what I think I heard in the discussion around CREDIBLE, is there is a mixed sentiment about are the results credible or incredible. And the committee members can't ignore the mortality, but the data are uneven, and reasons why it may not make sense.

The issue of, if this were to be approved, in the label reflecting the uncertainty raised by
CREDIBLE, as well as the need for further information from data which are emerging, and I'll call APEKS-NP as emerging data, and that will emerge sooner, that could then be incorporated to either increase or decrease the concern from CREDIBLE when fully vetted; and then future studies to better define this, based upon the state of the art, when the data available will be available.

There were many issues around the MIC, around iron overload, and around serious infection that make this complicated to use outside of the areas carefully studied. Then the question, which we also cannot answer, is how to view this in light of infection with organisms with no known treatment, and whether or not this has a potential role in that setting, where there's no known treatment for a pathogen, and what might be helpful to the community but would obviously need the caveats that CREDIBLE raised.

I think that captures the overarching sentiment with lots of other discussion that had been aired.
Anything that committee members would like to add to that CREDIBLE synthesis?

(No response.)

DR. BADEN: If not, then we can move to the actual vote. Before I move to the vote, anything else from the agency about the CREDIBLE discussion that you'd like us to touch on?

DR. NAMBIAR: Nothing for now; thank you.

DR. BADEN: Okay.

So we will now proceed with question 2. We'll 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 have entered your vote. Please press the button firmly that corresponds to your vote.

If you are unsure of your vote or you 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.
into the record. Next, we will go around the room, and each individual who voted will state their name and their vote into the record. You can also state the reason why you voted as you did if you want to. We'll continue in this same manner until we come around the room to the last voting member.

What I will do now is read the question, and then we'll see if there are any questions about the question before we answer the question.

Has the applicant provided substantial evidence of the efficacy and sufficient evidence of the safety of cefiderocol for the treatment of complicated urinary tract infections, cUTI, including pyelonephritis, in patients with limited or no alternative treatment options? If yes, please provide any recommendations concerning labeling. If no, what additional studies/analyses are needed?

Any questions about the question?

(No response.)

DR. BADEN: I think it's straightforward.

If no discussion on the question, we'll now begin
the voting process.

(Voting.)

DR. BADEN: Excellent. Even Dr. Smith has already voted.

DR. HOTAKI: For the record, the vote is 14 yes, 2 no, zero abstentions.

DR. BADEN: So now, we will start with Dr. Moore. What was your vote and any comments, part A and B.

DR. MOORE: I voted yes, and I have no additional comments, other than perhaps the sponsor could provide a phonetic spelling --

(Laughter.)

DR. MOORE: -- or phonetic pronunciation of the drug, which I've heard pronounced six different ways today.

(Laughter.)

DR. BADEN: Dr. May?

DR. MAY: I voted no because of the concerning mortality differences in the CREDIBLE study, and because of it, I don't think that a single study is sufficient in this case.
So the other question was, I think, what else is needed. I think, in this case, it should be two studies at least, where the second one maybe would be designed as a non-inferiority on the survival rate.

DR. DELEO: I voted yes, and the reason I voted yes is based in part on the proposed indication, which we definitely need new therapeutics. And the cUTI data, to me, were compelling. I mean, I have no issue there. And getting to part A, I think the recommendations that you suggested, that would be along the lines of what I would suggest as well.

DR. BADEN: Thank you. Dr. Lyons?

DR. LYONS: I voted yes, and I just wanted to say I wanted to agree with all the points that have been brought up, up to this point, but also that, for the specific indication that's addressed and the question for the complicated urinary tract infections, yes, I do believe the sponsor has satisfied requirements for that indication. But for other, more serious infections, pneumonias, and
other more complicated infections not involving urinary tract infections, there needs to be more studies.

I think we need to -- again, agreeing with everybody's point that has been brought up to this point, reviewing all the data, including from the APEKS study that's coming in, and then figuring out where we need to go with a more robust design study, a randomized, double-blind, controlled study, potentially being done here in the United States, as well as other locations, given the logistical limitations, of course, to answer the questions that have been brought up and the points that have been brought up during this discussion so far. Thank you.

DR. BADEN: Thank you. And please state your name and how you voted before you give your comments. Ms. Thomas?

MS. THOMAS: Jill Thomas, patient representative. I voted yes for the use of complicated urinary tract infections, however, I think there should be more data for other uses.
DR. BADEN: Dr. Walker?

DR. WALKER: Hi. Roblena Walker. I voted yes. And just to be honest, I was a little torn here. I've been quiet most of the day; well, all day, huh? I've just been listening. But I thought about my 90-year-old grandmother, who suffered from a urinary tract infection when she was, like, 88. So then I listened to the public comments when the physicians came and stood before us and told us about some of the patients that could have benefitted from this.

All things considered, I do agree with what has been expressed here, and I think that there is an opportunity to take what has been discussed and develop it into another study, as Dr. Lyons has said, to look at other areas such as pneumonia and such. But other than that, those are my thoughts.

DR. BADEN: Thank you. Dr. Le?

DR. LE: Jennifer Le. I voted yes. The only thing I wanted to comment on was related to the safety profile. The sample size in these trials were small, so to truly ascertain, the
safety profile needs to be further looked at.

So I recommend continuing to assess this, particularly as they relate to liver function, hematologic test, seizures, and cardiac arrhythmias. And particularly for liver function, we saw a healthy woman who died without any prior medical history, who subsequently developed that insufficiency.

DR. BADEN: Thank you. Dr. Follmann?

DR. FOLLMANN: I'm Dean Follmann. I voted yes. I thought the evidence was pretty strong for cUTI in the cUTI study, and also the cUTI subgroup in the CREDIBLE study was consistent with what we saw in that study.

I also felt the potential mortality signal we saw in CREDIBLE didn't really apply in my mind to the cUTI question, so I didn't worry so much about interpreting it. It would have been different if we were to deciding on HABP/VABP and BSI.

DR. CLARK: Nina Clark. I voted yes. I thought the cUTI study was well designed, and I did
not think those data should be negated by the CREDIBLE study, given its design and given the unmet need for treating these infections. I was also reassured by the APEKS data.

I agree with others about getting more data on other serious infections and that the labeling should be consistent with the cUTI study population. I also thought that liver function monitoring should be recommended.

DR. GRIPSHOVER: Hi. I'm Barb Gripshover. I voted yes, as I thought the cUTI showed actually comparable clinical response and superior microbiological response when compared to imipenem for complicated UTIs.

As Dr. Follmann said, the mortality difference seen in the CREDIBLE-CR study was not seen in the small UTI portion of that study population. But as we mentioned in the discussion, if it's approved for UTI as a drug, it will be used for desperate clinical infections outside of the urinary tract as well, so I think the label should include a warning of the increased mortality in its
use for monotherapy for HCAP/VAP in bloodstream
infections due to highly resistant non-fermenters
in the CREDIBLE study.

DR. BADEN: Thank you.

Dr. Baden. I voted yes. I think the data from the cUTI study were straightforward and demonstrated meaningful activity. I think there needs to be caution about the superiority claim, the nature of the outcome of clinical versus microbiologic. There's nuance there. It's meaningful. It was measured.

On the other hand, the clinical meaning is more nuanced, and I think the mortality concern is less clear but much more meaningful and how to balance those observations. But I think establishing non-inferiority, the cUTI study did that.

I think the issue of how to position this in relation to the unmet need, meaning not for every susceptible E. coli UTI; and is this positioned in a way where it is for -- and I know it's not through the LPAD pathway, but the concept
of organisms that are difficult to treat so that its targeting not just cUTI, but it is in the context of where it's difficult to treat pathogens.

Then obviously, the mortality issue needs to be clearly visible, although the uncertainties around it noted as previously discussed.

Dr. Weina?

DR. WEINA: Peter Weina. I voted no. I know we need new drugs. I know we are losing the battle to the bugs that are a lot smarter than any of us are, but we don't have to necessarily feed the monster.

I know we've grown to be accepting of small sample sizes for trials, too, but what we really have here is a single study driven by the definition of eradication that has colored our view of the data. We keep talking about superiority based on the criteria of the composite data, but when you actually look at the clinical data, it's really just non-inferiority, which is how the study was designed, even though we keep talking about superiority.
Therefore, the evidence, not necessarily substantial evidence, but there is evidence of some efficacy. So to answer the question very specifically, is there substantial evidence, I really had to say no there.

We also need to acknowledge, as it's been said before, and I just want to really put an exclamation point on that, the public hearing portion of the meeting vividly demonstrated that this drug, when the door is cracked open for approval for any kind of indication, is going to be quickly and widely used off-label.

We can't ignore the mortality difference that we saw because we haven't explained it. So just to ignore it when we have a single cUTI study, basing the approval on, I think is potentially reckless. Thank you.

DR. GREEN: Michael Green. I voted yes. Having said that, the approval for one indication does carry with it the likelihood for off-label use for cefiderocol, or however you pronounce this drug. While I'm confident that there is no excess
mortality signal for the treatment of complicated
UTI, I cannot make that conclusion for the
treatment of other sites, and syndromes, and
perhaps acinetobacter, in general, that may be
undertaken if the drug is approved.

The sponsor's review of the individual
fatalities from the patients in the CREDIBLE study
with elevated MICs was somewhat reassuring, though
it did not fully eliminate all of my concerns.

The balance between the need for additional
new and novel antibiotics for the treatment of
multi-drug-resistant, gram-negative bacteria and
the concern of, as of yet, unexplained potential
mortality signal outside of the urinary tract is
exceptionally challenging. The need for these
drugs is present today, and, clearly, some patients
will benefit as soon as the drug is available
commercially.

Having said this, I again refer my
recommendations for the label, and perhaps
including a black-box warning relating to mortality
until this issue is resolved, and follow-up studies
described in my response given earlier to
question 1 for the agency to review. Thank you.

DR. BADEN: Thank you. And before
Dr. Ofotokun, Dr. Smith, do you have your comments?

DR. SMITH: Yes. I voted yes. The data
from the cUTI was compelling and is consistent with
how it's excreted within the urine, and probably
explains a lot of the efficacy.

I do think -- I agree with the last
speaker -- that we should consider some sort of
circle that underlines warning, whether that's a
black-box or however that is done; that its use in
systemic infection, we don't have enough data, and
it looks like we have a very strong mortality
signal to not have that indication or that use. I
don't know exactly how that goes, but I think they
should consider that.

DR. BADEN: Thank you. Dr. Ofotokun?

DR. OFOTOKUN: Igho Ofotokun. I voted yes
for the same reasons that have been expressed by
others. I was persuaded by the data from the cUTI
study. The one thing I just wanted to reiterate is
that the data suggests that it's at least as good
as a standard of care, and I think it will be one
of the things that could be available in the
armamentarium as an alternative for people who need
it, for complicated urinary tract infection.

I also agree that there should be
additional studies to look at both the mortality
signal that was seen in the CREDIBLE study, as well
as the resistant data that was also seen in that
study, and that there should be a clear warning
that this indication is really for complicated UTI,
and not the other severe or serious infection that
was treated in the CREDIBLE study.

DR. BADEN: Dr. Siberry?

DR. SIBERRY: George Siberry. I voted yes.

With many of the reasons already said, I thought
the study did a good job demonstrating safety for
complicated UTIs and good clinical outcome.
However, the nature of UTIs, the fact that you're
less likely to have pathogens like acinetobacter as
the causative agent, and the concentration of this
drug in the urinary tract make that recommendation
limited to complicated UTIs.

So I think it's extremely important to have a warning about potential higher mortality with other types of infections.

I'd add that the complicated UTI studies showed that infusion over 1 hour was effective, so consideration should be given to 1- or 3-hour infusions for treating complicated UTIs. It may make it easier on nursing. I also would recommend that we consider a postmarketing requirement for getting PK and short-term safety data in pregnant women, and for accelerating the pediatric timeline, which really is going to take way too long to make this drug available for kids. Thank you.

DR. BADEN: Thank you.

So we have 14 voted yes, 2 voted no. The comments were largely concordant among all 16 panel members. This is potentially useful when no other options are available for resistant organisms in a cUTI, and that the label needs to strongly note the uncertainty associated with the CREDIBLE data.

The panel members who voted no wanted
additional studies before being comfortable that the efficacy outweighed the potential toxicity. The other 14 panel members want those data, but feel comfortable that it could be obtained after approval. But we all want data to better guide our understanding of the efficacy and the risk, particularly with the mortality signal. The future studies will need to depend on what the APEKS and other emerging data show, but I think there are clear directions as to what needs to be done.

Any other comments from the panel?

(No response.)

DR. BADEN: If not, then any comments from the agency?

DR. FARLEY: Sure. On behalf of the agency, we want to thank the committee for your valuable insight and recommendations today. These were particularly challenging data, and we appreciate both your thoroughness and thoughtfulness. We also thank the open public hearing speakers for their input. We thank the sponsor for their work preparing for this meeting.
and their responsiveness to us as we work together to prepare for this meeting.

The agency has not yet made a decision on the overall application, nor the various review issues that we have identified and highlighted for you today. Your input will be very carefully considered as we take that decision.

We wish everyone safe travel. We hope that the weather does not impact your travel today, and we're looking forward to seeing all of you again in 2020, where I'm sure that we'll have some similarly challenging issues for you to discuss. Thanks very much.

Adjournment

DR. BADEN: Thank you, and the meeting is now adjourned.

(Whereupon, at 4:02 p.m., the meeting was adjourned.)