FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEETING

(AMDAC)

Monday, September 9, 2024

9:00 a.m. to 4:08 p.m.

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

LaToya Bonner, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

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Division of Infectious Diseases

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Biostatistician

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Skaggs School of Pharmacy and Pharmaceutical

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Louis Stokes Cleveland Department of

Veterans Affairs (VA) Medical Center

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Case Western Reserve University

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Sociologist, UNC Chapel Hill Injury Prevention Research Center

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Roger Lewis, MD, PhD

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Arjun Srinivasan, MD

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(9:00 a.m.)

Call to Order

Introduction of Committee

DR. BADEN: It is now 9:00. Good morning, and welcome. I would first like to remind everyone to please mute your line when you're not speaking, and also a reminder to everyone to please silence your cell phones, smartphones, any other devices, like some of us still have pagers, if you have not already done so. For media and press, the FDA press contact is Chanapa Tantibanchachai. Her email is currently displayed.

My name is Dr. Lindsey Baden, and I will be chairing this meeting. I will now call the September 9, 2024 Antimicrobial Drug Advisory Committee meeting to order. We'll start by going around the table and introduce ourselves by stating our names and affiliations. We'll start with the FDA to my left and go around the table.

Dr. Farley?

DR. FARLEY: Good morning. John Farley,

Director of the Office of Infectious Diseases, CDER, FDA.

DR. KIM: Good morning. Peter Kim, Director, Division of Anti-Infectives in the Office of Infectious Diseases, CDER, FDA.

DR. GOPINATH: Good morning. Dr. Ramya Gopinath, Associate Director for Therapeutic Review, Division of Anti-Infectives, CDER, FDA.

DR. KOPACK: Good morning. Angela Kopack. I'm the clinical reviewer from the Division of Anti-Infectives, CDER, FDA.

DR. LI: Good morning. I'm Xianbin Li, a statistical reviewer from Office of Biostatistics, IV.

DR. SHEIKH: Good morning. Jalal Sheikh, clinical microbiology reviewer of this NDA in the Division of Anti-Infectives, Office of Infectious Diseases, CDER, FDA.

DR. ABODAKPI: Good morning. My name is Henrietta Abodakpi, and I am the primary clinical pharmacology reviewer for this application with the Division of Infectious Disease Pharmacology within

the Office of Clinical Pharmacology, CDER, FDA.

DR. JONIAK-GRANT: Good morning. I'm Elizabeth Joniak-Grant. I'm here today as the patient representative, and I'm also a sociologist at the UNC Chapel Hill Injury Prevention Research Center.

DR. GREEN: Good morning. My name is Michael Green. I'm a pediatric infectious disease specialist at the University of Pittsburgh School of Medicine and UPMC Children's Hospital, Pittsburgh. I have an interest in antimicrobial stewardship, infection prevention, and infections in children who've undergone transplant.

LCDR BONNER: Good morning. LaToya Bonner, DFO for this meeting, DACCM, CDER, FDA.

DR. BADEN: I'm Dr. Lindsey Baden. I'm an infectious disease specialist at Brigham and Women's Hospital, Dana Farber Cancer Institute in Boston, Massachusetts, and a Professor of Medicine at Harvard Medical School.

DR. HUNSBERGER: Sally Hunsberger. I'm a biostatistician, Deputy Director of Office of

Biostatistics at NIAID.

DR. PEREZ: I am Federico Perez, infectious diseases specialist at the Louis Stokes Cleveland VA Medical Center in Cleveland, Ohio.

DR. WALKER: Good morning. Dr. Roblena Walker, microbiologist for EMAGAHA, Inc. in Atlanta, Georgia, serving as the consumer representative.

DR. PATEL: Good morning. My name is Nimish Patel. I'm faculty and a clinical pharmacist at the Skaggs School of Pharmacy and Pharmaceutical Sciences at the University of California, San Diego.

DR. SRINIVASAN: Good morning. Arjun Srinivasan. I'm an infectious disease specialist by training. I'm the Deputy Director for Program Improvement at the Division of Healthcare Quality Promotion, United States Centers for Disease Control and Prevention.

DR. GRIPSHOVER: Good morning. I'm Barbara Gripshover. I'm an adult infectious disease specialist at University Hospitals Cleveland

Medical Center and a Professor of Medicine at Case Western Reserve University.

DR. LEWIS: Good morning. I'm Roger Lewis. I'm a Professor of Emergency Medicine at the David Geffen School of Medicine at UCLA and the senior medical scientist at Berry Consultants.

DR. CHANDRA: Good morning. I'm Richa Chandra. I am heading clinical development for global health at Novartis, and I'm representing industry on this committee.

DR. BADEN: Thank you.

For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly held. One goal is that this 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 for a productive, engaging 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 many 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 topics during breaks or lunch. Thank you.

Commander Bonner?

Conflict of Interest Statement

LCDR BONNER: Thank you.

LaToya Bonner, DFO. Good morning.

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, FACA, of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or

regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 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 their 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 discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interests of their own as well as those imputed to them, including those of their spouses and minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimonies; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves the discussion of new drug application 213972, for oral sulopenem etzadroxil/probenecid tablets consisting of 500 milligrams of sulopenem etzadroxil and 500 milligrams of probenecid, submitted by Iterum Therapeutics US Ltd, for the proposed indication of treatment of uncomplicated urinary tract infections caused by designated susceptible bacteria in adult women 18 years of age and older. This is a particular matters meeting from which specific

matters related to Iterum Therapeutics US Ltd new drug application 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. Richa Chandra is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Chandra's role at this meeting is to represent industry in general and not any particular company. Dr. Chandra is employed by Novartis Pharmaceuticals.

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. I will turn the floor back over to our chair.

Dr. Baden?

DR. BADEN: Thank you.

We will now proceed with the FDA introductory remarks from Dr. Peter Kim.

Dr. Peter Kim, the floor is yours.

FDA Opening Remarks - Peter Kim

DR. KIM: Good morning. My name is Peter Kim, and I am the Director of the Division of Anti-Infectives in the Office of Infectious Diseases, Office of New Drugs, CDER, FDA. I would like to welcome the advisory committee members, the applicant, Iterum Therapeutics, and the general

public attending both in person and online to today's meeting to discuss the new drug application for sulopenem etzadroxil/probenecid.

The purpose of today's meeting is to discuss, one, the overall benefits and risks of sulopenem etzadroxil/probenecid, also referred to as oral sulopenem, for the treatment of uncomplicated UTI caused by designated susceptible microorganisms in adult women 18 years of age and older; and two, considering the totality of the evidence in this application, we are interested in a discussion of considerations that would be important to convey to medical providers to ensure appropriate use of oral sulopenem.

Approximately 50 to 60 percent of adult women will have at least one uncomplicated UTI during their lifetime and 10 to 12 percent of adult women have at least one uUTI per year, with 20 to 30 percent of those being recurrent. For regulatory purposes, uUTIs occur in women with normal genital urinary anatomy and are characterized by dysuria, urinary frequency,

urgency, and suprapubic pain. In clinical practice, uUTIs are often diagnosed based on symptoms and a dipstick urinalysis positive for leukocyte esterase or nitrite.

Therapy for uUTI is often empiric, as baseline or post-baseline urine cultures are not typically recommended for the first incidence of uUTI. *E. coli* are the most common cause of uUTI, accounting for 75 to 95 percent of infections. Currently recommended treatment options follow.

First-line treatment options for uUTI include oral nitrofurantoin; trimethoprim sulfamethoxazole; fosfomycin; and pivmecillinam. Fluoroquinolones, including ciprofloxacin, are no longer considered first-line treatment for uUTI due to adverse reactions such as tendinopathies, QT prolongation, central nervous system effects, and peripheral neuropathy, as well as increasing rates of fluoroquinolone resistance. Other than pivmecillinam, beta-lactam agents, including amoxicillin/clavulanate, are considered alternative treatment options for uUTI, as in general,

beta-lactams are less effective and have more potential adverse reactions than other first-line antibacterial drugs.

While there are multiple FDA-approved oral antibacterial drugs for the treatment of uUTI, treatment options can be limited by adverse reactions and increasing antimicrobial resistance to first-line antibacterial drugs, including through the production of extended spectrum beta-lactamases. Carbapenem drugs are the mainstay of treatment for infections caused by ESBL producing pathogens, but all approved members of this class require intravenous administration and are generally reserved for treatment of culture-proven infections.

While an oral penem could potentially address an unmet need for treatment of uUTI caused by resistant bacteria, its use in an ambulatory setting, where treatment is most commonly empiric raises concern for inappropriate use, which may contribute to AMR.

Active-controlled trials designed for

findings of superiority or noninferiority are potential options to evaluate antibacterial drugs for the treatment of uUTI. For a noninferiority trial, it is important that the analysis population, whether it be the microbiologic intent to treat or the microbiologic modified intent-to-treat population, includes only patients in whom the baseline bacterial pathogen is fully susceptible to the active-controlled drug on in vitro susceptibility testing.

The applicant performed NI hypothesis testing in some populations that included patients with isolates that were not susceptible to the comparator. FDA finds this testing uninterpretable for regulatory purposes. Additionally, a treatment-delay, placebo-controlled trial design is acceptable in uUTI trials and allows for a finding of superiority of the study drug versus placebo.

FDA recommends that the primary efficacy endpoint for uUTI trials be based on overall response; that is a composite outcome of clinical and microbiologic responses. Microbiologic

outcomes are an important component of the composite endpoint. In an analysis of complicated urinary tract infection trials, discordant clinical and microbiologic outcomes at the test-of-cure visit were associated with late clinical failure, and this risk increased with time.

We note that the term "asymptomatic bacteriuria" is typically used to indicate the presence of bacteria in a urine sample collected in an individual without any symptoms of a UTI. This term may not be applicable to a patient who, following the diagnosis and treatment of UTI, has symptom resolution but whose treatment failed to eradicate the causative pathogen. We refer to this as microbiologic persistence. Therefore, FDA considers patients in uncomplicated and complicated UTI trials with post-treatment microbiologic persistence as microbiologic failures.

I will now provide a high-level summary of the efficacy findings from the applicant's uUTI development program. In phase 3 uUTI Trial 301, efficacy was established in the

ciprofloxacin-resistant population; however, efficacy was not established in the ciprofloxacin-susceptible population. In phase 3 uUTI Trial 310, efficacy was established in the amoxicillin/clavulanate-susceptible population. Of note, there were inconclusive results in the amoxicillin/clavulanate-resistant population due to small sample size.

In addition to the two uUTI trials, the applicant also conducted phase 3 trials in complicated UTI and complicated intra-abdominal infections. In complicated UTI Trial 302, IV to oral sulopenem did not demonstrate noninferiority versus the comparator IV to oral regimen in overall, that is clinical plus microbiologic response, using a 10 percent NI margin.

The differences were driven by microbiologic failure. In the complicated intra-abdominal infections, Trial 303, IV to oral sulopenem did not demonstrate noninferiority versus the comparator IV to oral regimen in clinical response, using a 10 percent NI margin.

Regarding the safety of oral sulopenem, the NDA contains an adequate safety database. Diarrhea was the most common adverse event in the phase 3 uUTI safety population but was generally mild and generally did not lead to treatment discontinuations. Mild ALT elevations were observed in a small proportion of sulopenem-treated patients. The identified safety risks could be mitigated through labeling.

Now, for some considerations, the two phase three uUTI trials studied oral sulopenem for the treatment of uUTI in an ambulatory setting and were not designed to evaluate the efficacy of oral sulopenem for the treatment of uUTI caused by resistant bacterial isolates or for the treatment of uUTI in patients who failed first-line treatment.

Of note, if approved, sulopenem etzadroxil/probenecid would be the first oral penem antibacterial drug marketed in the United States, and inappropriate use may contribute to antimicrobial resistance or increased

cross-resistance to other penem drugs.

Because IV sulopenem followed by oral sulopenem was found to be inferior to the active comparator regimen for complicated UTI in Trial 302, there is concern that if approved, oral sulopenem may be used off label in the treatment of complicated UTI or other infections as stepdown treatment. However, there are no data on the effectiveness of oral sulopenem as stepdown therapy following IV treatment of complicated UTI with another antibacterial drug.

While antimicrobial stewardship and consideration by guidelines committees may help to determine appropriate positioning of oral sulopenem, if approved, in the hierarchy of uUTI treatment options, a discussion of approaches to inform prescribers of relevant data submitted in this NDA to ensure the most appropriate use of oral sulopenem is warranted.

These are my references. Thank you for your attention, and we look forward to a robust discussion today.

DR. BADEN: Thank you, Dr. Kim.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with the applicant, such as consulting fees, travel expenses, honoraria, and interest in the applicant, including equity interests and those based upon the outcome of this 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 the issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with the presentations from Iterum Therapeutics.

Dr. Dunne, I think you will manage the discussion from the applicant. Thank you.

DR. DUNNE: Thank you, Dr. Baden.

Applicant Presentation - Michael Dunne

DR. DUNNE: Good morning, members of the advisory committee and FDA review team. Thank you for the opportunity to present our data supporting the efficacy and safety of oral sulopenem for the treatment of uncomplicated urinary tract infections. I'm Mike Dunne. I'm serving as consultant for Iterum Therapeutics this morning. I was formerly their chief scientific officer.

Here's the agenda for our presentation this morning. Following my brief introduction, Dr. Marjorie Golden will describe the significant unmet need for new therapies that can effectively treat uncomplicated urinary tract infections in this era of widely disseminated antibiotic-resistant pathogens. Next, I'll return to present the microbiology, pharmacology, and

clinical efficacy results; then Dr. Steven Aronin will present the safety data. Finally, I'll return to summarize the benefit-risk assessment for the use of sulopenem in this indication.

Few new antibiotics have been developed for uncomplicated UTI over the last three decades, and there have been rising rates of resistance to all of the commonly prescribed oral antibiotics. Pivmecillinam was originally approved in Europe in 1977 and was recently approved in the U.S. by FDA, but experience in the U.S. is lacking.

Uncomplicated urinary tract infection is one of the most common outpatient infections. Shown here are the total number of prescriptions per year in adult women for uncomplicated UTI in the U.S., generated from various claims databases, totaling about 40 million prescriptions a year. Nitrofurantoin, an antibiotic introduced in the 1950s, is most commonly prescribed.

DR. BADEN: Dr. Dunne?

DR. DUNNE: Yes, sir?

DR. BADEN: Can you speak up a little bit?

Some are not able to hear you clearly.

DR. DUNNE: Oh, is that right? Okay.

DR. BADEN: Thank you.

DR. DUNNE: Is that better? I'll get closer. Thanks for that. Let's start again.

Nitrofurantoin, an antibiotic introduced in the 1950s, is most commonly prescribed. Beta-lactams taken together are given about 38 percent of the time, quinolones 18 percent, and trimethoprim sulfate in 14 percent of cases. As you'll see shortly, substantial resistance now impacts all of these classes of antibiotics.

The structure of sulopenem is in the first box. As you can see, there is a sulfate in the core ring structure, and that makes it a thiopenem. This is the intravenous form of sulopenem. Sulopenem etzadroxil is a prodrug of sulopenem, and this is what is found in the oral formulation, which also contains probenecid, an orally available organic anion transport inhibitor that delays the excretion of sulopenem through the kidneys.

Oral sulopenem is formulated as a bilayer

tablet composed of sulopenem etzadroxil and probenecid. Relative to dosing each component separately, the construction of this bilayer tablet improves the absorption of sulopenem from the GI tract, as well as maximizes the impact of the effect of probenecid on prolonging the residence time of sulopenem in the serum, and consequently the exposure of sulopenem in the urine.

Like all beta-lactams, sulopenem has a high affinity for penicillin binding proteins, which in turn interrupts cell wall synthesis and provides broad activity against Enterobacterales, including the most common organisms found in the urinary tract, specifically *E. coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis*, which together are responsible for over 95 percent of all uncomplicated urinary tract infections. Our phase 3 program was designed in collaboration with the FDA and includes more than 5,900 patients. All four studies received special protocol agreements.

Today, we'll focus primarily on results from Studies 301 and 310 in women with uncomplicated

urinary tract infections. Study 302 evaluated IV sulopenem followed by oral sulopenem in patients with complicated urinary tract infections, and we'll review the outcomes of this study a little later in the presentation. We won't be covering results from Study 303 and complicated intra-abdominal infections today.

Sulopenem will address an unmet medical need for a reliable, effective treatment of uncomplicated urinary tract infections. Existing antibiotics do not provide confidence in coverage in treatment of uncomplicated UTI because resistance rates are now approaching and may exceed 20 percent for standard of care options, which challenges the use of empiric therapy for this infection.

Consistent results from Study 301 and 310 demonstrate benefit of treatment with sulopenem, and sulopenem was found to be safe and well tolerated in our clinical trials. Based on these results, the proposed indication is for sulopenem combined with probenecid for the treatment of

uncomplicated urinary tract infections caused by designated susceptible microorganisms in women over the age of 18.

Before I conclude my introductory remarks, I'd like to take a moment to highlight some important topics covering today's discussion. Our primary focus today is to present data from Studies 301 and 310, which together demonstrate that sulopenem is a safe and effective treatment option for patients with uncomplicated UTIs. We will also review the data from the 302 study in complicated urinary tract infection, as there are some interesting findings from that study.

There are two specific topics that the committee has been asked to consider. Is the overall benefit-risk assessment favorable for the use of sulopenem etzadroxil for this indication, and considering the totality of evidence of this application, what are the considerations that would be important to convey to medical providers to ensure appropriate use of sulopenem etzadroxil or probenecid? This second topic is more focused on

antibiotic stewardship, and then directly on ensuring that sulopenem is prescribed for the intended target patient population. Our presentation today is designed to enable a robust discussion of both of these topics.

With that introduction, I'll now turn over to Dr. Golden, who can provide us with a perspective on the challenges associated with the treatment of urinary tract infections today.

Applicant Presentation - Marjorie Golden

DR. GOLDEN: Thank you, and good morning. I am a paid consultant for Iterum. My name is Dr. Marjorie Golden. I'm an Associate Professor of Medicine and the Site Chief of Infectious Diseases at the St. Raphael Campus of Yale New Haven Hospital. I have a large outpatient clinical practice where I treat many women with recurrent uncomplicated urinary tract infections. We have seen increasing rates of infection with resistant pathogens, which is associated with prolonged duration of symptoms and often requires use of intravenous antibiotics. I'm pleased to be here

today to discuss the unmet medical need for safe, effective therapies for the treatment of uncomplicated urinary tract infections caused by antibiotic-resistant pathogens.

Urinary tract infections are the most common outpatient infections in women. In the United States, uncomplicated urinary tract infections account for approximately 40 million prescriptions per year, and it's estimated that 60 percent of women will have a urinary tract infection during their lifetime. The most common pathogens responsible for these infections include *E. coli, Klebsiella pneumoniae, and Proteus mirabilis*.

Recurrence rates for women with uncomplicated urinary tract infections approach 40 percent. Furthermore, among women who have already had more than one uncomplicated urinary tract infection, up to 50 percent can suffer multiple recurrences. Let's look at the most recent IDSA guidelines for the treatment of uncomplicated UTIs.

Historically, fofomycin and pivmecillinam have not generally been recommended for the

treatment of uncomplicated UTIs due to lower efficacy and lack of approval. Susceptibility testing for fosfomycin is not routinely performed in clinical laboratories. As mentioned, pivmecillinam was just recently approved by the FDA. Experience in the U.S. is lacking. Of all outpatient uncomplicated UTIs in the United States, 99 percent are treated with nitrofurantoin, trimethoprim sulfamethoxazole, quinolones, or beta-lactams. Each of these commonly prescribed antibiotics has its own risk-benefit profile.

Patients coming into my office with a UTI often have significant discomfort that affects their quality of life. Pain, need for frequent urination, and incontinence have major impacts on quality of life, and studies have documented increased rates of depression in women with recurrent UTIs.

In order to provide them with immediate symptomatic relief, the current standard of care is empiric antibiotic treatment with a short course of antibiotics. Following treatment, many patients

will achieve a full clinical cure with resolution of symptoms. Some patients, however, fail to respond clinically. In this case, I would obtain a clean-catch urine specimen to be sent for culture and susceptibility; then depending on severity of symptoms, may wait 2 days to use the results to guide subsequent antibiotic selection. Typically, a second short-course antibiotic will resolve their symptoms and result in clinical cure.

The choice of empiric antibiotics for patients with uncomplicated UTI is often challenging for practicing clinicians and is based on IDSA guidelines, as well as a thoughtful assessment of the patient's overall state, underlying medical conditions, and history of resistant pathogens. Let's look at a challenging yet relatively common scenario from my practice.

This patient is a 74-year-old woman with diabetes, interstitial lung disease, and Parkinson's disease, who presented with symptoms and urinalysis consistent with an uncomplicated UTI. She had a known sulfa allergy and history of

intolerable diarrhea with prior courses of fosfomycin. I generally prefer to avoid nitrofurantoin in elderly patients and those with interstitial lung disease, leaving me with no viable empiric oral option for what would turn out to be an uncomplicated UTI due to an ESBL producing strain of *E coli*.

This table summarizes the complexity of treating patients empirically in this representative clinical scenario. As you can see, we are faced with the problem of increasing resistance to current standard of care antibiotics. As a consequence, empiric treatment carries a risk of failure if the patient has an infection with an organism resistant to the prescribed antibiotic.

Presented here are data from an electronic records database that were collected and reviewed by Iterum and Becton Dickinson to evaluate prescriptions given to adult patients with a UTI in an outpatient setting. As shown in the first column, between 16 and 28 percent of patients received an antibiotic for which they had a

non-susceptible pathogen. Among these patients, approximately 36 percent had a clinical failure and required a second prescription. This failure rate is twice as high compared with patients who were treated with an antibiotic for which they had a susceptible pathogen at baseline.

IDSA's treatment guidelines recommend avoiding trimethoprim sulfamethoxazole if resistance prevalence is known to exceed 20 percent. These data show that we are already above this 20 percent threshold for trimethoprim sulfa, beta-lactams, and quinolones; therefore, from a guideline perspective, empiric use of these agents is not really a viable option for healthcare providers anymore.

To add to the complexity, we are also seeing a rapid increase in the rate of co-resistance to multiple agents. In this study of 588 *E. coli* isolates with confirmed resistance to levofloxacin, we see that 46 percent were resistant to both levofloxacin and a beta-lactam and 56 percent were resistant to both levofloxacin and trimethoprim

sulfamethoxazole.

We see a similar trend in isolates that are resistant to trimethoprim sulfamethoxazole. As you see, over 3 percent of the patients with uncomplicated UTIs in Iterum's program had an infecting organism that was non-susceptible to beta-lactams, fluoroquinolones, trimethoprim sulfa, and nitrofurantoin. These data highlight the reality that we are faced with. Antibiotic resistance to multiple agents is increasing, and we are losing the ability to treat our patients with uncomplicated UTIs with the antibiotics that we currently have in our arsenal.

One final point I'd like to discuss before concluding is management of asymptomatic bacteriuria. Based on current IDSA guidelines, screening or treatment for asymptomatic bacteriuria should only occur if a patient is pregnant or undergoing an endourologic procedure. The references shown here support the IDSA guidelines and include cases where treatment of asymptomatic bacteriuria is associated with subsequent

C. difficile colitis, as well as infection due to antibiotic-resistant bacteria.

I strongly endorse not ordering cultures on asymptomatic patients outside these two situations and often counsel both patients and referring providers not to obtain urine cultures in patients without symptoms of a urinary tract infection. I also strongly discourage these so-called proof-of-cure cultures.

In conclusion, millions of women suffer from uncomplicated urinary tract infections caused by antibiotic-resistant pathogens each year, and that number is increasing. The standard of care antibiotics that we once viewed as viable treatment options have become increasingly less effective, resulting in delay of clinical cure, need for multiple antibiotic courses, and risk of more serious adverse outcomes. As resistance to standard of care antibiotics increases, women with uncomplicated urinary tract infections need new safe and effective treatment options.

Thank you. I turn the presentation back to

Dr. Dunne.

Applicant Presentation - Michael Dunne

DR. DUNNE: Thank you, Dr. Golden.

So I'll now review the microbiology and pharmacology of sulopenem. Sulopenem has a broad spectrum activity against the most common organisms found in uncomplicated urinary tract infections. Presented here are surveillance data collected by IHMA between 2016 and 2017 and by the JMI Labs in 2019 from hospitalizations with either intra-abdominal or urinary tract infections.

As you can see, the MIC90 is quite low and has not changed over the 8 years surveillance has been performed against. Against *E. coli*, the MIC90 is 0.03 micrograms per mL. Across all organisms tested, the MIC90 is less than or equal to 0.25 micrograms per mL. It's worth pointing out that 90 percent of uncomplicated UTIs are caused by either *E. coli* or *Klebsiella pneumoniae*.

The activity of sulopenem is consistent with that of other available penems. Potency of sulopenem against *E. coli* and *Klebsiella* were

similar compared with meropenem and ertapenem. Against *Proteus mirabilis*, the MIC90 for sulopenem was similar to that of meropenem but less potent than ertapenem.

Sulopenem is rapidly distributed to most tissues to an extent similar to other beta-lactams. Plasma protein binding is very low, about 11 percent. Metabolism is predominantly driven by hydrolysis of the beta-lactam ring. Urinary excretion is the predominant route of elimination. The half-life of sulopenem is about an hour, typical of most beta-lactams.

Food was found to increase the bioavailability of the bilayer tablet from 40 to 60 percent. Probenecid was shown to increase exposure of sulopenem by around 50 percent. Sulopenem does not inhibit or induce P450 enzymes but is an avid substrate of the organic anion transporter number 3, though not of other transporters. Sulopenem etzadroxil is rapidly converted to sulopenem and is not measurable in plasma.

As with other beta-lactams, data from murine

thigh experiments show that the time above MIC is correlated with efficacy. This correlation is based on plasma exposures in a tissue-based infection. Presented here are mean sulopenem concentrations in the urine over time after oral dosing from phase 3 studies conducted in patients with urinary tract infections. The dotted line represents the sulopenem MIC90 for uropathogens associated with an uncomplicated UTI, and even at 10 hours, the levels of sulopenem in the urine are about 500 times that of the MIC90.

Finally, in vitro studies support a low likelihood of clinically relevant drug-drug interactions. There was no drug-drug interaction between itraconazole and oral sulopenem in a clinical study in healthy volunteers. As with all carbapenems, there was a significant effect on valproic acid observed with IV sulopenem and with sulopenem etzadroxil alone. This interaction decreases valproic acid levels and presumably increases the valproic acid metabolites. Literature suggests that the increase in the

valproic acid metabolites may increase the likelihood of liver toxicity.

In contrast, there was a minimal effect on valproic acid after multiple doses of oral sulopenem given as the bilayer tablet, which of course includes probenecid. Valproic acid plasma concentrations remain at levels greater than 90 percent relative to baseline when dosed with oral sulopenem, an unexpected finding that may be due to the probenecid.

Next, we'll focus on the efficacy results from the pivotal studies beginning with Study 301. Study 301 was a phase 3, randomized, multicenter, double-blind, active-controlled study in women with uncomplicated urinary tract infections. The study was conducted under special protocol agreement and designed in collaboration with the FDA. 1,671 women aged 18 years or older were randomized in a 1 to 1 fashion to receive either oral sulopenem twice daily for 5 days or oral ciprofloxacin twice daily for 3 days, with matching placebos for each regimen.

Urinalysis and urine cultures were done at baseline, day 3, day 5, day 12, which was the test-of-cure visit, and at the end of study on day 28. The primary endpoint was the proportion of patients with an overall response of success at day 12, which is a composite of both clinical success and microbiologic eradication. Thus, patients needed to have symptom resolution and a urine culture with less than 10 to the 3rd colony forming units per mL with no rescue antibacterial therapy.

Symptom resolution was based on typical UTI symptomatology, and microbiologic eradication was based on susceptibility testing, multilocus sequence typing, and resistance gene profiling. In this study, microbiologic eradication was confirmed with extensive in vitro testing beyond what is normally performed in a clinical setting. Outcome data will be presented with and without the benefit of these in vitro testing methodologies. We'd be happy to explain why we confirm the presence of the baseline pathogen at the test-of-cure visit with

these other methodologies if the committee is interested during the Q&A session.

Key secondary endpoints included an assessment of overall response at the end of treatment and end of study, as well as assessments of clinical success and microbiologic eradication. Primary analysis included two independent analysis populations, each with its own alpha assigned, a superiority test of oral sulopenem versus ciprofloxacin in the micro-MITTR population -- those are patients with organisms resistant to ciprofloxacin -- and a test for noninferiority of oral sulopenem versus ciprofloxacin in the micro-MITTS population; those are patients with a cipro-susceptible organism. These are the two populations specifically recognized for the effective outcome for regulatory purposes.

In order to assess the impact of the initial treatment decision, however, a hierarchical testing procedure was applied such that if the prespecified success criteria was met in either of these two

populations, a second step analysis for noninferiority was to be analyzed in the broader micro MITT population. The sequence of testing for the primary endpoint is not typical. At the time, the FDA was most interested in response in the susceptible and resistant population separately, so these analyses were prioritized.

However, in order not to lose the opportunity to understand the impact of treatment on the broader population, more typical of what would be observed in the clinical setting before organism identification and susceptibility testing results are available, this hierarchical testing procedure was prespecified, as noted.

Of the patients enrolled in Study 301, approximately two-thirds of the study population was in the micro-MITT population being they had greater than 10 to the 5th CFUs per mL of the baseline pathogen. Eighteen percent of the patients had an organism resistant to ciprofloxacin, so in accordance with the hierarchical testing method, first I will focus on

this micro-MITTR population.

In this population, patient baseline demographics were similar between the groups and were reflective of patients presenting with uncomplicated urinary tract infections, in general. Mean age was about 55, the majority of patients were white, approximately 40 percent were Hispanic or Latinx. More than half of the patients were enrolled in the United States. The median BMI was approximately 27 and patients had a mean creatinine clearance of approximately 69 milliliters per minute.

Presented here are the primary endpoint results of overall success at day 12 in the micro-MITTR population. Point estimates to the right of zero favor oral sulopenem. Sulopenem achieved statistical superiority to ciprofloxacin. 62.6 percent of patients receiving sulopenem compared with 36 percent of ciprofloxacin-treated patients achieved an overall response of success. Treatment difference was 26.6 percent. The 95 percent confidence interval on the difference in

outcomes did not include zero and the p-value was less than 0.001.

Also shown here is the FDA analysis of this endpoint. The FDA analysis differs from Iterum's assessment in two ways. First, you can see that the total number of subjects is different. After careful monitoring and quality assurance audits, Iterum could not validate the quality of the data from one particular site, so that data is excluded from the sponsor's endpoint assessment, but it is included in the FDA analysis. The FDA analysis also uses only genus and species of the baseline pathogen relative to the organism identified at the test of cure. As you can see, conclusions are the same with either approach.

Superiority of oral sulopenem was compared to ciprofloxacin and was achieved at the end of treatment on day 5, as well as at the end of study on day 28, both key secondary endpoints. A consistently better overall response for oral sulopenem-treated patients relative to cipro-treated patients was observed across the

target uropathogens, including *E. coli, Klebsiella pneumoniae, and Proteus mirabilis*.

Superiority was also observed in patients with pathogens non-susceptible to multiple classes of antibiotics. The top row of this figure represents the primary endpoint results in the micro-MITTR population. All of these patients of course had quinolone non-susceptible pathogens at baseline. The subsequent rows represent patients with pathogens non-susceptible to a quinolone, as well as to other classes of antibiotics.

The treatment differences were similar even for patients with highly drug-resistant organisms. Note that almost 5 percent of randomized patients in Study 301 with a positive urine culture at baseline had pathogens non-susceptible to all of the commonly used classes of oral antibiotics for treatment of UTI. As Dr. Golden discussed previously, multidrug resistance in the community is becoming an increasing problem for the treatment of uncomplicated UTIs and underscores the need for new treatment options.

Based on superiority being established in the non-susceptible population, the analysis of results was triggered in the micro-MITT population, which combines patients with both ciprofloxacin-susceptible as well as ciprofloxacin non-susceptible pathogens. Presented here is the overall response at day 12. 65.6 percent of oral sulopenem-treated patients compared to 67.9 percent of ciprofloxacin-treated patients achieved overall success.

The lower limit of the 95 percent confidence interval on the difference in treatment outcome was greater than the prespecified margin of minus 10 percent, demonstrating the noninferiority of oral sulopenem to ciprofloxacin in the broader population of patients with a positive urine culture at baseline regardless of susceptibility to cipro.

These outcomes are most relevant to the practicing clinician who must choose a treatment option before culture results become available. This also helps put into context the outcomes in

the culture-driven subpopulations. Looking further into the components of overall response, there were similar rates of clinical and microbiologic success seen in both arms. A consistent effect is seen across the components of the primary outcome measure.

Finally, I would like to turn to the results from the micro-MITTS population. In this population, oral sulopenem did not achieve the prespecified noninferiority margin for overall response compared with ciprofloxacin in patients with a baseline pathogen susceptible to ciprofloxacin. Overall success was seen in 67 percent of patients receiving oral sulopenem compared with 79 percent of patients receiving ciprofloxacin, and the lower limit of the confidence interval, the difference in outcomes was less than minus 10 percent.

The reasons for the difference in outcomes are provided here. The difference in response was driven by a higher rate of asymptomatic bacteriuria in patients treated with sulopenem. Thirteen

percent of patients treated with sulopenem compared to 4 percent on ciprofloxacin achieved symptom resolution but with a urine culture with greater than or equal to 10 to the 3rd colony forming units per mL of the baseline uropathogen. This was an unexpected outcome. Note that the clinical failure-only rates were similar.

If the patients with asymptomatic bacteria at day 12 were on a path to clinical failure, we would expect to see a lower clinical response rate at the day 28 visit; in fact, however, the clinical response at day 28 is consistent with what was seen at day 5 and day 12. This observation triggered a further analysis of asymptomatic bacteriuria and whether it predicts subsequent clinical failure.

This analysis showed that the presence of asymptomatic bacteriuria does not disproportionately affect the subsequent clinical failure rate relative to patients who had not been cured and does not predict clinical relapse. I'll walk you through the data here. 335 patients had a clinical success at day 5, the end of treatment

visit, but 31 of those had a clinical failure at day 12 one week later. Only 12 patients had asymptomatic bacteria at day 5, and one of those had a clinical failure at day 12. So having asymptomatic bacteria at day 5 did not predict clinical failure one week later at day 12.

Similarly, 339 patients had a clinical success at the day 12 test-of-cure visit. Of those, 20 patients had clinical failures at day 28, 16 days later. Seventy-four patients had asymptomatic bacteriuria at day 12, and of those, eight had clinical failures at day 28, resulting in the rate of clinical failure, which was similar to that of patients who had previously achieved both clinical and microbiologic success. So in this study, the presence of asymptomatic bacteriuria does not predict a subsequent clinical failure.

Turning now to the results from our second trial 310. Study 310 was a phase 3, randomized, multicenter, double-blind, active-controlled study in women with uncomplicated urinary tract infections. 2,222 women aged 18 years or older were

randomized in a 1 to 1 fashion to receive either sulopenem twice daily for 5 days with a high dose of amoxicillin/clavulanate also twice daily for 5 days with matching placebos for each regimen.

Urinalysis and urine cultures were done at baseline, day 5, day 12, which was the test-of-cure visit, and at the end of study on day 28. The primary endpoint was the proportion of patients with an overall response of success at day 12. This is consistent with the endpoint definition in our prior study.

In this study, we focused on the microbiologic response specifically on the genus and species of the identified pathogen at baseline and the test-of-cure visit. Key secondary endpoints included an assessment of overall response at the end of treatment and end of study, as well as assessments of clinical success and microbiologic eradication.

In this study, again, there was a hierarchical testing method prespecified for the primary endpoint, though the first step evaluated

noninferiority of oral sulopenem relative to amoxicillin/clavulanate in the micro-MITT population. If noninferiority was declared in the second [sic - first] step, we would test for noninferiority in the micro-MITTS population and note that this population was emphasized by the FDA. We would also test for superiority in the subpopulation of patients with organisms resistant to amoxicillin/clavulanate.

Presented here is the study disposition. Approximately half the study population was in the micro-MITT population, so had greater than 10 to the 5th CFU per mL of an Enterobacterales. Unexpectedly, only 3 percent of the patients had an organism resistant to amoxicillin/clavulanate. Based on the hierarchical testing procedure, first I'll focus on the results in the micro-MITT population.

In this population, baseline demographics were similar between the groups and were reflective of patients presenting with uncomplicated urinary tract infections in general. Mean age was about

50 years. The majority of patients were white and approximately 63 percent were Hispanic or Latinx. Median BMI was approximately 28 and patients had a median creatinine clearance of approximately 83 milliliters per minute.

Sulopenem demonstrated noninferiority in the micro-MITT population. Clinical success rates were very similar but microbiologic success per the protocol definition was higher for patients treated with sulopenem. The reasons for failure at the test-of-cure visit are provided here. Clinical failure rates were similar, but there was a higher rate of microbiologic failure, the majority of which was asymptomatic for patients treated with amoxicillin/clavulanate.

For Study 310, we prespecified an analysis to prospectively evaluate whether the presence of asymptomatic bacteria predicts for subsequent clinical relapse. It's the same analysis I shared previously when we were doing the results from Study 301. Consistent with Study 301, we confirmed that asymptomatic bacteriuria at day 5 and at

day 12 did not predict for clinical failure at day 12 or day 28, respectively. This reaffirms that asymptomatic bacteriuria is not a surrogate marker for subsequent clinical failure for patients who receive oral sulopenem for treatment of uncomplicated urinary tract infections.

As you recall in Study 301, sulopenem was not noninferior to ciprofloxacin in the cipro-susceptible population. Here, you can see the results of the comparison of sulo with amoxicillin/clavulanate in this same ciprofloxacin-susceptible population, where outcomes are similar for both treatment regimens, though there is now more asymptomatic bacteriuria in the amoxicillin/clavulanate regimen.

With noninferiority demonstrated in the micro-MITT population, we next assessed the benefits of sulopenem in the micro-MITTS population. In this analysis, sulopenem was superior to amoxicillin/clavulanate, as the lower limit of the confidence interval did not include zero. Clinical success rates were very similar;

that is, in the micro-MITT population, microbiologic success was more often achieved for patients treated with sulopenem. The reasons for failure are outlined again here. Asymptomatic bacteriuria was more often seen in patients treated with amoxicillin/clavulanate.

We again observed the benefit of sulopenem in each study timepoint when compared to patients receiving amoxicillin/clavulanate. As you can see, at the end of treatment on day 5 and at the final visit on day 28, sulopenem was not inferior to amoxicillin/clavulanate. Sulopenem also demonstrated consistent effects for the most common baseline pathogens, including *E. coli* and *Klebsiella pneumoniae*, and *P. mirabilis*.

Next, we assessed the population of patients with organisms resistant to amoxicillin. Due to the small sample size in the micro-MITTR population and the imbalance in randomization to the treatment groups, there was insufficient power to draw any conclusions about a treatment effect. Presented here are the results of the primary efficacy

endpoint of overall response at the day 12 visit, including clinical and microbiologic success. 52.4 percent of the patients in the sulopenem group compared to 68 percent of patients in the amoxicillin/clavulanate group achieved an overall response of success.

In summary, data from two randomized, active-controlled studies demonstrate that oral sulopenem is an effective antibiotic treatment option for women with uncomplicated urinary tract infections. In the micro-MITT population, sulopenem was not inferior to ciprofloxacin and amoxicillin/clavulanate when assessing overall response at the test-of-cure visit. In Study 301, among patients with uropathogens resistant to ciprofloxacin, sulopenem demonstrated a superior overall response rate. In Study 310, due to a limited sample size, conclusions could not be drawn in this subset of patients.

Finally, when looking at patients with susceptible infections, oral sulopenem did not achieve noninferiority compared to ciprofloxacin.

This was primarily driven by a lower portion of patients with asymptomatic bacteriuria in the ciprofloxacin group. In Study 310, among patients with susceptible infections, susceptible organisms, sulopenem demonstrated superiority compared to amoxicillin/clavulanate.

Furthermore, when looking at the rate of clinical success across the two studies in various analysis populations, we see a consistent response for sulopenem relative to the comparator, which supports the use of sulopenem as a treatment option for women with uncomplicated urinary tract infections.

Although Iterum has not submitted an application for treatment of complicated urinary tract infection, we thought it would be helpful to review the data from this trial. Study 302 was designed according to FDA guidance and is similar to other complicated UTI studies that have been performed recently. Notably, the primary endpoint in the study is the same as the two uncomplicated UTI studies, allowing a further explanation of the

components of the overall response in a different patient population.

Study 302 was a phase 3, randomized, multicenter, double-blind, double-dummy study in patients with complicated urinary tract infections. The study was conducted under a special protocol agreement and aligned with existing FDA guidance. 1,395 patients aged 18 years and older were randomized in a 1 to 1 fashion to receive either IV sulopenem for 5 days, followed by oral sulopenem twice a day for 5 days, or IV ertapenem for 5 days followed by either ciprofloxacin or amoxicillin/clavulanate twice a day for 5 days based on the susceptibility of their baseline pathogen.

Urinalysis and urine cultures were done at baseline, day 5, and end of treatment on day 10, day 21, and at the end of study on day 28. The objective of the trial was to establish noninferiority of the overall response in patients treated with sulopenem to that of patients treated with ertapenem.

In Study 302, sulopenem did not meet the prespecified primary endpoint. 67.8 percent of patients treated with sulopenem compared with 73.9 percent of those treated with ertapenem achieved an overall response of success at day 21. The treatment difference was minus 6.1 percent and the lower bound of the 95 percent confidence interval was less than minus 10 percent, demonstrating that sulopenem was not noninferior to ertapenem for the treatment of complicated UTIs.

As in the uncomplicated UTI study, let's look to the reasons for non-response in this study to better understand this overall outcome. Similar to the micro-MITTS population of Study 301, the primary reason for non-response was a greater rate of asymptomatic bacteriuria in patients treated with sulopenem, which occurred in 21 percent of sulopenem-treated patients compared to 13 percent of ertapenem-treated patients. Even though the sulopenem-treated patients had a higher rate of asymptomatic bacteriuria, clinical response was similar at both the end of treatment day 10, as

well as the late follow-up visit at day 28.

In contrast to the uncomplicated UTI study in which patients received only sulopenem or ciprofloxacin, patients here received at least 5 days of an IV penem before starting their oral stepdown therapy to either sulopenem on one arm or ciprofloxacin for patients with a cipro-susceptible organism at baseline or amoxicillin/clavulanate for the other patients; so the assessment of outcome needs to be addressed by each of the IV oral regimens separately as provided in the following slide.

Here's the overall response and rate of asymptomatic bacteriuria in sulopenem- and ertapenem-treated patients. This is the primary endpoint that you saw in the previous slide. Here is the breakdown of the outcome by the specific IV oral regimen that patients received. Patients treated with a beta-lactam, whether IV sulopenem or IV sulopenem to oral sulopenem, or IV ertapenem or IV ertapenem followed by amoxicillin/clavulanate, all had a similar rate of asymptomatic bacteriuria

post-treatment.

The overall success rates on each regimen are similar, but these asymptomatic bacteriuria rates after treatment with a beta-lactam are all higher than the asymptomatic bacteriuria rate observed when ciprofloxacin is the stepdown option, and these outcomes mirror exactly what was seen in the uncomplicated UTI studies. The higher asymptomatic bacteriuria rates are not a sulopenem specific issue but rather associated with any beta-lactam, in this case sulopenem, ertapenem, amoxicillin/clavulanate.

There are some other findings of interest in this trial relative to the value proposition of a stepdown from IV to oral therapy for cUTI and the design of future trials to address that unmet medical need. For those analyses, we'll focus mostly on the comparisons among the beta-lactams.

This is a busy slide, so if there are questions about this, I'm happy to answer during the Q&A because there's a lot going on here. There are 444 patients assigned to sulopenem and a

similar number to ertapenem. Of those, 54 remained on IV sulopenem and 141 remained on ertapenem. The outcome rates were similar. Note that 87 more patients on IV ertapenem could not step down to an oral regimen relative to those randomized to IV sulopenem.

In the second line, you can see that patients who stepped down from IV to oral sulopenem had a similar success rate to those who remained on IV ertapenem, but why is there a difference in the number of patients who could step down to oral therapy? The protocol had three requirements for stepdown after 5 days of IV treatment. First, patients needed to be able to tolerate oral medication; second, there must be improvement of the signs and symptoms of the infection by day 5; and third, the baseline pathogen must be susceptible to the drugs included in the oral stepdown regimen.

We're not showing it on this slide, but the distribution of residual symptoms were the same for patients on either regimen at day 5 if the last

criteria was not met for more patients randomized to ertapenem. 106 of the 141 patients who remained on ertapenem did so because their baseline pathogen was resistant to both ciprofloxacin and amoxicillin/clavulanate. There were no patients who could not step down to oral sulopenem due to resistance of the baseline pathogen.

This observation represents the value proposition for oral sulopenem in this indication. As these are all post hoc analyses where the primary endpoint was not met, these data do not provide evidence to justify a recommendation for oral sulopenem for stepdown from an IV in the treatment of cUTI, but it is clear from the data that there's a potential need for an oral agent in this setting.

There are already eight IV antibiotics approved to treat cUTI, so there really doesn't seem to be a need for another IV agent. How we could generate data that specifically supports sulopenem as an oral stepdown option would be a good topic for a future discussion. That's not the

claim that we're talking about now, but we do understand that there's something going on there that might require some further study.

In both complicated [sic - uncomplicated] UTI studies, we examine the rate of resistance selection after treatment. First, I will review Study 301. This graph shows cultures isolated from patients treated with sulopenem broken down by their sulopenem MIC both at screening and at test of cure. These isolates are not just limited to qualifying baseline pathogens but include rather any Enterobacterales at any concentration density isolated at the screening and the test-of-cure visit.

You can see that the distribution of organisms by MIC before and after treatment is very similar. In addition, the MIC50 and the MIC90 were also similar pre- and post- treatment. Also, sulopenem treatment did not select for resistant organisms in this study. There was only one patient who had a post-baseline isolate where MIC was 4-fold higher than the MIC of the baseline

isolate. We looked for those because that could be a sign that there's an issue there, but we only saw one patient in that study.

These are the ciprofloxacin-treated patients. This is the micro-MITTS population, and these are patients who were chosen specifically because they did not have a resistant pathogen at baseline initially, but here resistant isolates emerge as little as 2 weeks after treatment, with over 40 percent of the 84 pathogens identified now resistant to ciprofloxacin.

The results for sulopenem-treated patients in Study 310 are presented here. Again, the MIC50 and MIC90 were similar pre- and post-treatment. Oral sulopenem did not select for sulopenem-resistant organisms in this study. Among patients with a susceptible isolate at baseline treated with amoxicillin/clavulanate; however, non-susceptible isolates were seen in 12 percent of patients after treatment.

Now, I'd like to ask Dr. Aronin to walk us through the safety data.

Applicant Presentation - Steven Aronin

DR. ARONIN: Good morning. Thank you, Dr. Dunne.

I'm Steve Aronin, Senior Vice President and the Head of Clinical Development at Iterum Therapeutics. I'm also a practicing infectious disease physician, and I've been treating patients with UTIs for the past 30 years. Thank you for the opportunity to present our safety data demonstrating that oral sulopenem is safe and well tolerated relative to ciprofloxacin and amoxicillin/clavulanate.

2,970 patients have been treated with sulopenem across the entire phase 3 program. This includes 1,940 patients with uncomplicated urinary tract infections that were treated with oral sulopenem in Study 301 and Study 310. Overall, the safety profile for oral sulopenem was consistent across phase 3 studies, and no new safety signals have been identified beyond those already known for beta-lactams.

Today, I will focus on the combined results

from Studies 301 and 310, as these studies were designed to demonstrate the safety of oral sulopenem for our proposed indication. In the phase 3 uncomplicated UTI integrated analysis set, oral sulopenem has a similar safety profile as the comparators. Treatment-emergent adverse events were more common among oral sulopenem-treated patients than comparator-treated patients. As you will see, this is largely driven by higher rates of diarrhea and loose stool in patients on oral sulopenem.

The premature discontinuation rates due to treatment-emergent adverse events are comparable in the two groups. There was one death, a patient who received oral sulopenem for uncomplicated UTI with poorly differentiated adenocarcinoma of the lung that occurred more than 5 months after study completion and was not considered related to study drug. The incidence of nausea, headache, and vomiting were comparable in the two groups.

Diarrhea and loose stool were reported more frequently by patients in the sulopenem arm.

Events of diarrhea were mostly mild, self-limited, and generally did not lead to treatment discontinuation. The mean time to resolution of diarrhea was 3.9 days in the oral sulopenem group compared to 2.8 days in the comparator group. Notably, no *Clostridioides difficile* infections were observed in patients treated with sulopenem. Few patients treated with oral sulopenem discontinued treatment due to a treatment-related adverse event. Discontinuations due to treatment-related diarrhea were balanced in both arms. Discontinuations due to other adverse events were also balanced in both treatment arms.

Now, looking at laboratory parameters, few patients developed clinically significant ALT or AST elevations during the uUTI studies, which was consistent with the outcomes in the overall phase 3 safety population. Presented here are the rate of ALT and AST elevations in patients with normal parameters at baseline. During the studies, 2 patients receiving oral sulopenem developed ALT values of greater than 3 times to 5 times the upper

limit of normal and one patient developed ALT values of greater than 5 times to 10 times the upper limit of normal. For AST during the studies, one patient receiving oral sulopenem developed values of greater than 3 times to 5 times the upper limit of normal and 2 patients developed AST values of greater than 5 times to 10 times the upper limit of normal.

Importantly, in both 301 and Study 310, there were no patients in either treatment arm with elevations of ALT or AST greater than 10 times the upper limit of normal and no patients fulfilled the criteria for Hy's law. One patient in Study 302 in patients with complicated UTI did meet the criteria for Hy's law. This patient on intravenous sulopenem was a 75-year-old man with a complicated urinary tract infection without pyelonephritis. He received 5 days of IV sulopenem followed by 2 days of oral sulopenem.

Notably, the patient was on several concomitant medications, including the exclusionary medication valproic acid at a dose of

300 milligrams twice a day. The laboratory parameters show that this patient had normal liver function values at baseline, elevated values at day 5 after receiving IV sulopenem at the same time as valproic acid, and the subsequent reduction in values by end of treatment at day 10, at which time he was off of therapy for 3 days, ultimately reducing to normal by test of cure at day 21.

The patient's valproic acid levels were reduced by day 5, as expected on IV sulopenem. As previously described by Dr. Dunne, this interaction decreases valproic acid levels and presumably increases the valproic acid metabolite. Literature suggests it is the increase in the valproic acid metabolite that may be responsible for liver toxicity, and in our patient, the increase in LFTs. As with other penems, our proposed label for oral sulopenem includes a warning about concomitant use of valproic acid.

In conclusion, oral sulopenem was found to be safe and well tolerated relative to ciprofloxacin and amoxicillin/clavulanate, and no

new safety signals have been identified beyond those already known for beta-lactams. The main adverse event occurring in more patients on oral sulopenem was diarrhea. These events were mostly mild, self-limited, and generally did not lead to discontinuation of treatment. No *C. diff* infections were observed in patients treated with sulopenem. Importantly, we did not observe a difference in the adverse event profile for elderly patients.

Thank you. I will now turn the presentation back to Dr. Dunne.

Applicant Presentation - Michael Dunne

DR. DUNNE: Thank you, Dr. Aronin.

I'll conclude with the discussion of the benefit-risk assessment of oral sulopenem for the treatment of uncomplicated urinary tract infections in women. Resistance to standard of care antibiotics is increasing at a rapid rate, limiting the options we have to safely and effectively treat patients with an uncomplicated UTI, as demonstrated by resistance rates observed in this study

conducted by Becton Dickinson over 2 million urine isolates collected between 2013 and 2018 and confirmed in the two studies presented here today.

Importantly, more than 3 percent of the randomized patients in Study 301 and 310 with a positive urine culture at baseline had pathogens resistant to all of the commonly used classes of oral antibiotics for treatment of uncomplicated UTI. These data suggest that we need new agents that can effectively treat patients who may have a non-susceptible pathogen at baseline, avoiding the consequence of a prolonged, untreated UTI.

Sulopenem meets this unmet medical need and provides an effective treatment option for patients with uncomplicated UTIs. Overall response rate was similar across treatment groups in the patient population that will be encountered by the treating physician and was noninferior to presently accepted standards of care for treatment of this infection. Mild self-limiting adverse events were seen more frequently in patients treated with sulopenem, but these did not lead to a higher rate of

discontinuation from treatment.

FDA has posed two topics for discussion to the advisory committee today. The first question relates to the overall benefit-risk in the use of sulopenem etzadroxil/probenecid for treatment of uncomplicated urinary tract infections. I think the data presented here today confirms that sulopenem is a safe and effective antibiotic option for this indication.

The second topic opens a broader discussion related to the stewardship and the appropriate use of sulopenem post-approval. Our presentation today has been focused on data that supports the intended claim which in turn drove the specific patient population, defined the null hypothesis, and was the subject of a special protocol agreement with the FDA. Having said that, we do appreciate that guidance to the prescriber at the time the choice of antibiotic is made could enable appropriate use of sulopenem.

Optimally, there would be a point-of-care diagnostic test to alert the prescribers to

patients who may have an organism resisting to existing therapies, but we do not have those tools available today. We really need them, but we don't have them. We were trying to think of something we could do to help the conversation we're going to have here today, so we looked at some demographic characteristics of the women with uncomplicated UTIs in our program in case there was a variable which could help prioritize patients that are most likely to benefit from sulopenem. This would have to be a variable available at the moment when the patient is in the office saying, "I have a UTI; what can you do for me?" It can't be fancy. It has to be something available at that time.

So we started by going back to the demographic characteristics of patients with quinolone susceptible and resistant isolates at baseline in Study 301. As you can see here, women with resistant isolates tended to be older. We then looked to see if this age-related association with resistant uropathogens was supported in the literature. In this paper published in 2016 from a

large data set of women with uncomplicated urinary tract infections, you can see that resistance rates for *E. coli*, *Klebsiella*, and *Proteus* all generally increase with age. I'll just let you look at that; there's a lot going on in this slide, so all of them.

We then looked at our own data, pooling Studies 301 and 310, and found a similar result. Women over the age of 65 were more likely to have a resistant pathogen for basically all the antibiotics that we looked at, but even more troubling is that resistance to multiple antibiotics -- that's seen in the lower row -- also correlated with increasing age.

With that, then we looked at treatment outcomes of patients over the age of 65 in the combined data set. As you can see, patients over the age of 65 treated with sulopenem had a higher success rate than those treated with comparators. The lower limit of the confidence interval on the difference and the outcomes did not include zero for overall success and clinical success.

Then we went back, and we looked at the breakdown of patients above and below the age of 65. You've seen the outcomes for patients over 65 in the previous slide, and here you can see that the lower limit of the difference in outcome for those under the age of 65 remains greater than minus 10; so there's a subpopulation that's coming out of the overall assessments, and perhaps we're seeing something a little bit more pronounced than in the overall population.

But for these observations to be useful for guiding empiric therapy, the findings would have to hold in the MITT population, as this is the population that had symptoms of a UTI and a consistent urinalysis, and before culture results are available, and as you can see, success rates for sulopenem-treated patients are higher and the confidence interval and the difference in outcome rates does not include zero. Similar benefits were seen in the mITT population. The findings in the MITTR population, they really help explain the improvement outcome rates in this over 65 patient

population overall, and again, they're consistent with the in vitro susceptibility findings that we saw in the populations that we studied.

Appropriate use is the hallmark of good antibiotic stewardship. Sulopenem has a spectrum of activity that addresses an important and critical unmet medical need. In two adequate and well-controlled trials, sulopenem has been shown to be both safe and effective. When integrated into care pathways for treatment of uncomplicated UTI, sulopenem could become an important treatment option.

But antibiotic use can put pressure on the colonizing flora and select for resistance over time. While it's encouraging that resistance selection was not identified in the sulopenem-treated patients in these two trials but was seen in the comparators, there will need to be ongoing evidence to ensure that it's used appropriately. The more we use it, the more likely you are to select resistant pathogens over time. That happens for every single antibiotic that

works.

Further discussion of the use of sulopenem in therapy for complicated urinary tract infections is warranted -- as the FDA is pointing out now, that is a bit of a concern -- but for sure, Iterum cannot recommend its use in that indication at this time with the data that we've provided. This just is not an option. We'd have to do something else. If there are any thoughts about what that could look like, what we could do to be helpful, we're happy to hear that from the panel.

There are a number of mitigation strategies which can be employed to guide appropriate use and you can see listed in this slide. Within the context of the claim being considered, there may be subpopulations of patients for whom initial therapy sulopenem is best supported, as we presented today, for women over the age of 65, for example. The database from these trials will of course be available for further research and to supplement data collected as real-world evidence to help focus on who might be the best patients to get sulopenem

for UTI up front before the cultures are available.

Based on these results, the proposed indication for oral sulopenem is for treatment of uncomplicated UTIs in women over the age of 18 caused by designated susceptible microorganisms. Thank you for your attention. We'd be happy to address any questions.

Clarifying Questions

DR. BADEN: Thank you, Dr. Dunne and team, for covering a broad array of data, and I'm sure the committee has many questions, so please be prepared, committee, for us to start the discussion.

We will now take clarifying questions for Iterum. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and end of your follow-up question with, "That

is all for my questions," so that we can move on to the next panel member.

Are there any clarifying questions? Please get LaToya's attention so you can get on the list of questions. Please remember, as I mentioned at the beginning of the meeting, for follow-on questions, please tilt your tent up so that we can have a thematic discussion but not to skip the line, and we will get through as many questions as we can. If we're not able to get through all questions by the 10:50 break, we will have the agency's presentation and clarifying questions, and we can come back to further discussion with the applicant after lunch, depending on the timing.

So we can start with the first question, and that is Dr. Joniak-Grant.

DR. JONIAK-GRANT: Thank you. Dr. Joniak-Grant. How was clinical response tracked at day 28, and was it the same across all days, like day 5, day 12?

DR. DUNNE: Yes. There was a patient symptom questionnaire that was filled out by the

patients, and that was the primary measure for clinical response over time. The investigators did their own clinical response assessment as well, but that PSAT, that questionnaire is what drove the clinical outcome response.

DR. JONIAK-GRANT: And what questions were on the questionnaire?

DR. DUNNE: Do we have that, Steve? We can get that for you after the break. It's very simple. It's a nice questionnaire. We can just pop it up, but it will take a little bit of time to pull that deck out of the data.

DR. JONIAK-GRANT: Thank you.

DR. BADEN: A follow-on question?

DR. GRIPSHOVER: Yes. I did notice in your briefing, that you also --

DR. BADEN: Speak into the microphone.

DR. GRIPSHOVER: Sorry. Barb Gripshover. I noticed in your briefing documents that investigators also had a clinical response --

DR. DUNNE: Yes.

DR. GRIPSHOVER: -- that was different than

the patient one, and I wondered how the investigator clinical response would be different than the patient.

DR. DUNNE: Yes. That happens all the time, really, I think. We have very specific questionnaires, questions of mild, moderate, and severe that the patients answer, and that's very, very detailed. And we pop that into the computer and it tells us they have this, that, and the response. The investigator is having more of a conversation with the patient, "Are you doing better, are you not doing better, how you feel?" So if the general impression is that they're getting better, that would be scored as such. The patient questionnaire has a lot more details on it, so they sometimes don't completely line up.

DR. GRIPSHOVER: Thank you.

DR. BADEN: Thank you.

Dr. Lewis?

DR. LEWIS: Thank you. Roger Lewis. I have two questions. The first probably should refer to the sponsor presentation, slide 35. This is

referring to the question of the alpha splitting design in 301. It also refers to page 67 of the 2023 CID publication, and if I can read one of the sentences from that publication.

It says, "Because these were separate objectives in mutually exclusive groups, alpha sharing to control the overall type 1 error rate was not required." So I'd like you to clarify the rationale for not sharing your alpha or splitting your alpha in these two separate paths to success in this trial design, and then I do have one follow-up question.

DR. DUNNE: That's a good question. I mean, we had our statisticians working on that rationale and discussed it with the division, so we thought it was probably justified, but I could go -- well, you need follow-up to that?

DR. LEWIS: I was simply going to offer that perhaps that rationale could be clarified in a follow-up according to the structure of the meeting.

DR. DUNNE: Okay. We can try to look into

that for you. You wanted to know what --

DR. LEWIS: To clarify the question, if you were doing separate hypothesis testing in two discordant populations, that's inferentially identical to doing two separate studies, and therefore each of those studies you could argue should get its own risk of a type 1 error result. But if you do that, then the result would be interpreted as one positive study and one negative study. So I'm trying to understand the specific rationale for that statement in your CID publication.

Another statistical point that you'll probably want to come back to is on your slide 49, if we may. So looking at the bottom table here, looking at the relationship of bacterial persistence at your primary endpoint day of day 21, instead of presenting a p-value, I'm wondering if in follow-up you could give the odds ratio for this association with its 95 percent confidence interval.

DR. DUNNE: Yes, we can try to do that.

DR. LEWIS: That'd be great. Thank you, and I have nothing more.

DR. DUNNE: Yes. Thank you.

DR. BADEN: Dr. Patel?

DR. PATEL: Good morning. Nimish Patel, University of California San Diego. It's clear that exposure matters, and that's why it's co-formulated with probenecid. On table 69 of the briefing document, it looks like there's an attempt to understand some of the potential reasons or predictors of overall response at the test-of-cure visit, and it looked like creatinine clearance had topped out. And you ended your presentation with women above the age of 65 as a potential demographic, but was there further assessment into those individuals with diminished renal function versus preserved renal function?

I was wondering if you could also provide some comment on the effect of weight. It seemed like a third of the population was either overweight or obese and whether or not that impacted exposure and ultimately impacted outcome.

DR. DUNNE: Okay. I think the first question is about creatinine clearance, does that matter on outcomes. We combined the 301 and 310 studies together to look at creatinine clearance. Let's put that guy up there. I think you can see that the outcomes are more similar than different. They are a little bit lower in creatinine clearance, less than 60 versus above 60, but they're kind of in the ballpark. It's not a radically different number between the two, and the comparator has a similar kind of thing happening. There are probably some different demographics.

The challenge with creatinine clearance is that if you use the Cockcroft-Gault equation, you're introducing age, and older patients are going to not respond as well because we saw that they have more pathogens. So creatinine clearance is complicated to just cleanly pull out as a variable, but we were interested in that, too, because you're probably asking do we need to adjust the dose in patients and all that, yes. I think it's hard to make an argument for that from this

particular data, and I think we're probably not going there at this point because you see that the outcomes drop even on the comparator arms. This is just probably a patient population thing.

You asked about obesity. I think that was with BMI. Would you like to know this kind of thing for BMI? Do we have that, Steve? I think that's just for that subpopulation of 301. Why don't we take a note on that, and we'll come back. It's very easy for us to do that. We can do it in the break, if that's ok.

Was there another question or it was just obesity and creatinine clearance.

DR. PATEL: That's all for me.

DR. DUNNE: Okay. Thanks.

DR. BADEN: Make sure you get LaToya's attention. If you have a follow-up, please rotate so we can have the thematic; if not, we'll get to people in order.

Next is myself on the list. Your slide 79, one of the elephants in the room, in my view, and I think we all are concerned about this, is the

induction, amplification, and dissemination of resistant organisms. Trying to understand these data, this is the emergence of ciprofloxacin resistance being at the test of cure -- .

DR. DUNNE: Correct?

DR. BADEN: -- largely, 40 percent.

DR. DUNNE: Correct, of the 84 isolates that we saw, yes.

DR. BADEN: Do you think that is a primary induction or unmasking, perhaps colonizing flora or susceptibility, to become more resistant in terms of the biology of what is going on there?

DR. DUNNE: So complicated, though; it's so complicated. We don't have a solid answer but we have some ideas. Quinolones are great drugs, and we've used them forever. They work in a lot of scenarios, and that's all good. They have an intracellular accumulation that is pretty substantial that you don't see with beta-lactams.

There's a paper from Nature about three years ago that showed that in the vaginal mucosa there are *E. coli*. It will get into the cells in

the vaginal mucosa. Those cells could ultimately be a reservoir for recolonizing the vaginal vault and probably the bladder over time. When you use cipro, you're probably doing a great job of getting rid of the intracellular organisms that are inside those vaginal cells, but there's a limit to that.

There's a certain AUC or MIC that Alan Forrest had come up with that talked about the effectiveness of a quinolone intracellularly, and you're starting to see a shift in that. Basically, there's a point in which the cipro will not work to kill off the organisms, and you're going to be selecting in the residual flora organisms that have a higher MIC to cipro. That's kind of complicated, but that's kind of where we are at the moment with things.

DR. BADEN: Sure. But just thinking about some of the the data that you may have or you could have, one is prior fluoroquinolone receipt of these patients may predispose them --

DR. DUNNE: Sure.

DR. BADEN: -- and at least in my mind, I

think the reservoir, the enterobacteriaceae, the intestine, any assessment of intestinal flora --

DR. DUNNE: Not in this study. That would have been a great thing to do, yes. No, we --

DR. BADEN: For sulopenem in particular because I worry that the induction of sulopenem resistance may be going on in a space that was not assessed.

DR. DUNNE: Yes.

DR. BADEN: So two questions there, prior fluoroquinolone receipt that may have predisposed, and you've already answered the question that there was no intestinal assessment.

DR. DUNNE: We didn't do that.

DR. BADEN: And as one could imagine, as CREs are in the community, carbapenem-resistant enterobacteriaceae, this might fuel that amplification substantially.

DR. DUNNE: Yes. I mean, that's what happens. Good antibiotics select for resistant pathogens. That's what happens. You're right on that.

I think to speak to your point about previous use of antibiotics, that's probably that paper that we presented that showed with age, the resistance rates to quinolones are going up. One has to assume that those women over time have seen quinolones in the past. We don't tend to collect historical data on previous UTIs. It's not reliable. There's a recall bias there which is staggering. We can't do that. That would have to get done at a community level where you're tracking people over time, looking to see whether they had resistance. I think that's it for stewardship.

The three things, I think age is a thing; you should think about that locally. I think knowing what the patient's prior exposures had been and whether they have a resistant pathogen, that's going to be really important. You can do that at a community level, the care pathway level locally when you have those cultures available. And thirdly, it's probably resistance in your community. If the resistance rates are high in the community, you factor that into your care pathway,

but we don't have historical data, Dr. Baden, on previous treatments.

DR. BADEN: Thank you.

Dr. Chandra, you have a follow-on?

DR. CHANDRA: Yes. I was just curious about the 302 study. Did you see any emergence of resistance in that study?

DR. DUNNE: No, we did not see resistance in that study either.

DR. CHANDRA: Okay. Thanks.

DR. DUNNE: Yes. No, we did not.

DR. BADEN: Dr. Green?

DR. GREEN: Thank you. Michael Green. This is a question for Dr. Golden. I'll give you a moment if you want to come to the microphone. My question is, it seems in your comments that I don't get the sense that you agree with the FDA's definition of overall response or success, and I'm not sure whether the agency has applied that for all UTI studies. I suspect they have. Clearly, the lack of success of the drug in question here is impacted by the fact that they're looking at

microbiology and persistence, or perhaps recurrence; that is being seen at later follow-up.

So I'm wondering if you can just comment for me and educate us as to what we're supposed to do with that information. Is it asymptomatic bacteria or is it really persistence and not asymptomatic bacteria, as was mentioned in the introductory comments by the agency? Thank you.

DR. GOLDEN: Thank you. It's obviously a very complicated and I think somewhat controversial issue. I don't know if we have the slide that looks at the residual organisms, the genus and species versus -- I think to answer, I will talk about that more.

So to answer the question, I think, first, is it persistence of the original infecting organism or are you picking up colonization with a different strain of organism, I think is a really important question. You would have to do testing that's outside the normal clinical testing. We don't do pulse field gel electrophoresis to see if *E. coli* at the end of treatment is the same strain

as what the initial treating strain was. So what I can tell you is that, in practice, we don't do proof-of-cure culture; so if the patient is given a course of, let's say, 3 days of antibiotic for an uncomplicated cystitis, we don't typically see them in follow-up. We'll counsel, "Call me if you're not better." If you're not better, then we want to do additional testing.

I think it's such a relevant question because what we're all really worried about is overuse of antibiotics and overprescribing of antibiotics, and all the collateral damage from antibiotics. So as a clinician -- and I do a lot of work related to care pathway development and antibiotic stewardship in our institution -- we're really focused on giving the least amount of antibiotic that we possibly can. I don't want to find out that somebody has asymptomatic bacteriuria because I don't want to give more antibiotic. I'm certainly not going to challenge what the FDA decides the endpoint is going to be, but in clinical practice, that's what we do.

DR. GREEN: So I also do clinical practice and do stewardship. I guess a couple comments. I believe this was in the preparatory discussion that we received from the agency that really raised the question that applying the microbiologic tests that were done by the applicant, in the micro lab, they pick out one colony to do their testing on, so we never know for certain whether it's -- unless it's polymicrobial with different organisms or different genus and species, we don't know, and sometimes they go, "Oh, it has a different morphotype," so they'll work those up, and they'll say, "Oh, it's *pseudomonas* 1, *pseudomonas* 2," and then we'll see that they don't necessarily have the same susceptibility; sometimes they do.

Clearly, the concern here is the selection process. This is the first-in-class oral penem, and we all live and pray that our penems are going to last for a very long time because we're already into doing things in combination with our carbapenems because of resistance. So clearly what is pressing us as a committee, and I think the

agency, and I suspect even the applicant, is this concern that if we introduce this drug, we're going to have a broad impact and lose a life-saving class -- that is the carbapenems -- for probably more important infections.

So we're thinking about UTI and uncomplicated UTI -- that's the discussion on the table -- but in the back of all of our minds is what happens if this gets broadly used in the community and we no longer have a benefit of carbapenems and no new class really evolving to take its place? That's what I'd ask you to think about as a clinician when we see these persistent strains and trying to think about them.

DR. GOLDEN: What I would like to respond to in that is, right now, for example, if we have a patient who has an uncomplicated ESBL cystitis, we would use fosfomycin if we could, or we could use nitrofurantoin or trimethoprim sulfa. So I don't think that the availability of sulopenem would necessarily even mean it would be the first go-to drug. And the reason I say that is as somebody who

does a lot of interaction getting non-formulary antibiotics or restricted antibiotics approved in the outpatient setting, I can tell you that if I'm on the phone with an insurance company requesting sulopenem for a trimethoprim sulfa-susceptible isolate in somebody without a contraindication, they won't approve it.

So I think that although that process can be very onerous to the practicing clinician on a day to day basis, there's going to be a very important role for the insurers who have to approve that drug. So I don't think that approving the drug is going to open the floodgates of broad accessibility to the drug because it's still very difficult to access many other approved antibiotics that require prior authorization.

Then the second point is, for somebody who has no other options, they're actually getting carbapenems now. Somebody who has a resistant isolate, an ESBL isolate, and you can't use any of the typical drugs, they're getting IV ertapenem. So they're still getting a carbapenem. We would

just be changing the delivery, the actual drug, and then being able to get it orally as opposed to parenterally.

DR. BADEN: It seems you have triggered lots of discussion.

Arjun, you haven't spoken yet. I'll let you do the first follow-on.

DR. SRINIVASAN: Just a quick question on that point, which I think is a really good one that you're raising. But for this approved indication, the overwhelming majority of use would be in patients who never had a culture in the first place because there is no recommendation. Right now, the treatment is all empiric treatment unless there's a failure; correct?

DR. GOLDEN: Yes. Again, this is the lens of a clinician. I would envision really thinking about sulopenem in somebody who already has a history of multidrug resistance. Most of the people that I see who are going to be candidates for this drug have a long history -- 10, 20, 30 prior urinary tract infections -- so we have a

rich microbiologic history to review. So if somebody has had multiple infections with organisms that are susceptible to amox/clav or trimethoprim sulfa, that's what we're going to go to first. And in these patients, we often will get cultures right at the signs and symptoms because we know they have resistance and we know that they may be more likely to fail. So by the time we were to reach for sulopenem, they would, A, already have failed something else or we would have more microbiologic data to work with.

So I don't think the answer is going to be, "Oh, we have this 65-year-old woman who's never had a UTI before," and we're going to go right to sulopenem. I think that's what we all want to avoid.

DR. SRINIVASAN: Can I clarify --

DR. BADEN: Please.

DR. SRINIVASAN: -- that the approval, though, what we're voting on, would be the approval wouldn't come with all of those really important caveats; right? This would be approved for

treatment of uncomplicated urinary tract, or is there another way to caveat this?

DR. BADEN: No, no.

DR. SRINIVASAN: Yes. Thank you.

DR. BADEN: To clarify -- and Dr. Kim or Dr. Farley can jump in if I get it wrong -- we actually are not voting. So the agency will decide what to approve. But to your point, our discussion is going right to the agency for them -- and I guarantee you they are listening to us -- in their thinking about how to weigh the different pressure points. So the more we can discuss as a community right now these kinds of issues, drilling down, the more they have to think about as they bring the decision making forward.

Barbara?

DR. GRIPSHOVER: Hi. It's Barb Gripshover. Getting to that same issue, I noticed that in the second trial, half of the people didn't have positive cultures, and I think in the first, a third did, when you go from the total enrollment to the micro intent to treat. So if we were giving

that drug from the get-go, half of the people might not have even had a positive culture. I just think it's really important to emphasize that. We wouldn't want people who had simple cystitis to get it because it's not going to be that selected population, I guess.

DR. GOLDEN: I would respond, again, that I don't think this is going to be an antibiotic that you can just write a prescription and it's going to get filled. I think, virtually, every insurer is going to require prior authorization; and again, from my experience, you're not going to get that prior authorization without really substantial data behind your request.

DR. BADEN: Dr. Joniak-Grant?

Oh, I'm sorry. You have a follow-on?

DR. GRIPSHOVER: That is leaving a lot on the insurance companies.

DR. BADEN: Please speak into the microphone.

DR. GRIPSHOVER: Sorry. That is leaving a lot on the insurance companies, then, just to point

out. Thank you.

DR. GOLDEN: I think it's going to really be a very team-based approach to managing the administration of the medication; so clearly there's going to need to be a lot of education to prescribers, and I think that's where a lot of the guidelines societies are really helpful. There's so much continuing medical education that physicians get. I think people are very aware of antimicrobial resistance, it's gotten a lot of publicity, and then the insurance authorization can be one of many pieces. I certainly don't mean to put it all on them.

DR. BADEN: Dr. Joniak-Grant?

DR. JONIAK-GRANT: Thank you, Dr. Joniak-Grant. I wanted to go back to this issue about the microbiological failure. Cipro has less microbiological failure than sulopenem -- sorry, I'm still learning how to say that -- even though the clinical failure rates are about the same. So it suggests to me that clinicians are more likely to miss a microbiologic

failure with sulopenem than cipro.

There's kind of a 3 percent floating around of maybe they had microbiologic failure on cipro, but not clinical signs, whereas there's more of a difference of about 8 percent, and I'm wondering if that, in your opinion, should change how cultures are done if there's an 8 percent of people that aren't really showing clinical signs but do have this microbiological failure because that's almost 3 times as much as what you would be seeing with cipro. So if you could speak to that issue.

DR. GOLDEN: So one thing that's really interesting in this whole discussion is the lack of mention of pyuria, which is a piece of information that we often look at. There was a study that was published, I want to say even earlier this year -- and I'll have to pull it out during the break -- that actually proposed raising the cutoff of pyuria to like 230-240 white cells, which is way above what we typically think about. So none of that comes into that discussion, but I think, again, in clinical practice, the presence of pyuria

is really an important piece of information to supplement bacteriuria plus clinical symptoms to decide when to treat.

So I find it very difficult in clinical practice to even know what to make of, let's say, somebody who has symptoms and has only 1,000 or 2,000 bacteria, because that doesn't really meet the criteria for a urinary tract infection. So I think there's a lot of semantics about microbiologic failure versus bacterial persistence. And there are certainly many other infections where you treat somebody and you don't look for proof of cure, and the classic, somebody who's got group A strep pharyngitis and you give them a course of pen VK, you could go back and swab their throat and they're still carrying strep, and we don't necessarily consider them clinical failures; or you treat somebody with MRSA pneumonia, and if you haven't done a decolonization regimen, you swab their nasopharynx and you recover MRSA, we don't necessarily think of them as clinical failures.

So I think there is precedent in other

infections to think about your persistence of organisms and not necessarily equating that to clinical failure.

DR. BADEN: Do you have a follow-up?

DR. JONIAK-GRANT: Yes, just to follow up with that, talking about clinical failures, I guess that's where -- and maybe people on the panel can educate me more on this, too -- having this cutoff at day 28 seems a little short to me for being around patients. I remember even just in college how many women wouldn't get back to the health clinic for a month because they'd wait, they'd have some symptoms, and they'd see if their medication was working. They'd be like, "Well, do I need to go back; do I not? It's not really getting worse. It's gotten better. Oh, now another, 6 weeks later, now I am starting to feel worse," and then they would return.

So that's the other thing I'm trying to suss out here, clinical remission, for lack of a better word, at 28 days, is that a really good marker or is that maybe a bit short?

DR. GOLDEN: I don't know, Mike, if you have a comment on that.

DR. DUNNE: I mean, I think that's a study question. We could do that in a different study. We didn't do that here. The guidance is to go to day 28, and they had stopped therapy 23 days earlier. So I think if there was a burning problem, we probably would have come back sooner than that.

DR. BADEN: We have gotten to the break. The endpoint issue, there are several more questions we need to dig into on that. I think we may have to revisit this after lunch when we can bring you back for more Q&A.

I know, Dr. Lewis, you have a follow-on. Is it tightly to the discussion that was just happening?

(Dr. Lewis gestures yes.)

DR. BADEN: So we we need to just take that follow-on, and then we can go to break.

DR. LEWIS: Roger Lewis, and I love being what keeps you from break. Dr. Golden, I want to

come back to your phrase "rich microbiologic history," and I want to check my understanding of the point that you are making. My understanding is that there are clear recommendations for empiric therapy, which sort of implies the setting when uncomplicated UTI, in the setting where you you don't have that history, there's clearly guidelines or standardized approaches when you have a culture and a sensitivity result.

Are you suggesting that there's a class of patients for which we're halfway in between where we have partial information that informs the selection, so it's not truly empiric and that's not truly culture driven?

DR. GOLDEN: That's a great question. I think it's always empiric when you don't have the culture result in front of you. I think we're trying to make an educated guess when we see somebody who's had multiple prior infections. Certainly, you could have somebody who's always had a pan-sensitive *E. coli*, and this time around it's much more resistant than we expect. So it's always

empiric until you have that culture result in front of you, but if we're trying to make an educated guess, we do often rely on prior history to predict what might be there.

DR. LEWIS: Nothing else.

DR. BADEN: Thank you.

There are still more questions for the applicant, but as I said, we'll come back to this after lunch. We will take a 15-minute break and begin at 11:10, 5 minutes later than on the schedule. Thank you. We're now on break.

(Whereupon, at 10:56 a.m., a recess was taken, and meeting resumed at 11:10 a.m.)

DR. BADEN: Thank you, all. We will now resume from break.

We will now proceed with the FDA's presentation, starting with Dr. Kopack.

Dr. Kopack, the floor is yours.

FDA Presentation - Angela Kopack

DR. KOPACK: Thank you, and good morning. I am Angela Kopack, the clinical reviewer for this application. Dr. Li, the statistical reviewer, and

I will be presenting the efficacy and safety assessments. I will start with a brief regulatory history, followed by highlights of trial design and analysis of Trials 301 and 310. Dr. Li will then discuss the efficacy of sulopenem for uUTI, and I will then discuss the efficacy of sulopenem for cUTI and cIAI, followed by a discussion of the safety of sulopenem, and then summary and conclusions.

NDA 213972 was submitted in November of 2020 for the treatment of uUTI in adult women caused by designated susceptible microorganisms proven or strongly suspected to be non-susceptible to a quinolone. This NDA included Trials 301 in uUTI, 302 in cUTI, and 303 in complicated intra-abdominal infections. The NDA received a complete response due to lack of substantial evidence of effectiveness in July of 2021.

In Trial 301, sulopenem was superior to cipro for an overall response rate in the micro-MITTR or cipro-resistant population, but inferior to cipro in the micro-MITTS or

cipro-susceptible population. Both Trials 302 and 303 failed to meet their primary endpoints. It was recommended that the applicant conduct at least one additional adequate and well-controlled study in uUTI and consider use of a different comparator. This was done in Trial 310 using amoxicillin/clavulanate as the comparator, and the NDA was resubmitted in April of this year for the treatment of uUTI in adult women caused by designated organisms susceptible to sulopenem.

Both Trials 301 and 310 were phase 3, randomized, multi-center, double-blind studies in women aged 18 years and over using sulopenem etzadroxil/probenecid dosed 500 milligrams/500 milligrams twice a day for 5 days. In Trial 301, the active comparator was cipro 250 milligrams twice a day for 3 days, and then in 310, amox/clav 875 milligrams/125 milligrams twice a day for 5 days.

The primary endpoint was the same for both trials, being overall response, which is a composite of clinical and microbiological response

on day 12, which is the test of cure in three analysis populations, which I will review on the next slide. Clinical success is resolution of the baseline UTI symptoms with no new UTI symptoms, and microbiological success is the test-of-cure urine culture with less than 10 to the 3rd CFUs per mL of the baseline pathogen.

For the analysis populations, the micro-MITT was all randomized patients who received at least one dose of study drug and had 10 to the 5th or more CFUs per mL of the baseline uropathogen. The micro-MITTS, or susceptible population, is subjects with baseline pathogens susceptible to cipro in 301 and then susceptible to amox/clav in 310; and in the resistant population, or micro-MITTR, non-susceptible to cipro in 301 and non-susceptible to amox/clav in 310.

For the remainder of this presentation, when we refer to susceptibility, we are referencing susceptibility to the comparators. Non-inferiority testing using a 10 percent margin would be used in the micro-MITTS or susceptible population and

superiority testing would be used in the resistant population.

For the analysis methods, for Trials 301 and 310, the micro-MITTR and micro-MITTS populations were separate and essentially considered as two studies. Hierarchical testing was used to control overall type 1 error amongst the three analysis populations I just reviewed. In Trial 301, for the hierarchical testing, the first step was noninferiority in the micro-MITTS or superiority in the micro-MITTR, followed by noninferiority in the micro-MITT and superiority in the micro-MITTR. For 310, the first step in the hierarchy was noninferiority in the micro-MITT and second being noninferiority in the micro-MITTS or superiority in the micro-MITTR, and then superiority in the micro-MITT.

The thinking of FDA is the noninferiority testing in a micro-MITT population has limited interpretability because it includes pathogens that are resistant to the comparator. In Trial 310, before unblinding of results, FDA had recommended

that noninferiority first be tested in the micro-MITTS population rather than in the micro-MITT.

In both trials, interim analyses were performed for sample size re-estimation. In 301, there were two planned blinded interim analyses in the susceptible population when 33 and 66 percent of subjects had outcome data and one unblinded interim analysis for the resistant population. In 310, there was one planned blinded interim analysis. In Trial 301, changes were made to the statistical analysis plan after the interim analysis. Definitions for susceptibility and microbiologic persistence were changed with addition of whole genome sequencing and PCR.

Additionally, Sites 2O2 and 218 were excluded from the efficacy analysis. For both trials, the analysis method was the 95 percent confidence interval approach. For Trial 301, FDA used the original statistical analysis plan and included Site 2O2 for all analyses, as FDA did not agree with the protocol changes made after the

unblinded interim analysis or with exclusion of Site 202.

I will now turn it over to Dr. Li to present the efficacy of sulopenem for uUTI.

FDA Presentation - Xianbin Li

DR. LI: Good morning. My name is Xianbin Li, a statistical reviewer. I will be presenting on the efficacy of sulopenem for the treatment of uUTI. First, I will talk about the study population. In Trial 301, subjects were enrolled from Russia, Ukraine, and the United States. About 66 percent of the subjects were included in the micro-MITT population and 19 percent and 48 percent were in the micro-MITTR and S populations, respectively.

In Trial 310, all subjects were from the United States. About 45 percent of the subjects were included in the micro-MITT population. Only 3 percent were included in the micro-MITTR population. It is noted that the sample size did not reach the planned 134 subjects per arm. About 42 percent of the subjects were included in the

micro-MITTS population.

The two treatment groups were comparable in each population, except for the third and the fourth row, where there was a nominally significant difference, about 5 percent, between the two arms.

Age distribution from the two trials is shown in this table. In Trial 301, the proportion of subjects 60 years old or older were about 45 percent and 37 percent in the micro-MITTR and the S populations, respectively. In Trial 310 in the micro-MITT population, 22 percent of the subjects were 65 years old or older. Although not shown in this table, the proportion of subjects 60 years old or older were about 10 percent higher in Trial 301 than in Trial 310. Age distribution was similar between the two arms in each trial.

Regarding race in the two trials, the majority of subjects were white, about 90 percent, followed by black or African American, about 9 percent. The two arms were comparable. All other baselines were generally balanced.

Now, I'm going to talk about the primary

efficacy analysis. This table shows the impact of changes in SAP and the inclusion of Site 202 in the micro-MITTR population of Trial 301. The top row is the applicant's result with an updated SAP and excluding Site 202. The second row is FDA's analysis using the original SAP and including Site 202. In this analysis, the difference in overall response rates between the two arms decreased from 26.6 percent to 15.3 percent and the p-value was less significant than initially reported.

This graph shows overall response by study population in the two trials. In the comparator-resistant population of Trial 301, the first row, sulopenem was significantly better than ciprofloxacin. In the comparator-susceptible population of this trial, the second row, noninferiority was not established and sulopenem was significantly worse than ciprofloxacin. In Trial 310 in the comparator-resistant population, the fourth row, the sample size was too small to make any conclusion. Sulopenem was numerically

worse than the control arm. In the comparator-susceptible population, the fifth row, noninferiority was established; in fact, sulopenem was significantly better than the comparator.

This figure shows overall clinical and microbiological responses by study population. For each population, the first row is overall response. The second and third rows are clinical and microbiological responses. In the comparator-resistant population of Trial 301, shown in the top panel, all responses were better for sulopenem than for ciprofloxacin.

In the comparator-susceptible population of Trial 301, shown in the middle panel, in the overall response and the microbiological response, sulopenem was worse than ciprofloxacin, although clinical response rates were similar between the two arms. In the comparator-susceptible population of Trial 310, shown in the bottom panel, the overall responses and microbiological response reached were similar between the two arms. In all three populations, overall response was in the same

direction with the microbiological response.

This graph shows overall response by visit for the two trials. In each population, responses at the end of treatment, EOT, test of cure, TOC, and the final visit are shown in order. In the comparator-resistant population of Trial 301, the top panel, results favored sulopenem over ciprofloxacin at all visits. In the comparator-susceptible population of Trial 301, the middle panel, results for the two arms were similar at the end of treatment but favored ciprofloxacin over sulopenem at the last two visits. In the comparator-susceptible population of Trial 310, the bottom panel, results for the two arms were similar at the end of treatment but favored sulopenem over the comparator at the last two visits.

This graph shows subgroup analyses for the comparator-resistant population of Trial 301. The first panel is for age, the second is for creatinine clearance, and the third is for country. The treatment effects were generally similar for the subgroups in the first two panels; however, it

is noted that the last age group, the third row, had the lowest response rates in both arms among all age groups, although it had numerically the highest difference in response rate. There were no heterogeneous treatment effects identified for country, although point estimates for three countries appeared different.

This figure shows subgroup analyses for age and creatinine clearance for the comparator-susceptible population of Trial 310. Treatment effects were similar in the two subgroups. In the last age group, the large difference in response rates were mainly due to the low response rate in the comparator group.

In conclusion, in Trial 301, in the micro-MITTR population, superiority was established. In the micro-MITTS population, NI using a 10 percent margin was not established. Sulopenem was similar to ciprofloxacin for microbiological response. In Trial 310, in the micro-MITTS population, NI using a 10 percent margin and superiority were established. In the

micro-MITTR population, the trial did not enroll the planned sample size, so conclusions could not be drawn. The differences between arms were driven by microbiological response rather than a clinical success rate.

Thank you very much. Now, I will turn it over to Dr. Kopack.

FDA Presentation - Angela Kopack

DR. KOPACK: I will now discuss the efficacy of sulopenem for cUTI and cIAI. Trial 302 for cUTI was a phase 3, randomized, multicenter, double-blind study in adult men and women using sulopenem 1000 milligrams IV daily for at least 5 days followed by oral sulopenem 500 milligrams twice a day, to complete 7 to 10 days of total treatment; compared to ertapenem 1000 milligrams IV daily for at least 5 days followed by oral cipro 500 milligrams twice a day; or amox/clav 875 milligrams twice a day to complete 7 to 10 days of total treatment.

The primary endpoint was overall response, again, a composite of clinical and microbiologic

response at the test of cure, which was day 21 in the micro-MITT population. This was a noninferiority study using a 10 percent margin.

Here are the results for the primary endpoint, so overall response at test of cure. The lower bound of the 95 percent confidence interval was minus 13.9 percent, so Trial 302 failed to show noninferiority using a 10 percent margin. IV sulopenem followed by oral sulopenem was significantly worse than the active comparator.

This slide shows the two components of overall response, so microbiologic response and clinical response at different timepoints in the micro-MITT. First, looking at the microbiologic response, you can see that a day 5 and end-of-treatment visits, the two treatment arms had similar microbiologic response rates; however, at the test-of-cure visit, a significantly lower treatment effect emerged in the sulopenem arm compared to the ertapenem arm with the lower bound of the 95 percent confidence interval for the difference as minus 14.3 percent. Looking at

clinical response, you can see that at each visit, the clinical response rates were similar between the two treatment arms.

Here we have overall response at test of cure by stepdown category and pathogen susceptibility. First, focusing on the cipro-susceptible column, for cipro-susceptible pathogens, the overall response was 62.1 percent for subjects who stepped down from IV to oral sulopenem compared to an overall response of 83.3 percent in those who received IV ertapenem and stepped down to oral ciprofloxacin.

Looking at the next column with a cipro-resistant amox/clav-susceptible [sic - pathogen], the overall response was 47.3 percent for IV sulopenem to oral sulopenem compared to 56.1 percent for IV ertapenem to oral amox/clav. That final column, cipro versus amox/clav resistant, is included to highlight the subjects with pathogens resistant to both cipro and amox/clav often stepped down to oral therapy if in the sulopenem arm but stayed on IV if in the

ertapenem arm. There were 106 subjects who remained on IV ertapenem because their baseline pathogen was resistant to both cipro and amox/clav. We note that comparisons of outcomes between subjects who stepped down to oral therapy in the two groups are limited by being post-randomization subgroup analyses.

In conclusion, for Trial 302, sulopenem did not establish noninferiority to comparator in overall response using an NI margin of 10 percent. Differences were driven by microbiologic response rather than clinical response, and results suggested that differences were driven by inferior overall response in subjects with cipro-susceptible pathogens who stepped down to oral therapy.

Trial 303 was a phase 3, multicenter, double-blind, randomized trial comparing the efficacy, tolerability, and safety of IV sulopenem followed by oral sulopenem with that of IV ertapenem followed by either oral cipro and metronidazole or amox/clav for the treatment of complicated intra-abdominal infections. Here, the

primary endpoint was clinical response at the test of cure, which was day 28. The applicant conducted both a primary and post hoc analysis, and as you can see in Trial 303, sulopenem failed to show noninferiority using a 10 percent margin either based on the primary analysis or a post hoc analysis.

For overall efficacy conclusions, for Trial 301 in uUTI, efficacy was established in the cipro-resistant population but not in the cipro-susceptible population. For Trial 310, also in uUTI, efficacy was established in the amox/clav-susceptible population. There were inconclusive results in the amox/clav-resistant population due to the small sample size; and finally, efficacy was not established in complicated UTI or complicated intra-abdominal infections.

I will now discuss the safety of sulopenem and then provide summary and conclusions. The clinical safety database for sulopenem includes 2006 subjects who received IV and oral formulations

of sulopenem in the phase 1 and 2 studies. In the two uUTI trials, there were 1,932 subjects who received oral sulopenem for a median duration of 5 days. Please note that 8 subjects in the sulopenem arm from Site 218 in Trial 301 were excluded from FDA's safety database due to missing source documentation. 695 subjects were treated with IV and oral sulopenem for a median duration of 10 days in Trial 302, and in Trial 303, 335 subjects were treated with IV and oral sulopenem for a median duration of 9 days; so in total, for the FDA safety database, we have 4,968 sulopenem-treated subjects.

Now, looking at the phase 3 safety population for sulopenem and the deaths, there were 7 total deaths, a single death in the uUTI trials, a death due to lung cancer, and there were two other deaths due to malignancy in the other trials, but on review of the narratives, none of the 7 deaths were attributable to sulopenem.

Now, focusing on adverse events in the two uUTI trials, 301 and 310, there were six serious

adverse events in the sulopenem arm, all from Trial 301. Only one of these was attributed to sulopenem, a case of angioedema. The other SAEs were pyelonephritis, chest pain, small intestinal obstruction, presyncope, and the previously mentioned fatal case of lung cancer. Overall, 1.1 percent of sulopenem-treated subjects had an adverse event leading to study drug discontinuation, and these were mainly gastrointestinal in nature and included diarrhea, nausea, vomiting, abdominal pain, and gastroesophageal reflux disease, and most adverse events were mild with severe adverse events being uncommon.

Continuing to look at adverse events in the uUTI Trials 301 and 310, there were more subjects in the sulopenem arm, 21.5 percent, that had an adverse event compared to subjects that received amox/clav or cipro. This difference was largely accounted for by diarrhea, which was the most common adverse event in the sulopenem arm, occurring in 10 percent of sulopenem-treated

subjects.

Other adverse events that were seen were nausea, vulvovaginal mycotic infection, headache, vomiting, and abdominal pain. Diarrhea was an adverse event of special interest during the development program. Most cases of diarrhea were mild, and treatment discontinuations due to diarrhea were rare, occurring in 0.3 percent of sulopenem-treated subjects. There were no cases of *Clostridioides difficile* infection in the sulopenem arm and no serious adverse events of diarrhea.

ALT elevations were seen in the sulopenem phase 3 trials; however, significant hepatotoxicity was not noted. One subject from Trial 302 with normal baseline liver function tests met laboratory criteria for Hy's law after 5 days of sulopenem, but remained on study drug with a switch to oral sulopenem on days 6 and 7, and near normalization of liver enzymes by day 10.

In Trials 301 and 310, slightly more subjects, six, in the sulopenem group had an ALT 3 to less than 5 times the upper limit of

normal compared to one subject each in the cipro and amox/clav arm. There was one subject in Trial 301 who had greater than 5 times upper limit of normal ALT elevation at the test of cure but was asymptomatic, and the abnormalities resolved 5 days later.

Across the four phase 3 trials in the sulopenem group, 1.1 percent of subjects had at least one post-baseline ALT elevation greater than 3 times the upper limit of normal compared to 0.7 percent in the comparator. Of these subjects, nine sulopenem subjects had an ALT more than 5 times the upper limit of normal and one had an ALT more than 10 times the upper limit of normal. Only one of these was from the uUTI trials, the subject from Trial 301 that was just discussed. Overall, attribution of causality to sulopenem was confounded by the subjects underlying medical conditions and/or concomitant medications.

In conclusion for safety, there was an adequate safety database. Diarrhea was the most common adverse event in the phase 3 uUTI safety

population but was generally mild. Treatment discontinuations due to diarrhea were uncommon. Mild ALT elevations were seen in a small proportion of sulopenem-treated subjects but in general were not treatment limiting. Overall at this time, it appears sulopenem has a reasonable safety profile and the identified safety risks may be mitigated through labeling.

Finally, although Trials 301 and 310 had different comparators and efficacy was shown in discordant populations, they provide evidence of benefit of oral sulopenem for the treatment of uUTI in adult women caused by organisms susceptible to sulopenem. The efficacy of oral sulopenem, as stepdown therapy following IV therapy for complicated urinary tract infections, has not been established. If sulopenem is approved, communication to medical providers for the lack of efficacy of oral sulopenem as stepdown therapy for cUTI will be important.

Thank you. At this time, I will ask Dr. Sheikh, the clinical microbiology reviewer, to

present the microbiology assessment.

FDA Presentation - Jalal Sheikh

DR. SHEIKH: Thank you, Dr. Kopack.

Good morning. This is Jalal Sheikh, clinical microbiology reviewer of this NDA in the Division of Anti-Infectives, Office of Infectious Disease, CDER, FDA. Before presenting the clinical microbiology assessment of sulopenem antimicrobial activity, let me clarify very briefly the structural difference between penems and carbapenems because penems are commonly mistaken as carbapenems.

As shown in this slide, both penems and carbapenems share great similarities; however, penems have an unsaturated 5-membered thiazoline ring fused to the 4-membered beta-lactam ring as sulfur atom occupies at position 1 of the heterocyclic ring, altering the 3-dimensional structure of the drug molecule.

In contrast, carbapenems' beta-lactam ring fused to an unsaturated 5-membered pyrroline ring with a carbon atom at position 1. The sulfur atom

in penems contributes to a smaller bond angle that reduces the intra-ring stress, protecting it against enzymatic degradation by dehydropeptidase 1 enzyme. To avoid this enzymatic degradation, carbapenems require either a methyl substituent on the C1 carbon or co-administration with a DHP-1 inhibitor, for example cilastatin and imipenem.

The mechanism of action for sulopenem has been elucidated in different in vitro studies. The bactericidal activity of sulopenem is the result of inhibiting the transpeptidase enzymes, that is penicillin binding proteins, from cross-linking peptidoglycan; therefore, sulopenem induces cell lysis as a result of cell wall synthesis inhibition.

Sulopenem has high affinity for penicillin binding protein 2; however, it preferentially binds to other penicillin binding proteins in the following order of affinity. Penicillin binding proteins of gram negative bacteria are more difficult for beta-lactams to access, as they are located in the periplasmic space, which is

protected by outer membrane; however, the ionization and molecular weight of penems, including sulopenem, allow them to easily diffuse through outer membrane proteins such as OmpK in *Klebsiella pneumoniae* and OmpF in *E. coli*.

Speaking of the mechanisms of resistance for sulopenem, as we know, sulopenem is a member of the beta-lactam drugs; resistance may be caused by one or more of the four well-characterized mechanisms. Bacteria may alter penicillin binding proteins, thereby the antimicrobial drug can no longer effectively bind to them.

Bacteria may also possess and express a wide range of beta-lactamases that facilitate the hydrolysis of beta-lactam ring, preventing antimicrobial activity of sulopenem. Gram negative bacteria may modify outer membrane proteins, limiting or preventing access to the periplasmic space and its penicillin binding proteins. And finally, organisms may overexpress efflux pumps that actively expel the antimicrobial as they enter the cell, preventing and limiting access to the

target site.

The applicant also submitted clinical microbiology data from other in vitro studies. Notably among them, we found sulopenem showed bactericidal mode of action by time-kill assay at concentration 4 times or higher than MIC against tested *E. coli* and *Klebsiella pneumoniae* isolates, and bactericidal activity was maintained through the 24-hour time period. The spontaneous mutation frequency was determined in vitro as 1 times 10 to the power minus 8 with a 2-fold or less MIC increase. Sulopenem had poor activity against *Pseudomonas aeruginosa* and *Acinetobacter baumanni* isolates.

The in vitro activity data of sulopenem and other FDA-approved carbapenems -- namely meropenem, ertapenem and imipenem -- were submitted for comparison. The minimum inhibitory concentration, MIC 50/90 values, which indicate the minimum drug concentration that inhibit the growth of 50 percent and 90 percent of tested isolates against different bacterial species, were evaluated in various

surveillance studies.

From this table, it has been demonstrated that against *E. coli* and *Klebsiella pneumoniae* isolates, sulopenem had similar MIC 50/90 values within 1 to 2 dilutions to meropenem and ertapenem but lower than imipenem. Against *Proteus mirabilis* isolates, the MIC 50/90 values of sulopenem were higher than ertapenem and meropenem; however, sulopenem, meropenem, and ertapenem MIC 50/90 values are lower than imipenem.

The in vitro activity of sulopenem against fluoroquinolone-susceptible and fluoroquinolone-resistant *E. coli* isolates are almost similar with only one dilution difference in MIC90. Similarly, the in vitro activity of sulopenem against phenotypic ESBL-negative and phenotypic ESBL-positive isolates are almost similar against *E. coli* isolates; however, this is different in *Klebsiella pneumoniae* isolates. It is possible that the ESBL content of *Klebsiella pneumoniae* isolates are different than *E. coli* isolates. As expected, sulopenem has very little

to no activity against carbapenem-resistant Enterobacterales or CRE isolates.

The in vivo activity of sulopenem and its oral prodrug, sulopenem etzadroxil, evaluated in vivo in three animal gerbil otitis media models against *Haemophilus influenza*. Sulopenem and sulopenem etzadroxil demonstrated in vivo activity against these infection models by determining 50 percent protective dose, or PD50, compared to other drugs.

As my statistical and clinical colleagues provided the details of sulopenem clinical program, I'd like to emphasize some of the highlights pertinent to clinical microbiology discipline. In clinical trials, the primary efficacy endpoint was the outcome of overall response, which is combined clinical and microbiological response at TOC visit at day 12.

Microbiological success or eradication was defined when a urine culture obtained at TOC demonstrated less than 10 to the 3rd CFU per mL of the baseline uropathogen, and microbiological

failure or persistence was defined when a urine culture obtained at TOC grew greater than or equal to 10 to 3rd CFU per mL of the same genus and species as the baseline, regardless of antimicrobial susceptibility or genetic dissimilarity as determined by molecular testing, for example, whole genome sequencing or pulse field gel electrophoresis or PCR.

This table summarizes the total baseline predominant UTI pathogens isolated from the subjects in the micro-MITTR, that is cipro-resistant population of Trial 301 and micro-MITTS, that is amox/clav-susceptible population in Trial 310. *E. coli* was isolated at the highest frequency at baseline, followed by *Klebsiella pneumoniae* and *Proteus mirabilis* in both treatment arms of the clinical trials.

This slide summarizes the distribution of baseline isolates of UTI pathogens by their antibacterial resistance parameters in Trials 301 and 310. The first row represents the prevalence of phenotypic ESBL-positive isolates in micro-MITT

populations. The phenotypic ESBL was determined that meet any of the MIC thresholds of either ceftriaxone, imipenem, meropenem, or ertapenem to greater than one microgram per mL. These isolates were further characterized by multiplex PCR for the presence of beta-lactamase encoding genes.

If we take a closer look, this slide summarizes the subgroup analysis of overall response by ESBL status in Trials 301 and 310. As shown in the top part of this table, in Trial 301, the treatment difference was 26 percent among ESBL-positive isolates in the micro-MITTR or cipro-resistant populations. A similar difference of 27 percent was observed with ESBL-negative isolates. Sulopenem did better compared to ciprofloxacin in both ESBL-positive and ESBL-negative micro-MITTR populations.

In contrast, this is quite different in the micro-MITTS or cipro-susceptible populations in Trial 301. The treatment difference was negative 16 percent and negative 12 percent among ESBL-positive and ESBL-negative isolates,

respectively, in sulopenem and comparator control arms. At the bottom part of this table, in Trial 310, the treatment difference was 15 percent among ESBL-positive isolates in the micro-MITTS or amox/clav-susceptible populations. The difference was smaller at 5.7 percent in ESBL-negative populations of Trial 310. Sulopenem also did better compared to amox/clav in both ESBL-positive and ESBL-negative micro-MITTS population.

We further took a deeper dive to understand the sulopenem activity against predominant beta-lactamase genes present in baseline *E. coli* and *Klebsiella pneumoniae* isolates. This slide and the next slide summarize the MIC range, MIC 50/90 values, and clinical and microbiological responses at TOC of the baseline isolates. Data were confirmed to contain predominant beta-lactamase genes, for example, AmpC, CTX-M, TEM, and SHV.

This table is for ESBL isolates from the micro-MITT population in Trial 301. Sulopenem was active against most of these isolates. Favorable clinical and microbiological response was achieved.

Similarly, this table summarizes the activity of sulopenem against the ESBL isolates of Trial 310, and we have seen similar results.

Finally, I'll end my presentation with this summary slide. Overall, sulopenem demonstrated similar in vitro activity against most targeted species compared to meropenem and ertapenem; however, this activity appeared better than imipenem. Sulopenem had no discernible activity against *Pseudomonas aeruginosa* and *Acinetobacter baumanni* isolates.

The in vivo activity of sulopenem was demonstrated in animal therapeutic infection models. Sulopenem demonstrated similar activity against fluoroquinolone-resistant and fluoroquinolone-susceptible isolates. Sulopenem demonstrated activity against certain beta-lactamase-containing isolates, for example, AmpC, CTX-M, TEM, SHV, both in vitro and in clinical infections.

Thanks for your attention. Now, my clinical pharmacologic colleague, Dr. Abodakpi, will

continue with her presentation. Thank you.

FDA Presentation - Henrietta Abodakpi

DR. ABODAKPI: Good morning, everyone. My name is Henrietta Abodakpi, and I am the primary clinical pharmacology reviewer for this application. I'll begin with the pharmacokinetic highlights for oral sulopenem with a focus on the PK of the sulopenem component unless otherwise specified.

Oral sulopenem has an absolute bioavailability of 40 percent under fasted conditions, which improves to 64 percent under fed conditions, and it's 11 percent bound to plasma protein. Oral sulopenem is formulated as the prodrug sulopenem etzadroxil, which is hydrolyzed by esterases to active sulopenem. Active sulopenem has a plasma half-life of approximately 1 hour and is primarily excreted in urine, with the unchanged form accounting for 26.9 percent of total urinary recovery. Renal impairment is associated with increased sulopenem plasma exposures of 2-, 3- and 7.4- fold for mild, moderate, and severe renal

impairment, respectively, as summarized in the table.

Drug-drug interactions for oral sulopenem are primarily driven by the probenecid component, which is an inhibitor of the organic anion transporters, OAT1 and OAT 3, and this is the basis for its co-formulation with sulopenem, which is an OAT 3 substrate, and thus the inclusion of probenecid in the formulation increases sulopenem plasma exposures.

I will focus my presentation on the key clinical pharmacology considerations for our review, and these include the adequacy of the dosages evaluated for the treatment of uUTI and cUTI, specifically looking at the strength of supportive evidence from probability of target attainment, or PTA, analyses, and pharmacokinetic, pharmacodynamic, or PK/PD, perspectives, on the clinical trial efficacy outcomes. I will also provide a brief clinical pharmacology perspective on the contribution of probenecid, and finally, the recommendations for use in the setting of renal

impairment.

For most antibacterial indications, dose selection is informed by the probability of achieving the PK/PD target determined in a nonclinical infection model relevant to clinical efficacy; however, for uUTIs, there's a lack of an established nonclinical model, and there are knowledge gaps about urine-specific PK/PD parameters, the appropriate bacteriologic endpoint, as well as the relative importance of urinary versus plasma drug exposures in PTA analyses. Therefore, there are limitations to the use of PTA to assess the adequacy of a proposed drug dosage for the treatment of uUTI, and nonetheless, PT analyses were conducted in support of sulopenem dosage selection.

Dose fractionation studies were conducted in a murine thigh, as well as an in vitro 1-compartment infection model; however, concerns with the design of the murine infection model studies limited their utility. The in vitro studies suggested that sulopenem exhibits both

time- and concentration-dependent killing. Nonetheless, free time above MIC was selected as the most relevant PK/PD index based on the highest observed R-squared value amongst the three traditional PK/PD indices and the mechanism of bacterial killing attributed to the beta-lactam class.

The applicant relied on the in vivo targets from the murine thigh infection model for initial dose selection; however, the FDA found these targets unreliable due to concerns with study design and the limited interpretability of the ensuing results. Subsequent in vitro target determination studies were used to justify retaining the dosage used in uUTI Trial 301 for Trial 310. These in vitro targets were derived from 10 Enterobacterales isolates, specifically 6 *E. coli* and 4 *Klebsiella pneumoniae* isolates, with sulopenem MICs covering a clinically relevant range of 0.03 to 0.5 micrograms per mL, and the median targets for stasis 1 log and 2-log kill were 40.9, 50.2, and 62.6 percent free time above MIC,

respectively.

This slide demonstrates the probability of achieving the in vitro PK/PD targets in both plasma and urine, and the results are only shown under fed conditions because oral sulopenem is recommended to be administered with food to increase bioavailability. The probability of achieving the target for stasis is greater than 90 percent up to an MIC of 0.25 micrograms per mL in plasma and up to an MIC of 8 micrograms per mL in urine. For the more conservative 2-log kill target, urine-based PTA remains above 90 percent up to an MIC of 2 micrograms per mL.

So overall, the results of the urine- and plasma exposure-based PTA analyses evaluating the probability of achieving the in vitro PK/PD targets support the efficacy of 500 milligrams sulopenem etzadroxil in combination with 500 milligrams probenecid twice daily. However, given the previously noted uncertainties, the PTA results alone are insufficient to inform dose optimization, and there are no clinical dose-ranging studies to

ascertain whether the proposed dosage for the treatment of uUTI is fully optimized. Furthermore, PTA results cannot predict sulopenem's performance against different comparators. The differences in PK/PD attributes between drug classes may help contextualize the observed clinical trial outcomes.

For cUTI, Trial 302 evaluated a 1000-milligram dose of sulopenem administered as a 3-hour IV infusion for at least 5 days followed by optional stepdown therapy with 500 milligrams sulopenem etzadroxil in combination with 500 milligrams probenecid twice daily. Selection of this dosage was informed by the in vivo PK/PD targets deemed unreliable by the FDA to inform dose selection, and therefore PTA could not ascertain the appropriateness of the dose regimen.

Furthermore, the bioavailability of oral sulopenem is 40 to 64 percent relative to the IV formulation, which raises concerns about the adequacy of the oral stepdown dosage; and where probenecid is concerned, its mechanism of action as an OAT inhibitor is leveraged to increase plasma

drug exposures by decreasing renal clearance. Multiple dose administration of 500 milligrams probenecid increases sulopenem plasma AUC by 1.8-fold while decreasing renal clearance by 1.9-fold; but since sulopenem has a short plasma half-life, the cumulative amount of sulopenem recovered in urine over a 24-hour period remains similar in the presence and absence of probenecid. Given the importance of urinary drug concentrations for the effective treatment of uUTIs, the contribution of probenecid to the efficacy of oral sulopenem for uUTI is unclear.

The applicant does not propose alternative dosage recommendations for patients with renal impairment, but similar to probenecid, renal impairment decreases sulopenem renal clearance but the available data are inconclusive on the efficacy implications. Increases in sulopenem plasma exposures are observed with decreasing renal function, but in subjects with mild, moderate, and severe renal impairment, these increases are not considered clinically significant.

Given sulopenem's short half-life and the 5-day duration of treatment for uUTI, the general dosage is expected to be safe in patients with mild, moderate, and severe renal impairment; however, because the PK and safety of oral sulopenem have not been evaluated in patients with creatinine clearance less than 15 mLs per minute or those on hemodialysis, use is not recommended in these subpopulations.

In summary, the various limitations notwithstanding, the PTA results support the efficacy of 500 milligrams sulopenem etzadroxil in combination with 500 milligrams probenecid twice daily for the treatment of uUTI. The available data are inconclusive on the contribution of probenecid to the efficacy of oral sulopenem in the treatment of uUTI. And finally, use of oral sulopenem is expected to be safe in the setting of mild, moderate, and severe renal impairment but is not recommended in patients with creatinine clearance less than 15 mLs per minute and patients on hemodialysis. That's it for me. Thank you for

your time.

Clarifying Questions

DR. BADEN: Wow! I think tremendous presentations of complicated data, very provocative from my perspective, and things we need to think about in this application.

We will now take clarifying questions for the FDA. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you, and the end of your follow-up question with, "This is all for my questions," so we can move on to the next panel member.

Are there clarifying questions for the presenters? We will continue with the same format as we had earlier. I'll start with, hopefully, a simple question for Dr. Sheikh you.

Thank you very much for reviewing the

pharmacology and the structures. Is it safe to say thiopenems/carbapenems, that the induction of resistance by 1 confers resistance to the other? You have a microphone in front of you.

DR. SHEIKH: Thank you. This is Jalal Sheikh, clinical microbiology reviewer at FDA. Thanks for the question. As I've shown, the structure of both penems and carbapenems, there are great similarities in the structure. There is only a little difference. We believe that penems and carbapenems, a cross-resistant exists. So whenever penems double up resistance [sic - penem is resistant], we believe it will be cross-resistant to other carbapenems.

DR. BADEN: Thank you. That is a concern we should share, so thank you.

Dr. Lewis?

DR. LEWIS: Roger Lewis. I have two questions for Dr. Kopack. The first is, you specifically mentioned that the FDA recommended, in their consultations on the design of 310, a recommendation for a different comparator than had

been used for 301. So my first question is, what was the rationale for that recommendation?

DR. KOPACK: Hi. This is Angela Kopack, the clinical reviewer. I think with the differences in the resistant and susceptible, the difference in efficacy, we wanted to see with the use of a different comparator, and I'll ask if anybody else that was involved with that wants to step in.

DR. KIM: Hi. This is Peter Kim, FDA. The recommendation was specifically to consider utilizing a first-line antibacterial as a comparator in Study 310.

DR. LEWIS: Just to clarify your response, Dr. Kim, my understanding is that amoxicillin/clavulanate is actually not first line but is considered an alternative therapy. So was the design of 310 consistent with the FDA's recommendation for an alternative comparator?

DR. KIM: We agree that amox/clav would not be considered first line as per IDSA guidelines.

DR. LEWIS: Okay. Thank you

My second question has to do with a specific

comment by Dr. Kopack regarding the ordering of noninferiority testing for Study 310. If I understood correctly, the agency recommended that the highest level of a hierarchical testing in 310 start with noninferiority testing in the micro-MITT susceptible population, and the sponsor selected to have their first order of testing for the combined population. If I understand the results correctly, ordering of the testing wouldn't actually have made a difference.

Is that correct?

DR. KOPACK: I'm going to ask my statistical colleagues to help out on this one.

DR. LI: This is Xianbin Li. Yes, there's no difference because if we start from step 2, we would get the same results. We were not interested in the first step. That's why we did not recommend the testing in step 1.

DR. BADEN: Dr. Rubin, did you have something to add?

DR. RUBIN: Yes. This is Dan Rubin. I'm a secondary statistical reviewer for the FDA for this

application.

Could you please display FDA main slide 24.

DR. BADEN: And talk into the microphone so we can all hear you. Thank you.

DR. RUBIN: Thank you, Dr. Lewis. You're correct that before unblinding results in Trial 310, the FDA had recommended the micro-MITTS be assessed for noninferiority in the first level of the hierarchy. The applicant chose to move forward without taking that recommendation. We do find noninferiority in the micro-MITT challenging to interpret just because patients can have infections due to pathogens that are resistant to the comparator, but as you had discussed, and as my colleague Dr. Li had noted, in the first level of the hierarchical testing, the analysis was able to pass through that first gate, and therefore to conduct an analysis of noninferiority. And the micro-MITT as to the second level, we did consider to have the same alpha protection and rigor as a prespecified primary analysis, so it would not have made a difference had the order been changed.

Thank you.

DR. LEWIS: Thank you very much. I have nothing else.

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

DR. GREEN: Well, actually it was to Dr. Lewis' first question -- Mike Green -- so it's back to Dr. Kim. In fact, if we look at current recommendations, neither comparator for either 301 or 310 is a currently first-line recommended treatment for urinary tract infection. What should the applicant test it against, or do we need new ideas, guidelines, because we're not recommending amox/clav, and cipro is no longer recommended more on the basis of adverse events than on the basis of efficacy? Thank you.

DR. KIM: Peter Kim, FDA, and thank you for the question, Dr. Green. Certainly, new ideas, say treatment guidelines, would be welcomed. We have recommended for consideration nitrofurantoin as an option as a comparator in uUTI trials as of recently.

DR. BADEN: Thank you, and that's always going to be a moving target.

Follow on? No. Then, Dr. Walker.

DR. WALKER: Thank you, Dr. Baden. Dr. Roblena Walker. I want to switch gears here for a second. Regardless of how we look on the outside, we all have similar features on the inside; however, when it comes to urinary health, we know that people of color have a higher prevalence of that. So that kind of leads me to this very robust study where you have 5900 of participants in it, and then it dwindles down.

I'm just curious as to why the population was so low amongst African Americans when we know that in the U.S., African American women are second to American Indian, and then what considerations were taken, if any, among the population for those who were going through perimenopause, or menopause, or postmenopause? And then amongst that population, how many of those patients may have already had some type of healthcare-related UTI? Thank you.

DR. GOPINATH: Dr. Kim, you want to take

this?

DR. KIM: This is Peter Kim, FDA. Thank you for the multi-pronged question. I think as far as demographics, I think we'd have to refer you back to the sponsor as far as the conduct of the trial. Certainly, we would encourage diversity in clinical trials. Depending on where the trials are conducted, that may or may not occur. I'm sorry. There were a number of other components to your question.

DR. WALKER: I was just curious as to, amongst the population, what factors, if any, were considered amongst the population, if they were going through perimenopause, menopause, or postmenopause, and if there were any individuals within those demographics that may have acquired a healthcare-related UTI; just curious.

DR. KIM: This is Peter Kim, FDA. I think for that I'd have to refer you back to the sponsor to answer that.

DR. WALKER: Thank you.

DR. BADEN: So what I will do is, not now,

for the sponsor to take note of these questions, and then when we come back to more Q&A with you, please respond.

Dr. Green, do you have another question?

DR. GREEN: I do, although it may sound familiar. This is either to Dr. Kopack, or if Dr. Kim wants to do it. From the point of view of the agency, I wonder if you could share your perspective on the importance of persistence at I guess it's the end-of-treatment culture; again, trying to understand your side of this equation. Thank you.

DR. KIM: Peter Kim, FDA, and thank you, Dr. Green, for the question. We certainly acknowledge that what we may ask for in a clinical trial may be different from what may be considered in clinical practice. From our perspective, microbiologic outcome is an important component of the composite endpoint; it's objective as well. There has been literature published noting the importance of treating bacteriuria in pregnant women and also in treating bacteriuria in renal

transplant patients.

We also delved deeper into this consideration, looking at not specifically uncomplicated UTI but complicated UTI trials that were submitted to the FDA between 2011 and 2019, a total of 13 randomized-controlled trials, and attempted to answer this question further. And we found that individuals who had discordant response, that is clinical cure but microbiologic failure, actually had a higher incidence of clinical failure the longer the late follow-up visit occurred. So we consider microbiologic response an important component to the composite; and again, we acknowledge that's in complicated UTI and not uUTI.

DR. BADEN: We have a couple of follow-ups. I'll go to Dr. Joniak, first, and then I will do my follow-up.

DR. JONIAK-GRANT: Thank you.

Dr. Joniak-Grant. Speaking to that point about consequences, is there data out there that can tell us what are potential consequences, short term and long term, of a microbiologic failure without

clinical symptoms for patients? I'm thinking if there's chronic inflammation, what happens down the road. What are we talking about when we talk about the impact on patients for those disparate results?

DR. GOPINATH: Dr. Kim, you want to take that?

DR. KIM: There are a couple of instances where there's concern specifically related to pregnant women who have ongoing asymptomatic bacteria. There's literature to suggest that they have a higher risk of pyelonephritis, so more severe complicated urinary tract infection; then also in patients who have had a renal transplant, there is literature to suggest that if they have asymptomatic bacteriuria, they may be at increased risk for bacteremia, and then the additional understanding that we've developed related to complicated urinary tract infections.

DR. BADEN: Dr. Kim, thank you for expanding on that, and I think the issue of this endpoint is so important as we think about this.

Just from a design standpoint, I think one

has to be careful in the asymptomatic bacteria, to remove it from one group but not another. So either it's not viewed as a valid part of the endpoint, then you have to look at all your analyses without them, or it is viewed as part of the valid endpoint, and you've got to look at all your analyses with it. So I think the data having been shared over the last 4 hours speaks to how complicated development in the antimicrobial space is because of the number of moving parts and when kinetically you're aware of critical information.

Now, the issue of asymptomatic bacteria and the validity as part of the endpoint, I'm not sure that true asymptomatic bacteria is the same as post-infection treatment resolution, bacteria still present in the urine. So even though in pregnancy, and in certain kinds of orthopedic situations, we may worry about that complicating the condition, I'm not sure that applies, and I do wonder.

Henrietta, your comments were very provocative in that the probenecid may be changing the behavior of the thiopenem in the urine to

actually help eradicate a culture issue in terms of the pharmacodynamics that we're thinking about, which for me at least makes it complicated to really think through the biology because we're altering drug concentrations in spaces we're assessing.

I just say that because it further complicates, for me, understanding the endpoints presented and how do we integrate that into the overall efficacy assessment, given that we've seen a variety of analyses with or without the ASB, if I can use that acronym.

Dr. Farley, please comment, because to me this is central to how we think about these data and the genre of studies.

DR. FARLEY: Sure. John Farley for the agency, and I may not be able to meet that high expectation, Dr. Baden. What I do want to point out is a couple of things.

I think that the agency acknowledges that in uncomplicated urinary tract infection, the clinical implications of microbiologic persistence are not

well known and that, in fact, in clinical practice, most women are not recultured at the end of a treatment course, necessarily. What the agency is about is trial design meeting the standards of an adequate and well-controlled trial to establish substantial evidence of effectiveness; and in this setting, most of the trials that will be conducted will be noninferiority studies against an active comparator. That's largely due to patient acceptance.

I would note, however, that placebo-controlled trials remain acceptable to the agency in this space. They may not be acceptable to clinicians trying to implement the trial in the field, but in fact, for example, the cipro-resistant population in 301, one could consider that to be a putative placebo notwithstanding concentration of the drug, et cetera, which may give it some activity, even in the setting of resistance based on plasma measurements.

For the noninferiority margin justification

for uncomplicated urinary tract infections, that justification is based on the Asbach and Ferry studies. That is in the appendices of our uncomplicated UTI guidance, which is cited in Dr. Kim's references. In both of those studies, success was based on both clinical response, as well as microbiologic response. So the trials were designed predefining clinical success in the trial as both microbiologic response, as well as clinical response.

If you don't meet both, you are not a success in the trial, and from the agency's interpretation, microbiologic persistence meets the definition of a failure in the clinical trial. That's been the best we can do in this situation, and we acknowledge that we don't fully understand the clinical implications of microbiologic persistence, but nonetheless, patients with microbiologic persistence are in fact failures in the clinical trial. Thanks.

DR. BADEN: Thank you, Dr. Farley. I think it's important to understand the definitions that

we as a community have agreed upon because they're the best definitions we have, and they make sense at some level; so thank you for clarifying.

I think Dr. Chandra has a follow-on comment as well.

DR. CHANDRA: Dr. Kim, I just wanted to confirm that there are no studies in uncomplicated UTI in non-pregnant or non-immunocompromised patients where we have seen any implication, long-term implication, of this discordant result in terms of clinical resolution of symptoms but persistent bacteriuria.

DR. KIM: This is Peter Kim. So is that a question or is that a statement?

DR. CHANDRA: Just to confirm, there are no studies that you're aware of in non-pregnant and non-immunocompromised patients with uncomplicated malaria [sic - UTI], where we have seen that discordant results have clinical implication long term?

DR. KIM: This is true.

DR. CHANDRA: Thanks. And the other

question was regarding the probenecid levels. I think one of the slides that sponsor had shown in urinary concentrations, it seemed like the levels were about 400 to 500 times higher than the MICs. Is that your understanding as well? And then, what is the implication of probenecid in that sense, in that context? Thanks.

DR. ABODAKPI: Hi. Thanks for your question. This is Henrietta Abodakpi. It's not sufficiently clear how much we can extrapolate from the observation that sulopenem urine concentrations exceed MIC by however many fold. Conventional wisdom is that for the effective treatment of uUTIs, you want to use a drug that's efficiently cleared in urine so that you can concentrate the drug in urine, but there's still a decent amount of uncertainty as far as urine-specific PK/PD parameters.

So it's not clear what fold exposure that target would be. We still view it within the lens of conventional PK/PD PTA analyses, and through that lens, we evaluated the probability of

achieving the in vitro PK/PD targets in both urine and plasma given the uncertainties about whether or not looking at urine exclusively would be sufficient for a uUTI indication, but ultimately, we certainly can't argue the observation that urine exposures are higher than the MIC90. It's hard to make any sort of definitive statement or conclusion about the the overall implications for efficacy.

DR. CHANDRA: Thank you.

DR. BADEN: Thank you.

Dr. Hunsberger?

DR. HUNSBERGER: So this discussion is mostly around my question, and maybe it's already been answered, but I found slide 32 very revealing to me because it really demonstrates how the clinical endpoint is really consistent across studies, but it's the microbiologic endpoint that's really flipping, and especially with the comparator arm. So I just find that the clinical endpoint is so much more stable, and that makes me want to believe that more. So I think this discussion where you're trying to get at what's going on, do

we believe that, or is that just noise since it's flipping so much?

That also makes me want to ask, did you look at that by age, make this figure by age? Because I think one of the things we're talking about is, is there a subgroup that you know more about, and maybe age is related to have you had a lot more infections. So have you done this figure by age so that we can see if it's stable for clinical but less stable for the microbiologic?

DR. LI: This is Xianbin Li. We have not looked at the three outcomes by age. We've only looked at the outcome for overall response.

DR. BADEN: And I think Dr. Walker was getting at the age issue and menopause, which changes a UTI risk substantially, and the biology of the flora.

DR. HUNSBERGER: Thank you.

DR. BADEN: Dr. Lewis?

DR. LEWIS: I'm struggling a little bit with aligning some of the ways we look at populations or subpopulations, clinical context, and the study

design. I just want to think about three different populations defined by whether or not the isolate is known to be resistant to a first-line therapy -- using the term specifically -- known to be sensitive to a first-line therapy, or the patient is in a setting where we don't know if they have an isolate or whether it's resistant.

For the group in which we know the isolate is resistant to a first-line agent, it seems to me it's a pretty clear-cut unmet need, and the trials partially inform the efficacy of the proposed agents. In the setting in which we don't yet know the isolate's characteristic, or frankly if a culture will grow -- which is actually the most common setting in my clinical practice, to put this into perspective -- the estimates of efficacy for the primary endpoint in that population, whether you call it empiric therapy or partially informed therapy -- like the patient had an ESBL last time they were in your institution -- that estimate is actually very informative to that clinical practice because although you don't know which subpopulation

the patient will ultimately fall into, you have to make an estimate based on the available information. And it's a heterogeneous population, and the utility of your treatment selection is based on an average of efficacy over culture positive, culture negative, culture-positive resistant, and culture-positive sensitive patients. That's my preamble.

The place that I would like some clarification from our regulatory colleagues is the agency's emphasis on demonstrating noninferiority on the micro-MITT susceptible population, where I'm thinking of susceptible to an accepted first-line agent. My confusion, or lack of understanding, is that, to me, that seems like a population that does not have an unmet need; and therefore I'd like to understand better the agency's emphasis on the need to demonstrate noninferiority on this population that does not have an unmet need.

DR. FARLEY: Thanks, Dr. Lewis, and as usual, a thoughtful question. Development programs are long and take a long time, and I think at the

time the advice was provided to the applicant, it appeared that the applicant was seeking a niche for this product as a first-line agent, something that one would use similar to nitrofurantoin, and I think that that was the spirit in which the advice was provided.

From a clinical trial design point of view, for a noninferiority study, we all acknowledge that the pathogen that the patient has needs to be susceptible to the comparator; so that's something that's kind of non-negotiable from a clinical trial design point of view and the principles of noninferiority study design. I think that that was the context in which the advice was provided.

We'll get more into that this afternoon because, obviously, this sort of goes to the first discussion question, and I'll provide some clarity on the record later. But I think that's the answer to your question; that development programs take place over a long period of time, and we understood, and we actually still understand, from the applicant's application and the way they phrase

the indication in their new drug application, that they are seeking a use of the product that appears to be as a first-line agent. Thanks.

DR. LEWIS: Thank you. Nothing more.

DR. BADEN: So I have a follow-on to Dr. Lewis, but I will save that for a discussion later about that second population, which may be the money shot.

I think we have time for one or two more before we go to lunch, and then we'll continue the discussion after lunch.

Dr. Perez?

DR. PEREZ: Thank you. Federico Perez from the Cleveland VA. This is a question for Dr. Sheikh. Thank you for your insightful presentation on the microbiological aspects of these trials. In both Trials 301 and 302, it appears that the efficacy of sulopenem drops from 60 percent in ciprofloxacin susceptible to 48-47 percent in ciprofloxacin-resistant population. I'm referring to slides 31 and 41. And yet in your discussion, you were very clear

that the activity is similar in vitro between fluoroquinolone-resistant and fluoroquinolone-susceptible strains, and that the drug sulopenem is active against the ESBLs in these isolates.

So I'm wondering if there is still room for some microbiological basis for this discrepancy and, in particular, whether *Klebsiella* species that are fluoroquinolone resistant may be playing a role. And I'm thinking this is a genus and species where non-beta-lactamase factors like expression of efflux pumps and mutations in outer membrane proteins are very important in providing cross-resistance between fluoroquinolones and carbapenems, et cetera. Thank you.

DR. SHEIKH: Thank you, Dr. Perez. This is Jalal Sheikh from FDA. So excellent questions, and there are a lot of plausible explanations. And you are asking mainly for micro-MITTS populations in Trial 301?

DR. PEREZ: The resistant, MITTR.

DR. SHEIKH: Oh. Micro-MITTR population in Trial 301, right?

DR. PEREZ: Yes, and also in Trial 302. If we go to slide 41, there is a group, and there's one column cipro susceptible and another column cipro resistant, and there's a discrepancy between 62 overall response versus 47, kind of mirroring those same numbers that we see for Trial 301 in the MITTR.

DR. SHEIKH: Yes. To answer your questions, add to your comment, there is a difference between *E. coli* and *Klebsiella pneumoniae*, and we know that *Klebsiella pneumoniae*, in my presentation, I have shown that *Klebsiella pneumoniae* MIC values are higher than *E. coli*, but we are not sure that this is driven by either *E. coli* or *Klebsiella pneumoniae* because almost 84 percent of the isolates belong to *E. coli*, and probably 6 to 7, or maybe 8 percent isolates are *Klebsiella pneumoniae*.

So I don't think that this is driven by *Klebsiella pneumoniae*, but I defer to the applicant if they have any additional thoughts on that.

DR. PEREZ: Thank you.

DR. BADEN: Another issue for the applicant

to consider in the post-lunch discussion time.

So it's now 12:37. We will break for lunch. We'll reconvene again in this room at 1:35 p.m. Eastern Time. Please take any personal belongings you may want with you at this time. Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during the lunch break. Additionally, you should plan to reconvene around 1:30 to ensure you're seated, and we reconvene at 1:35.

In the afternoon, we will have continued discussion with both the applicant and the agency, as there are many more questions I know committee members have. We're now at lunch.

(Whereupon, at 12:38 p.m., a lunch recess was taken, and meeting resumed at 1:35 p.m.)

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

(1:35 p.m.)

Clarifying Questions (continued)

DR. BADEN: It's 1:35, and we shall resume. We have 10 minutes for continued Q&A, then we have the open public hearing segment at 1:45. When that concludes, we'll resume with clarifying questions for both the agency and the applicant.

I think, Dr. Patel, you had a question before the break for the agency.

DR. PATEL: Yes. If they could pull up slide 59. I think before the morning break, one of the items of concern was the widespread use of sulopenem and the potential for blowing out all of the other carbapenems. I think this slide gets at the point the MICs are somewhat related, but this right here I think demonstrates related isolates that are naive to sulopenem. But I wasn't sure if the sponsor had provided any data where if you induce resistance in these isolates, what happens to the MICs of the other carbapenems; and I guess that might be a question for the applicant to

address when they come back.

DR. SHEIKH: Thank you, Dr. Patel. This is Jalal Sheikh, clinical microbiology reviewer at FDA. In this slide, we're comparing the in vitro MIC 50/90 values compared to other FDA-approved carbapenems, and your question is whether there is any data on inducible resistance.

In vitro, if we take a look, the mutation frequency was evaluated in vitro 1 times 10 to the minus 8, and in serial passage mutation when you have 10 or more serial passages, it can generate the mutations not only against sulopenem but cross-resistant to other carbapenems.

DR. PATEL: Okay, so that data exists. To what extent does the MIC travel with the other carbapenems? I think we always worry about how it will affect the other carbapenems if it's overused. So are we talking about like a 1-log change or a 1-tube dilution?

DR. SHEIKH: We don't have any specific data, but since there's the possibility of having cross-resistance, it could be any dilution. We

don't know exactly, but I defer to the applicant if they have any insights on this kind of data.

DR. BADEN: So I think at this point, we can have our questions to both the agency and the applicant. So, Dr. Dunne, from the applicant's standpoint, the question that's been raised is if resistance is induced by sulopenem, would that affect the other beta-lactams, particularly the carbapenems? Is that likely to occur?

DR. DUNNE: I think it's probably likely to occur. They're all working the same way, and when we did the serial passage experiments, eventually the organisms are resistant to the -- that works either way, if induced with ertapenem, you'd have sulopenem. It's the same. It's going to be the same thing.

DR. BADEN: Same mechanism.

DR. DUNNE: It's still hard to get that, the frequency, 1 to 10 to the 8th. You have to do 15 serial pass experiments to see some problems, so it's pretty uncommon and hard to do that. But yes, that could happen, and I'd assume that it's going

to be a class effect if that occurs.

DR. BADEN: Okay. Thank you.

Dr. Green, you have a follow-on?

DR. GREEN: Yes, it's a quick follow-on. Did you identify what the mechanism was that you selected for with serial passing? Was that a loss of a porin? Was it a development of a beta-lactamase?

DR. DUNNE: That is a good question. We have that experiment on the laptop. Let me look for you. I'll get back to you. It was a complicated experiment, you can imagine, so I don't remember exactly. I don't want to give you the wrong answer.

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

DR. CHANDRA: Just a follow-on question.

DR. BADEN: Please use your microphone.

DR. CHANDRA: How many folds MIC?

DR. DUNNE: It was 2-fold, I believe, in that experiment.

DR. SHEIKH: This is Jalal Sheikh again from

FDA. It could be when you do the serial passage mutations, based on how many days you are doing, it could be 2-fold from several folds, and it also depends on what kind of isolates you are using. *E. coli* could be different from *Klebsiella pneumoniae* or other different species.

DR. CHANDRA: Sorry. My question was, with sulopenem, in the experiment, how much did it increase?

DR. SHEIKH: It usually starts with at least, I should say, 2-fold, but it could be more in different species.

DR. CHANDRA: Thank you.

DR. BADEN: I have a short question since we have 4 minutes, and this is a pharmacology question to both the agency, Henrietta, and applicant

Henrietta, in your comments, you raised the issue that particularly the oral dosing, I got the sense that you're not convinced that the oral dosing has been completely worked out. Do you think it's being underdosed?

DR. ABODAKPI: Thanks for the question.

This is Henrietta Abodakpi. Yes, that is a challenging question. There isn't sufficient data to be able to definitively state whether or not underdosing is a concern here, especially since sulopenem did demonstrate noninferiority against the comparator. There aren't any dose-ranging studies that have been conducted to further explore that possibility, and given the complexities of sulopenem's PK/PD and the various knowledge gaps and uncertainties that I pointed out in the studies that have been conducted to date, it's hard to say, at least strictly from a PK/PD perspective.

DR. BADEN: Thank you.

Dr. Dunne, are you satisfied with the dosimetry, and what are your thoughts on optimizing the oral dose?

DR. DUNNE: I totally understand. I think in the urine, we have like a ton of drug. I don't think doubling the dose in the urine would really help us. There's a lot in there. It's covered for the whole time, whether it's AUC over MIC, or time over MIC, or whatever, that I don't think -- I

think the question that may come up -- and this is related to the cUTI question and what are we doing there -- is the plasma exposures where they need to be? That is a completely valid question.

I think when we do our target attainment, in the urine, it's the 50 percent and the 40 percent for 1 log reduction, and we've got more than enough in the urine. In the plasma, it's like right on the bubble. If you do *E. coli* with either fed or fasted in the plasma, I think we're pretty good. I think you'll get at least 1 log reduction. The *Klebsiellas* drift, another like MIC, other dilution up. So I think in the fed state, those will be covered. In the fasted state, like the MIC85, it's covered; it's not perfect. But that's for the oral, which that's not a claim that we're doing, but I'm drifting into where could this be going.

In the fed state, I think it's probably going to be ok. Most of the organisms are really *E. coli*, *Klebsiella*, and a handful of other guys. The urine, I think we have way more drug than we need. You raised your question about the

probenecid, too. We don't need the probenecid, really, for the urine thing. I think that's a good point. We were doing that to develop it in case we wanted to have a systemic exposure in the plasma; then I think we do need to have that because compliance with what would have to be a QID regimen would be really hard. That's what we were thinking about.

I think it actually works just fine for the UTI the way it comes together. It helps actually absorb more drug out of the GI tract. I do not understand exactly what that is but, in fact, the bioavailability is higher when we use the probenecid in that blend. So there's some kind of magical thing going on there, but that I think is why the probenecid is useful. Again, we thought about it more for the systemic infections rather than for the urine infections.

Open Public Hearing

DR. BADEN: Thank you.

The question was well placed because we're at 1:45, so we're going to move to the open public

hearing session. When this is completed, we'll come back to the clarifying questions. So we will now begin the open public hearing session.

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 relationship that you may have with the applicant. For example, the financial information may include the applicant's payment of your travel, lodging, or other expenses in connection with your participation in the 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 you 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 will be a variety of opinions. One of our goals for 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.

Speaker number 1, please unmute yourself online and introduce yourself. Please state your name and any organization you're representing for the record. You have 10 minutes. Speaker number 1, please begin.

DR. AHMAD: Good afternoon. I'm Neha Ahmad,

a research fellow speaking on behalf of Public Citizen's Health Research Group. We don't have any financial conflicts of interest. The committee today is tasked with discussing the benefits and the risks of the use of the oral drug, sulopenem, for uncomplicated UTIs in adult women. Increasing rates of antimicrobial resistance in many U.S. communities do highlight the need for novel therapies to treat UTIs.

From the data presented, including Trials 301 and 310, oral sulopenem seems to have efficacy in treating some uncomplicated UTIs when isolate is susceptible; however, the potential for broad application of the medication for empiric treatment of uncomplicated UTIs comes with a significant risk of increasing antimicrobial resistance, as the committee has been discussing this morning

Although antimicrobial resistance is on the rise, it's relatively rare that urinary isolates for community-acquired infections are resistant to all existing first-line treatments for uncomplicated UTIs. In a recent retrospective

analysis by Kay [ph] and others, researchers found that while the U.S. resistance rate to fluoroquinolones and trimethoprim sulfamethoxazole was significant, around 21 percent and 25 percent, respectively, the resistance rate to nitrofurantoin was only 3.8 percent.

Furthermore, in this sample, which evaluated over 1.5 million *E. coli* urinary isolates from outpatients between 2011 and 2019, only 3.8 percent of isolates were resistant to all three first-line agents or were ESBL producers. In other words, if clinicians work in communities where urinary isolates are often resistant to one class of medication, it does not therefore imply that they are resistant to all first-line classes of medication.

Given their cross-reactivity with carbapenems, usage of oral penems for uncomplicated UTIs does hold the risk of furthering antimicrobial resistance to an important class of medications that is the mainstay of treatment for multidrug-resistant organisms. Furthermore, there

is insufficient evidence that oral sulopenem is superior to existing first-line therapies to treat uncomplicated UTIs.

In Trial 301, oral sulopenem failed to demonstrate noninferiority to ciprofloxacin in populations that were sensitive to ciprofloxacin. Although in Trial 310, sulopenem successfully compared to augmentin, as we've discussed, augmentin is not a first-line medication for the treatment of UTIs and in meta-analyses has demonstrated inferiority to therapies such as ciprofloxacin and trimethoprim sulfamethoxazole.

If sulopenem is approved for uncomplicated UTIs, there is a considerable risk that it will be used to treat UTIs that could be successfully treated with other drugs and that it would be used off label either as a first-line treatment for complicated UTIs or as stepdown therapy following IV therapy of complicated UTIs.

The applicant suggested this morning that insurance prior authorization may be an adequate barrier to widespread usage of the drug; however,

we are concerned that this strategy, even in combination with language and the labeling of the drug and communication with prescribers, may be insufficient to mitigate the risk of increasing antimicrobial resistance. Furthermore, judicious regulation that would prevent overutilization of this drug is the appropriate purview of the FDA and not of insurance companies.

If the drug is approved, we urge the committee to advise the FDA to require postmarket studies to assess the frequency of off-label use of sulopenem, the frequency of its use to treat uncomplicated UTIs that could be successfully treated with other drugs, and any changes in the antimicrobial resistance patterns for uncomplicated UTIs and communities where oral sulopenem may be widely prescribed. If postmarket studies demonstrate the need for additional and more robust risk management strategies, such strategies should be promptly implemented. Thank you for your time and attention.

DR. BADEN: Speaker number 1, thank you for

your comments.

Speaker number 2, please step up to the podium and introduce yourself. Please state your name and any organization you're representing for the record. You have 5 minutes.

DR. ZUCKERMAN: Thank you. I'm Dr. Diana Zuckerman, president of the National Center for Health Research. Our center is a nonprofit, public health think-tank that scrutinizes the safety and effectiveness of medical products, and we don't accept funding from any companies or entities that make those products, so we have no conflicts of interest. I just want to say this is my first in-person advisory committee meeting since 2020.

Thank you for the opportunity to share my views today, and thanks for the important work of this advisory committee. My expertise is based on my current work, as well as my experience and postdoctoral training in epidemiology and public health, and a former faculty member and researcher at Yale and Harvard. I've also previously served as professional staff in the U.S. Congress, HHS,

and the White House. I'm a founding board member of the Alliance for a Stronger FDA, which educates Congress about the need to financially support the essential work of the FDA.

We all know antibiotic resistance is a serious problem, so we take this FDA meeting very seriously. As a woman, I'm very familiar with UTIs, and I know they're very common and can interfere with daily life; however, UTIs are a acute illness with very obvious symptoms, so research on a medication for UTIs should focus on patient-centered symptoms and outcomes, not the bacteria in the urine of asymptomatic women who have already been treated, and a composite measure of both clinical and bacterial measures seems to me extremely inappropriate from a scientific point of view.

FDA usually relies on surrogate endpoints when the clinical endpoint would take years to study, so surrogate endpoints are a way to complete studies more quickly, such as a surrogate endpoint that predicts if a drug reduces the chance of

long-term disability or death. But since UTI is an acute illness, we don't need a surrogate endpoint for an uncomplicated UTI. All that matters is that the infection does not progress and the symptoms go away. We know if the UTI symptoms have disappeared, or not, in a week, or at most, a few weeks.

Panel members have mentioned that there can be bacteria in the urine of asymptomatic women that do not affect a woman's health. In fact, research shows that giving antibiotics to asymptomatic women can result in more symptomatic urinary tract infections. Bacteria in urine may show which patients are more likely to have a recurrence of a UTI, but it's not proven to predict whether a particular antibiotic makes a recurrence less likely because some patients are just more likely to have a recurrence than others regardless of the treatment they get.

Most important, an uncomplicated UTI is not life threatening. If antibiotic treatment is delayed for a week or two, it will still be

successful. Meanwhile, there are ways that women can deal with this, drinking plenty of fluids, avoiding alcohol, swimming and baths, and other behavior changes that can be helpful. And in some cases, UTIs even go away by themselves. And of course, as you know, there are other antibiotic choices for patients like those studied in these trials, so there's no urgent need to approve a new treatment that hasn't been adequately proven to have long-term benefits compared to amoxicillin or cipro.

Doctors don't order urine cultures for patients whose symptoms go away after treatment, as has been stated, so measuring urine cultures has no relevance to the practice of medicine in the real world when it's being measured after treatment. As we all know, cipro can have serious side effects, so an alternative to cipro would be welcomed if it were as effective as cipro, but safer.

But the serious risks of cipro were not known right away when it was first approved. It was found out years later after many, many women

had taken the drug, or people had taken the drug, so the studies that we look at today are much too small and much too short term to determine what rare, serious, long-term complications may be, and whether the drug really is as safe as cipro. We know that it is more likely to have side effects that are as unpleasant as UTI symptoms.

In summary, as many of you have stated, there are problems with these studies. The patients studied by the sponsors were not necessarily the patients who might possibly be most likely to benefit from these drugs. If the drug is intended for those patients who have had multiple UTIs, it should have been studied on those patients. These different patient characteristics mean we cannot know from the studies presented today whether this drug would be safe and effective in patients who would most need it as an alternative to existing antibiotics.

Thank you very much for the opportunity to speak today, and I'd be happy to answer any questions. And I just want to add, this is not a

first-line drug. Thank you.

Clarifying Questions (continued)

DR. BADEN: Thank you.

The open public hearing portion of this meeting has now concluded and we'll no longer take comments from the audience. We will resume clarifying questions until 2:45. We'll see how the conversation goes. What I'd ask panel members, we can ask questions of both the agency and the applicant, so we'll have one set of questions for both. We need to specify who we wish to respond.

Looking at the list, I will start with the first question, and then I see, Dr. Perez, you're on the list, and if others, please indicate. This is to Dr. Kopack, but Dr. Dunne may want to respond as well. You mentioned the 302 and 303 studies, systemic studies of complicated UTI and intra-abdominal infection, and they didn't work. Isn't that concerning about the overall activity of this agent for these serious infections?

DR. KOPACK: Angela Kopack from the FDA. Thank you for that question. I would say the

applicant is not seeking those indications. Also, turning that back to the advisory committee, that's one of the reasons we've called you all here today, and we're looking forward to hearing the discussion and your thoughts.

DR. BADEN: I can try to provoke you to respond, but right back at us.

Dr. Dunne, we're being asked to evaluate the efficacy activity for uncomplicated UTI, yet there are two large data sets, complicated UTI and complicated intra-abdominal infection, where efficacy was not shown. Help me think through how those data fit into the uncomplicated UTI, and how do we weigh those data as we consider the question before us?

DR. DUNNE: Sure, I understand. Certainly, complicated UTI is a head scratcher really because that is the same place we're trying to go with uncomplicated UTI, so we do need to address that at some point. I think it's the same theme for both the 302 study and the 301 study. There was a difference in the rate of, we'll call it

symptomatic bacterial -- I know it's a little controversial right now -- in patients who got cipro either in 301 or 302, so at least there's a common theme. That was the reason it didn't work in both of those.

I think if we'd used amox/clav as the stepdown agent in 302, it probably would have shown noninferiority because in that little subset we had, that was a 93 percent powered subset and we showed reasonable efficacy. You could imagine that we would repeat that 302 study again just like we did in the uUTI program, and I'd be optimistic that we could show that it would work. It would not take away that question about whether cipro as a stepdown is better than sulopenem for a stepdown. I totally agree with that, and I don't think there's anything we can do about that. That's just the nature of the way cipro works. It's different than beta-lactams. So that one, I think we kind of touched on that in some detail.

Intra-abdominal infection is a really hairy kind of indication, to be honest with you. The

patients that are in that study are highly variable. These are people, they're almost all getting some kind of surgery. They have literally complicated intra-abdominal processes that are hard to control across the arms, so at the end of the day, that study was not noninferior, and part of the problem was our fault.

The first time we ran the data, there were programming errors. That's why you saw it at minus 12, and then we redid it at minus 10. That is a big problem. You can't just do that, but we felt the need to do that. There were clearly programming errors that were missing endpoints that we did not see until I looked at the top-line data and said, "Holy cow. This is not working." So that's why there are two analyses in there but, oh well, that's not the way it works. We tried to do it, and at the end of the day, we're still minus 10.3.

The organisms that are involved in intra-abdominal are a little different than uUTI. They're a very different panel of organisms. The

E. coli tends to be UPEC in cUTI and in UTI, but it's a completely different bunch of ETEC, other *E. coli's* there. So the organisms are kind of different. MICs are similar, but the pathophysiology is kind of different.

So while we did not meet noninferiority in intra-abdominal studies, I don't think it necessarily says that it's not working. It was pretty close, but it was not noninferior -- I don't try to make that go away -- but I don't know that there's anything in the intra-abdominal program which says, "Oh, this isn't going to work for UTI." They're just different indications. They're hard things to study. Yes.

DR. BADEN: And I think from your earlier comment, this is where the systemic dosimetry may make a difference.

DR. DUNNE: You know, it could really, and I think for complicated UTI, given the organisms that we're looking at, we're pretty close on the IV and oral doses that we picked, and there it could go up a little bit more. I'm not disagreeing that it

couldn't. For intra-abdominal, it's a totally different deal because the tissue penetration into all these infected spaces is really complicated. There were a handful of patients. I think some of the difference ended up being in the complicated intra-abdominal. The ertapenem people had a little bit better activity in a handful of the abscesses. There were certain patients that had abscess that did a little better -- if you had an abscess, you did a little better on the erta arm than you did on the sulo arm.

I don't know what to make of that. I don't want to read into it because it was kind of a small end, but that might be what you're getting at. There could be things we don't know yet about the dose that we used in the complicated intra-abdominal infection that wasn't quite right for the tissue penetration that we needed.

DR. BADEN: Thank you.

Dr. Perez? New question.

DR. PEREZ: Thank you. Federico Perez at Cleveland VA. There's been a quest to develop an

oral carbapenem for decades, and that was part of the introduction to this drug. There are countries, however, like Japan, where there are examples of oral penems to be more precise, and a question that I had is whether there is evidence of the impact that this has in the emergence of carbapenem resistance and whether there are any associations or any lessons that can be learned from the experience in countries like Japan. It's kind of outside of the material of this, but I wonder if that has been addressed by the sponsor or the agency. Thank you.

DR. SHEIKH: Thank you, Dr. Perez. This is a great question. This is Jalal Sheikh from FDA. To our knowledge, sulopenem has not been approved anywhere in the world, so there is no data of drug resistance available. We think if sulopenem is approved, one may presume that it could be used widely as empiric therapy. This is one of the reasons we are seeking advice from our AC members, those who are expert in this field, and I would like to defer to the applicant, Iterum, if they

have any additional thoughts on that issue for resistance development for oral sulopenem.

DR. DUNNE: Yes, it could definitely happen. I mean, I don't see how we could say that you cannot select for resistance. All antibiotics that work, select for resistance; that's the way the whole thing works. I think it is about using it in the right patient population.

What can we say? There are 40 million women that have a UTI every year. Five percent of those do not have an oral therapy. That's 5,000 women a day are getting UTIs because they have no oral therapy, but at some point, we've got to get in the game and we've got to do something for patients where there is not an option. So I think we need this on the market. There's clearly a problem for patients.

The judicious use piece is really hard for the sponsor to own. There are a lot of people involved in getting that right. We will not be marketing it for anything other than uncomplicated UTI. That's our plan. There's a whole series of

reasons for that. So we wouldn't be pushing it anywhere else, but we would be there to support if there's a medical need for it in another indication. We would be open to talking to people about doing that, looking into it, because I think it could play a role in other spaces if we study it properly. We do not have the data in cUTI that says you should use it for stepdown. I think it could work there, but we do not have data for that right now.

I think we will do things like the public speaker was saying. We will certainly do surveillance. We always do surveillance after we get approved; that's pretty standard. We're happy to work with people that want to work with our database to look for other populations of patients that might be best served by using this component, and then you can do some real-world evidence studies later. We can support those kinds of studies in the field down the road.

I think if we want to treat people that have resistant organisms, we need an antibiotic to do

that, and I think we're at that point now in UTI. I know we talked a lot about what is the right comparator agent. That was a hard conversation. It's really hard. We totally get the points that you were making when we were working this out, but the IDSA guidelines are like 13 years old. There's nothing to say. There's no new thing. That is a problem.

So when you go through the list of the first-line agents, they're not really that first line anymore. There's 20 percent resistance to all of those things, and you can't really use them, and they don't cover all the organisms. Nitrofurantoin is a nice drug, but that was 50 years ago. It doesn't cover *Klebsiella*. That's kind of a gap. So I'm not disagreeing with your choice for that, that's an option, but that was kind of problematic as well. We got to amox/clav because, yeah, that's what was left. That's what we're left with. That's why we're sitting here today because we don't have, obviously, super great oral agents to treat UTIs. So I'll stop there.

DR. BADEN: Thank you.

Dr. Farley, you have a follow-on.

DR. FARLEY: Thanks very much. Just to follow on to the resistance question, which I think was a very good one, for the committee, as Dr. Dunne alluded to, should the drug be approved, new antibacterials are generally required to conduct a U.S. surveillance study for five years after the introduction of the drug to the U.S. market to monitor for changes in susceptibility of relevant bacteria to the drug.

I think that the Japanese cases, we haven't had time to explore this yet, but information that the PMDA, which is the Japanese regulatory authority, could help us advise on the design of that monitoring. In addition, the FDA in parallel often works with CDC on monitoring resistance surveillance as new drugs are introduced; so just some additional information for the committee. Thanks.

DR. BADEN: Two comments on that. One is, it depends on the overall selective pressure in the

community, so I don't know offhand in Japan if they use antibiotics the way we do, which can affect the induction, amplification, and detection. But I don't think that's here or there. It's another system. We need to understand it.

The other piece, to both Dr. Farley and Dr. Dunne, I don't want to admonish, but I want to admonish you and our community on the diagnostics. How well are we diagnosing UTI? How well are we tracking susceptibility in our patients with the symptoms, and what can we do to help elevate this issue? I worry that we're flying relatively blind to what's going on with the uro flora and its resistance, and I don't know either of your thoughts on what we can do to elevate this because I think this will help guide rational therapy in the clinic. It comes to a payer issue.

DR. DUNNE: I can start, if you want.

DR. BADEN: Or maybe I can ask our CDC colleague, if we can get them to elevate. I know AMR is a big concern of the agency, but to me this is a collective field issue for all of us, not

anyone element in this room; and how do we raise this issue so we can actually know what is infecting our patients and know for the resistance profile?

DR. DUNNE: I'll start, but I know there are a lot of other people. We totally need better tools to diagnose what patients need. We need point-of-care diagnostics. It's easy to say that, but the whole diagnostics field, the business side of diagnostics is really, really hard. It is very difficult for companies to get out and have something that works, all the research they have to put into it, and they get it into the market, and then there's a competitor like six months later, and then they've got a big problem. This has been a problem as long as the 20 years that I've been working in pharma. This has been a problem all over the place, but we need to do a better job.

I think, just for UTI for a second, we can't be growing stuff and putting in an [indiscernible - 5:40:40] place. We've got to stop doing that because that's the whole problem here.

It's 3 days, you get the thing; that's done. We can't do that anymore. I don't have any biases, but there's a nanopore technology that people can look in and Google up that is really very interesting. They can sequence the entire urine in 3 hours, and you can find out if there are resistance genes in that urine that can say, "Okay. We don't see any TEM 1's, we don't see any of that, you're good; oh, we do see that." That would be really, really great. It's like 2 grand for the little gizmo, it plugs into a laptop, it's not complicated.

But the ability for somebody to actually get that out to all the -- that is really hard. That's going to take some time. That's I think, Dr. Baden, what you're talking about. We all need to work together on that to make it happen. We'd be happy to work with diagnostic companies if they wanted to do that; that would be fine. I think that's the way to go, but culturing a thing, we're done with that. We've got to move to something else. It's not working for uncomplicated UTI, and

there's no reason why we can't get to a better place at the end of the day.

DR. BADEN: I was provoking discussion.

Arjun, I succeeded in provoking you.

DR. SRINIVASAN: Well, I think it's an incredibly important issue that you're naming. Sorry. Yes, this is an incredibly important issue, but the bigger challenge -- and I think this is exactly what you're getting at, Lindsey, is the whole of society has to come to the table to call out this problem and address it; because right now, the biggest barrier to the development of these products, it's payment because the way that medicine is paid for in this country is you get a payment for an episode of care. So that's why if you're getting reimbursed X amount and there's a diagnostic that costs $400, no one's going to do it because you can't afford it. The patient can't afford it, the insurance company, it's a bundled payment.

So this is the real problem, and it's trying to figure out what's a new payment construct that

would allow some of these new technologies to be paid because I think we all agree they're fundamentally important, and they're only going to become even more important as resistance increases, and we need to know. We need to know at the point of care whether we think this therapy is likely to be effective. So it's incredibly important. There's no easy solution, and it is going to take everybody coming around the table to try to figure out what the solution is.

DR. BADEN: Thank you.

Dr. Green?

DR. GREEN: Thanks very much. This is a question to Dr. Dunne, and really, it's in follow-up to answers that Dr. Golden gave to my question this morning.

DR. DUNNE: Yes?

DR. GREEN: I'm wondering what you think is the feasibility of carrying out a study in the population, where she envisioned where this drug would have value and could be first line. Because I think if we had those data to discuss, we could

be having a very different conversation, really, and have the answers to our question. I know that you've been delayed in being able to come to this committee, and previously, I think in 2020, brought data forward.

So your thoughts on doing a study, and thinking about it, it was either over 65, or those with a history of recurrent infections, or those with a history of known infection with organisms resistant to, say, ciprofloxacin, which is where your drug succeeded. Thank you.

DR. DUNNE: Yes. No, that's interesting. I think it wouldn't have to be us. If someone can do studies in women over 65, that would not -- UTI is not a difficult area to study. I think that could be done. We could be supportive of those studies after the fact; that would be fine. I think the first failure kind of thing, you've got an antibiotic, you failed, and then you get a culture, and then you use -- you could do that, but I don't see that really as giving us any insight that we're not getting from these studies that we just did. I

think it's going to work in that setting.

The question is, what happens to people that are treated with the wrong antibiotic for 3 or 4 days? Does that count? Because that sounds bad to me. Just to treat those people after they failed, that's kind of tricky. I think if you're in a community, though, that is using this judiciously, you will develop a track record, a history of patients that get treated, what their organisms look like previously if you have that available, and we can have some real-world evidence about who might be the best population to get this upfront.

DR. GREEN: So my problem with your answer is that you're saying if we have approval, we'd certainly help other people maybe answer those questions, but our problem are the concerns with giving approval with the data that we have now with the unknowns and the concerns for resistance that can happen from the cross-resistance of sulopenem with the carbapenem class.

So again, I'm asking you and your company,

what is the feasibility rather than you thinking you would support someone else once you have the indication and the approval in pocket. This is our problem.

DR. DUNNE: Yes, sure.

DR. GREEN: I think we're obviously uncertain as to what we would do. We're not done with our thinking and our discussion today, as is the agency. Thank you.

DR. DUNNE: Those are phase 4 studies that we do. We do phase 4 studies all the time, actually. Sometimes they're post-approval commitments, sometimes we just choose to do them. That's totally reasonable.

DR. BADEN: Thank you.

We have more questions, but I know Dr. Dunne, from our morning discussion, you prepared several responses to many of the morning questions. So it'd be great to review those responses, and then we can come back to more questions.

DR. DUNNE: Yes. We've got five questions.

I think we captured them but, please, if I've got them wrong, let me know and we can redirect.

The first question was about assessment of the clinical response.

DR. BADEN: And I think you had slides. Are they going to pull up?

DR. DUNNE: Yes, we're going to have some slides.

DR. BADEN: So while you respond, they can pull up your slides.

DR. DUNNE: This is about the assessment of clinical response. We had the patient questionnaire and we had the investigators' response. This is the Patient Symptom Questionnaire that each patient filled out. You can't read any of that. This is basically the questions that were asked: pain , burning frequency, urgency; mild, moderate, severe; impact on daily activities; and they had to fill out that form with those kinds of questions. We sum them up. That is what went into the clinical response variable for the primary endpoint.

The investigators also were asked their impressions of response. If in discussion with the patient they felt that the pre-therapy signs and symptoms had resolved and that no antibiotics were required, that would be clinical success. Failure was any of those things in that box. So they had their own category of things that they also checked off; that was the investigator determined clinical response.

The 301 study, we were able to just quickly back there look at what happened when you look at the patient determined clinical success and the investigator determined clinical success, and you can see from the forest plots, they kind of line up on top of each other. So we've got slightly different data sets, but the messaging is pretty much the same. That was in the 301 study, and then in the 310 study, it's a similar story, really.

So I think it's important to get the perspective of the patient and the investigator. It's nice that they line up. I think the investigators know what they should be asking

about, and it tends to -- I think when the patients have their questionnaire, it also gets them thinking about things they can tell the investigators, so we like to to have both of those available.

Did that answer that question?

DR. JONIAK-GRANT: Yes, just one quick follow-up. Would every symptom that they previously reported have to be marked as resolved or no symptoms for it to be considered a clinical success?

DR. DUNNE: Yes, eventually that had to go away.

DR. JONIAK-GRANT: Okay.

DR. DUNNE: Yes, and we have like a zillion slides. The symptom scores go to zero. We rank them 0 to 5 depending on mild, moderate, severe, and then they all go away over time.

DR. JONIAK-GRANT: Thank you.

DR. DUNNE: You're welcome.

DR. CHANDRA: A clarifying question?

DR. DUNNE: Yes, Richa?

DR. BADEN: Please.

DR. CHANDRA: Just a clarifying question on that. For that endpoint, primary endpoint, whether it was patient response or investigator response.

DR. DUNNE: Patient. It was the patient response, yes, and the investigator response was supportive of that.

Okay. Super. So the next question was about adding the odds ratio for that ASB assessment. So we just flipped it around there, and the p-values are the same with the odds ratios, and we put a confidence interval on the odds ratio as well. That was for the 301 study, and then this is for the 310 study. It's pretty much the same message, but now you can see odds ratios.

Is that is that what you were looking for?

DR. CHANDRA: Yes.

DR. DUNNE: Let's go to the first one. We can do that.

DR. BADEN: Dr. Lewis, do you want to comment on this?

DR. LEWIS: So I have to admit, I'm confused

here. The percentage of clinical failure at day 28 appears -- oh, okay. I was looking for the asymptomatic bacteriuria as being a risk factor for clinical failure. What you've shown is the opposite odds ratio, the inverse, which is the protective effect of not having asymptomatic bacteriuria to protect you. So the limit I was looking for is 1 over 0.22, to show that the data are consistent up to at least a 4- or almost 5-fold increase in the risk of clinical failure, the outcome, with the presence of asymptomatic bacteriuria. I'm surprised you chose to show the opposite odds ratio.

DR. DUNNE: They just did it over lunch, so this is --

DR. LEWIS: I'm sorry?

DR. DUNNE: This is what the stats guys did over lunch.

DR. LEWIS: I'm surprised.

DR. DUNNE: Okay.

Alright. Then there was a question about overall success by BMI, and I think it looks pretty

similar by different groupings of BMI, a little better in the R area because of reasons we don't understand, but the BMI didn't really throw off the outcomes in any of those different groups.

Then there was a question about enrollment of African American patients. This is from the 301 study. Half of this study was in the U.S. You can see half of it was ex-U.S., so we see the African American enrollment is about 10 percent in this study. Then in the 310 study, this was all in the U.S., and I think African American enrollment is higher there, about 16 percent. That's roughly in line with the demographics that we look for. Normally, it's a little higher than -- there's a study recently looking at studies in general. About 8 percent of studies that get submitted to FDA have African Americans, but this is, I think, in the right ballpark.

Did that address part of your question?

DR. WALKER: Dr. Walker. It does, but I think I was more concerned about how you went about gathering these populations. What part of the

U.S., what region within the U.S. was this study done in?

DR. DUNNE: There were like 50 centers all over the country.

DR. WALKER: All over the country.

DR. DUNNE: Yes, it's pretty much spread out.

DR. WALKER: Okay.

DR. DUNNE: We are somewhat dependent on centers that do these studies. They're not everywhere; they're places where people do studies. But it's north U.S., south U.S., kind of of similar distributions.

DR. WALKER: Perfect. Then my follow-up to that was, within these particular demographics, did you all look at perimenopausal and postmenopausal?

DR. DUNNE: Okay. I have a slide on it that may get you closer to that. We didn't ask a specific question about menopause; that was not in -- so all we can give you is outcome by age. It's not exactly what you're looking for but it's the closest that we could come up with, and that's

this one here.

Again, you saw a little bit of this before, but now we've broken it down to 75, 65, 60, 55; it's not a specific menopause question, but I think older women do seem to do a little better when they got this. I think that's because they had more infections over time and they had more resistant pathogens. I'm not sure it's a menopause related issue, but it tracks with that.

Does that help? It's the best we could do over the lunch kind of thing.

DR. WALKER: Thank you. I asked the question personally because I'm going through peri right now.

DR. DUNNE: Yeah, okay. There you go.

DR. WALKER: A personal point of privilege. Thank you.

DR. DUNNE: No problem.

Then this is the same thing. This ends up being the same question. There was a question about clinical and micro success, and a question about age. I'm not sure we got this exactly right,

but this is the clinical response, which I think you're right. It looked like that was easier to predict across all the subgroups. The micro is complicated. It was a little bit left and right there. Some of that was the ASB issue or the difference between cipro and sulopenem, so that got more complicated. But the clinical piece kind of lined up a little better across, and this is adding the age question into what you were getting to.

Did that address your question?

DR. HUNSBERGER: Yes. This is the one piece, and I was wondering how variable the micro part was, but yes, this is what looked consistent. What I was interested in, too, was whether it flipped back and forth when you looked at the microbiologic part of success, but this is the one piece, too, yes.

DR. DUNNE: Yes. You're right, it was obvious that the micro results were more variable across the studies --

DR. HUNSBERGER: Right.

DR. DUNNE: -- and within the patient

populations because I think the micro response was not as good on the comparator arm for the older women versus the younger women; so just a lot of variables flying around at the same time, but the clinical thing just sorted it all out at the end of the day.

DR. HUNSBERGER: Right. So the question to me is, is that variability due to measurement error? Are we measuring the right thing? This seems to be more consistent across population or age groups.

DR. DUNNE: And that is the question we've just been talking about; should we measure the micro afterwards, should we not? Of course, used micro, the failure was micro alone, micro plus clinical, clinical on all of those were failures. That's the way we did the program, but I think the point you're bringing out is you can see that in the data as well. The consistency is a little easier to read if you're just looking at the clinical outcomes alone.

DR. BADEN: Is that all of the questions

from this morning?

DR. DUNNE: Yes, I'm good with all the questions right now.

DR. BADEN: Do you have a follow-on or a new --

DR. CHANDRA: Yes, just a follow-on, on that point. When you did --

DR. BADEN: Talk into the microphone, please.

DR. CHANDRA: When you did NGS and PCR testing, and when you looked at the bacteria response, microbiological response, was it more consistent with clinical or less consistent, or still all over the place?

DR. DUNNE: That's a good question. I think the whole why did we do the whole genome, that's a whole other thing, and at this point, we'll just leave that aside. It is a little bit more consistent because we are looking at literally the same sequence organism as a result, as a cause for failure, as opposed to another *E. coli*. There are a lot of reasons why that is that works, it doesn't

work. It's a little bit tighter, but it's still complicated, the micro in UTIs, because urine is not sterile. So there's stuff all over the place, and we're trying to read the tea leaves to see is it the same one or not. It is hard. So thanks for asking.

DR. CHANDRA: Thank you.

DR. BADEN: Dr. Patel, you have a follow-up?

DR. PATEL: Yes. Can you pull the slide up again? So this morning you had created a case about women above the age of 65 as being the optimal population to use sulopenem, but my thought, above 75, it looked like the effect kind of went away. And I just wanted to see whether it's a collapsibility issue or if there's something else going on there.

DR. DUNNE: He's pulling the slide up now. I think what happens in the older group is that the end starts getting kind of small, so the confidence intervals are getting broader.

DR. PATEL: But it looks like that sweet spot is 60 --

DR. DUNNE: Sixty still hangs in there. It's just about there. It's kind of tipping over. But the reason we have this slide is to show that there's a whole lot of data here and that, directionally, age seems to be a variable. Eventually maybe it's not as much of a variable, but even 55 is drifting to the right-hand side. These are post hoc analyses that we're doing, so we're not trying to get too crazy. It's more descriptive than anything else, but I think it's consistent with what we saw in the in vitro part of the study where you see there's more resistance, and this is kind of fitting.

So your question was about is it still happening at 75? Is that your question?

DR. PATEL: Yes, because I walked away from this morning thinking the ideal population would be women above the age of 65, but it looks like there's kind of a falloff after 75. I mean, the diamond is on the right-hand side of the line, sure, but the precision is not as tight.

DR. DUNNE: Well, again, we didn't know we

were going to be doing this analysis. We only did this because we saw what the questions were here. We wanted to try something to be of some help, but we could do a lot more work on this. This is just one analysis. There are probably multiple variables which play into the answer here.

DR. BADEN: No, your point's well taken on post hoc. These are post hoc analyses out of service to us, but we should be careful about overinterpreting.

DR. DUNNE: Yes, that's right. And I think doing a prospective study based on this is totally reasonable. This is a directional finding, but it's a place we can go next.

DR. BADEN: Ramya, did you have a comment?

DR. GOPINATH: Thank you. I think this morning there was a question for FDA as well, I think from Dr. Patel, about the overall response by age, again, and by creatinine clearance, and I just wanted to turn it over to my colleague, Dr. Li, who did take a look at that during the break.

DR. LI: FDA slide 35, please. I'm trying

to answer Dr. Hunsberger's question in the morning by each group. I got the data for Study 310, the susceptible population. Microbiological response was in the same direction as the overall response. Clinical response was very similar between the two arms, although in the younger age group, the success proportion was about 5 percent higher. In other studies, clinical trials are very similar to them. Microbiological is in the same direction as clinical response. Thank you.

DR. BADEN: Thank you.

New line of questioning. Dr. Lewis?

DR. LEWIS: Roger Lewis. Thank you. I'm referring to the first question that the agency proposed. My question is going to be for the agency colleagues. The last sentence of question was, "Discuss the overall benefits and risks for the use of sulopenem etzadroxil --"

DR. BADEN: We will get to the question soon.

DR. LEWIS: Yes, but this is actually a much broader question.

DR. BADEN: Okay.

DR. LEWIS: You can indulge me and you can cut me off right when I'm done.

DR. BADEN: No. I would like to indulge you but, also, we will come to actually rigorous discussion of the questions.

DR. LEWIS: Okay. So my question has to do with benefits and risks because it seems to me that one of the challenges for the discussion today is that the benefits accrue within a particular subpopulation of women, those that either ultimately are shown to have a resistant organism to ciprofloxacin or to have an organism for which the best available agent is amoxicillin/clavulanate, whereas the risks accrue in a much broader population through the risks of developing antimicrobial resistance that then paralyzes our ability to treat other infections, and in some cases, much more serious infections.

So my question is, in general, the agency's thoughts about the phrase "risks and benefits," whether the risks and benefits questions are

intended to apply to just the population -- excuse me, just the participants receiving, or the patients receiving the agent under consideration, the population at whole, or is it reasonable to try to balance benefits in patients against risks in the broader population. So I'm looking for agency guidance on the interpretation of risks and benefits.

DR. KIM: Hi. This is Peter Kim, FDA. I think we'd be interested in all-encompassing discussion, so benefits and risks to the patient, as well as benefits and risks to society as well.

DR. BADEN: Well, you got your answer. We shall come back to that because I think that will be part of our rich discussion.

Arjun?

DR. SRINIVASAN: I'm just curious to hear a little more from you all. We had some discussion that, obviously, one of the big questions that comes up a lot is the potential stewardship of this agent, if it is approved. And I heard some discussion, and one idea is price it really high so

that everybody has to use insurance, and then the insurance companies could help be a barrier to getting the drug with the preauthorization. But I would guess that you all also have thought through other kinds of ways that the drug could be best stewarded and would love to hear some of the discussions and thoughts that you all have had in that domain.

DR. DUNNE: Yes, it's a good question. Normally, we are not asked that. Normally, pharma is not really brought into the stewardship discussions, but I'll at least put my ideas hat on for a second and think about that. I think there are certain things that we can do. We would only have teams that would be marketing the drug for the claim.

Just to be kind of business-like for a second, this outpatient is a completely different discussion than the inpatient because it's a totally, completely different world, so there's no overlap with what goes on there. I think the focus -- for us, this is an important area.

There's more than enough patients here that need this drug, so we can focus on UTI, and that's good for us as a business, but we do understand we need to participate in the solution at the end of the day.

I'm just saying, we will do the surveillance. We can do that. We can do surveillance in individual health centers if that's what people like. I think national surveillance is great. There are ways now to integrate all the -- LabCorp, for example, does a whole series of UTI cultures and all the clinics. Well, they pool all that data for the whole United States every night. So there are ways to bring that surveillance data back from what's going on commercially anyway all through the country and start having that available on websites, which anyone could track into in their community. We started talking to them about that kind of thing. We think that would be useful.

I think geography matters. I think doing some additional phase 4 types of studies or

supporting others that want to do that, to know in your community where can we best help you identify the right patient that could use this drug. The thing is, there's only so much that we can really do. It really just depends on the docs and the clinicians in the clinic having the information they need to tailor this therapy for their patient. As I was saying, in the healthcare centers, you'll have a patient's history. Like Marjorie was saying, you'll have all their UTI data, all their cultural results. We don't have that here. We can't help with that, but that can happen in the local clinics.

What else do you think we could do though? I'm just asking you. What could we do?

DR. SRINIVASAN: I think this is the fair question. I think some of this is the collaboration between all of us who are involved -- clinical societies, you all, FDA, CDC, public health perspectives -- because like you're saying, I think the vision is not that this becomes, "Oh, this is a first-line therapy for

anyone with an uncomplicated --" what I hear you all saying is, "No, the correct use of this drug, it's a much narrower slice of that pie."

I think that's the issue, is if the drug is approved, it's doing what we can do together to make sure that the people who want to use this drug really understand what is the right therapeutic application for this drug. I think that's going to be a -- and some of it will be dependent on labeling and all that kind of stuff.

But as we know, with due respect to FDA, most people don't really scrutinize the label, so a lot of it it comes down to the education. And that is where I think the collaborations are important because the education that comes from the company, oftentimes, that is where most people will get a lot of their information on this. So I think there are places we could collaborate there.

DR. DUNNE: Yes, there's symposia that we can support and things like that.

DR. SRINIVASAN: Yes.

DR. DUNNE: And I know it sounds kind of

wonky, but working with Medicare and working with insurance companies to get them the data they need to be able to do the preauthorization, that's really important. We do that behind the scenes all the time; because where do they get the information they might need on a national basis be able to decide what they should and shouldn't cover? We do talk to them about various components of whatever product it is that we're working on.

I think we internally have been thinking that that older population is probably a good place to target. When we started off, we weren't really thinking about this for younger women with UTIs, not that they don't need good drugs, too, but that wasn't really the original plan. This age data just came out like a month ago, and we didn't even know we had this, and then we're finding it. But that's what happens. You stay in the game, do explorations of your data sets, and maybe we can work with people to come up with guidelines, which help.

DR. BADEN: Just as a follow-on, why target

an epidemiologic parameter if you could target a microbiologic parameter? So if you were able to have in real time resistance testing --

DR. DUNNE: Oh, perfect.

DR. BADEN: -- would that be the way to guide this?

DR. DUNNE: Yes, totally.

DR. BADEN: Just thinking that, because I worry when we say 75 and older. We're now branding a population, maybe a population that's never been on antibiotic before --

DR. DUNNE: Sure.

DR. BADEN: -- versus a 40 year old who's had 30 UTIs in the last 30 months and maybe very different.

DR. DUNNE: Yes.

DR. BADEN: So conceptually, it sounds like you agree we'd want to go to the place where it's diagnostic, if it's timely, and would be the way in which to guide care.

DR. DUNNE: That is number one, is point-of-care diagnostic. Everything else is

secondary, and we can't be growing it and testing it.

DR. BADEN: I just wanted to make sure we were going down the path of picking age or something, and that worries me.

DR. DUNNE: Only until there's a point of care --

DR. BADEN: No, no. I hear you.

DR. DUNNE: -- but definitely in the short term.

DR. BADEN: But there are different ways to get there, but the idea is we're identifying who's likely to have a resistant bug.

DR. DUNNE: Yes.

DR. BADEN: That's what we're trying to identify, and then what tools do we have in a timely fashion to guide that.

DR. DUNNE: That's right.

DR. BADEN: Dr. Green?

DR. GREEN: Thank you. This is going to be a question for Dr. Li and his statistical colleagues at FDA, but if I could have the

applicant's slide 49 back up. It's the one that you modified, and unfortunately the modification didn't answer my question.

So we're presented the success rate at 28 days, and we see this value of a 10.8 percent failure rate at 28 days if there was the presence of persistent bacteriuria and 5.9 percent if there was overall success and no persistent bacteriuria. When it was presented, it was said that they're not different, but there's that value of 0.128 at doubling, and this was not a study question, so power wasn't built into the analysis.

So my question to the statistician, since the study wasn't powered on this, how do I think about this result? I think that's what Dr. Lewis was trying to get to, is if we had 200 more patients, would that p-value have changed? In one that's being used widely, all of a sudden do we see a higher rate of failure that's really statistically real because we have this difference of -- we have an unknown knowledge as to whether persistence is clinically important or not.

This is the only data that was presented that suggested that persistence maybe was important at 28 days because those are mathematically different, and statistically I might think there's a trend towards there being a difference. So your thoughts on that, sir.

DR. LI: Hello. This is Xianbin Li, reviewer for this NDA. Basically, my understanding is that the sample size is very small. For example, in the first panel, one group is only 13 subjects, so probably there's no sufficient power to test the difference we want to test. Even if there's no difference and the p-value was greater than .05, we still cannot conclude there's no difference.

DR. GREEN: No, no, but I'm looking at the the bottom half of this, where 8 out of 74 failed versus 20 out of 339. That's why I really wanted to look because the top one is not high enough, and the difference mathematically is not different there. They only had the one clinical failure. It's the bottom one that's troubling because,

again, we have a microbiologic endpoint, and that is why we're meeting today. We don't know the meaning of that microbiologic endpoint. That bottom half of this slide suggests that there might be meaning to that microbiologic endpoint. So I'm just, again, trying to get context in my mind and help the committee get context in their minds.

Do you think it's not powerful enough? That's your answer. We can't answer on power.

DR. BADEN: Dr. Dunne may have a comment, too.

DR. DUNNE: So I totally agree. This was a post hoc analysis because we were trying to figure out what went on. Yes, we're with you. For the second study, we prespecified this analysis so we would have better grounds for being able to say what we would find is real or not. I think these days, there's still not a lot of clinical failure after [indiscernible - 06:15:18] so the numbers are smaller.

This is a prespecified analysis. I think it's reasonably powered. It's the same. So I

agree with you, the first one, you were a little, it looks very interesting, but that's why we said we're going to do this prospectively in the second study. I think this has a little bit more weight than the first one, and seeing it both times, that feels a little bit more compelling to me.

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

DR. LEWIS: Yes. If we can go back to the modified version of slide 49, the one that had the odds ratio turned around. Oh, I'm sorry.

DR. BADEN: The after-lunch slide.

(Laughter.)

DR. LEWIS: I'm sorry.

DR. BADEN: They didn't have time to digest it. We need to be careful not to overinterpret things pulled together over lunch. We still need to make sure we understand the data accurately.

DR. LEWIS: Yes, but I think the answer to Dr. Green's question is that the odds ratio, showing the increased risk in that study associated with persistent bacteriuria, was an odds ratio of

1.83. It's 1.83, and then the upper limit of that confidence interval would be 1 over the 0.22 that they showed, so it's a number between 4 and 5. So those data are consistent with there being a substantial elevated risk, but as Dr. Li pointed out, with the very small numbers, there's also tremendous uncertainty, so they don't demonstrate anything, and the cautions about an overinterpretation are well taken.

With respect to using the data from Study 310 to address the same question, I think there is evidence, given the different resistance patterns, that those studies actually enrolled fundamentally different populations. So I would not agree with the assertion that this same table, based on the data in Study 310, actually answers the same question as this table addresses in Study 301.

DR. DUNNE: Why is that?

DR. LEWIS: Because the antibiotic resistance patterns were so very different. In 310, you ended up with virtually nobody who was

resistant to your comparator, so it tells me that you were sampling from different populations, and I don't have any way to --

DR. BADEN: And with different antibiotics being used, the comparator.

DR. LEWIS: Yes, although in this particular table, this is being restricted to patients who are treated with a single antibiotic, so the issue of the population that they're sampling from. I think those are separate pieces of information that address questions in two different populations, so it's probably not rigorously defensible to collapse them.

DR. DUNNE: Yes, there's a lot going on. These are sulo patients in both arms --

DR. LEWIS: Correct.

DR. DUNNE: -- so the resistance wouldn't really matter because there was no resistance.

DR. LEWIS: No, the resistance level that you obtained in Study 310, if I remember correctly, was a very low level of resistance.

DR. DUNNE: To amox/clav.

DR. LEWIS: I'm talking amox/clav now.

DR. DUNNE: Yes, but not to sulo; zero for sulo.

DR. LEWIS: Absolutely.

DR. DUNNE: And zero here and zero in the next one.

DR. LEWIS: Correct.

DR. DUNNE: But the quinolone resistant rate was probably 18 percent, so that's the same. This is good because we've got a lot of facts to go through. Again, I don't know if we wanted too much time, but we just tried to follow up with this --

DR. LEWIS: Understood.

DR. DUNNE: -- to see if we could get some direction going, but this is the beginning of something. This is not the purpose of doing these trials. This just came out of the studies, and we're just offering it to people to see if it's interesting and you want to take it further with another study, another population.

DR. LEWIS: Okay. Your point is well taken. Thank you.

DR. BADEN: I think, in part, this is why antimicrobial studies are so complicated. Because of exactly the different ways to look at it that we all think are very important, studies may not be designed to look at some of these subgroups.

Dr. Chandra?

DR. CHANDRA: Actually, I have the same point. Can you show quinolone resistance in this study, 310? Then we can compare.

DR. DUNNE: Well, I'll look it up for you, Richa. I don't remember what it is, but it was not terribly dissimilar.

DR. BADEN: Are you pulling up more information? If not, then, Arjun, did you have a follow-on or new question?

(No audible response.)

DR. BADEN: New question. Then, Barbara?

DR. GRIPSHOVER: And this is just a quick follow-on. I also noticed that the populations were very different, and I was trying to figure out why. I did notice the second study excluded long-term care residents, so do you know how many

people in the first study might have been from long-term care, which was not an exclusion in that study? Because also in reviewing that, the populations are very different, and that was really the only big difference I saw in the inclusion/exclusion criteria. Thank you.

DR. DUNNE: I'm not sure long-term care people were in 301. We'd have to check for you. I don't know, but I'll look into that.

DR. BADEN: And I think there are two more new questions, and then I do want to get to the discussion because I don't want to disappoint Dr. Lewis.

Sally, did you have a question?

(No audible response.)

DR. BADEN: Then, Arjun?

DR. SRINIVASAN: It's somewhat related. I was wondering if you could say a little bit about that study population in 310. The resistance, I mean, it's really striking, how low the resistance --

DR. DUNNE: Okay. Let's talk about that.

DR. SRINIVASAN: Yes.

DR. DUNNE: That's what you want to know; why is that resistance rate so low.

DR. SRINIVASAN: Yes. I'm curious to know.

DR. DUNNE: That was pretty wild --

DR. SRINIVASAN: Yes.

DR. DUNNE: -- like it was 3 percent. What is that about? I don't know. I'm going to say I don't know. That's not what you normally see, but this was post-COVID, so something was going on, I think, that we did not anticipate. Resistance rates in the hospital went way up during COVID -- that's well established -- but in the community, people weren't going to the docs as much. So I don't know, but we think that may be playing a role.

When we looked at IHMA, they were doing some surveys, and they were going from 18, 20 percent. Amox/clav, the resistance rate was like 18 percent in 301. Theirs went down from 18, 15, 0, 5, so it's bouncing back up. So something may have been happening outside of the study in the outpatient

arena, not in the inpatient. I don't know. We don't really know beyond that, but it was really, yes, kind of interesting.

In a sense, that's kind of weird, but 97 percent of the patients in this study had organisms that were susceptible to amox/clav, which is really great because, normally, you would not say that. So I think that just adds to our confidence that amox/clav was a reasonable comparator in that second study, a total accident, and we didn't know that, but yes.

DR. BADEN: Well, Dr. Dunne, I'm very impressed that we are post-COVID. Thank you for having solved that problem. And I think we're still in the middle of COVID, but the COVID effect on everything we do is palpable; and as you point out, I'm sure it influenced the dynamics of the studies that you have conducted, so thank you for sharing.

I would like to now close the clarifying questions part of this meeting, and now I'd like to proceed to the charge to the committee from

Dr. Kim. And after we have the charge to the committee, I think many committee members I know have some strong views to share for us to make sure we think through the many issues that have been raised.

Dr. Kim?

Charge to the Committee - Peter Kim

DR. KIM: Thanks, Dr. Baden.

Good afternoon. My name is Peter Kim, the Director of the Division of Anti-Infectives, and I will be presenting the charge to the committee. Before providing the charge, I would like to reiterate some points of consideration mentioned this morning.

As noted during the course of the presentations today, the applicant conducted two phase 3 uUTI trials, which evaluated oral sulopenem for the treatment of uUTI in an ambulatory setting and were not specifically designed to evaluate the efficacy of oral sulopenem for the treatment of uUTI caused by resistant bacterial isolates or for the treatment of uUTI in patients who failed

first-line treatment. If approved, sulopenem etzadroxil/probenecid would be the first oral penem antibacterial drug marketed in the United States, and inappropriate use may contribute to antimicrobial resistance or increase cross-resistance to other penem drugs.

Because IV sulopenem followed by oral sulopenem was found to be inferior to the active comparator regimen for cUTI in Trial 302, there is concern that if approved, oral sulopenem may be used off label in the treatment of complicated UTI or other infections as stepdown treatment; however, there are no data on the effectiveness of oral sulopenem as stepdown therapy following IV treatment of complicated UTI with another antibacterial drug.

While antimicrobial stewardship and considerations by guidelines committees may help to determine appropriate positioning of oral sulopenem, if approved, in the hierarchy of uUTI treatment options, a discussion of approaches to inform prescribers of relevant data submitted in

this NDA to ensure the most appropriate use of oral sulopenem is warranted.

Now, the charge to the committee. Discussion item 1. The applicant is seeking an indication for sulopenem etzadroxil probenecid in adult women 18 years of age and older for the treatment of uncomplicated UTI caused by designated susceptible microorganisms. Discuss the overall benefits and risks for the use of sulopenem etzadroxil probenecid P for this indication.

Discussion item number 2. Considering the totality of the evidence in this application, discuss considerations that would be important for medical providers to know to ensure appropriate use of sulopenem etzadroxil probenecid. Thank you.

DR. BADEN: Thank you, Dr. Kim.

Questions to the Committee and Discussion

DR. BADEN: The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments. We will now proceed with the questions to the committee and panel

discussions. I'd like to remind the public observers that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel. After I read each question, we'll pause for any questions or comments concerning its wording.

As Dr. Kim just mentioned, the applicant is seeking an indication for sulopenem in adult women greater than 18 years of age for the treatment of uncomplicated urinary tract infection caused by designated susceptible microorganisms. Discuss the overall benefits and risks for the use of sulopenem for this indication.

Are there questions about the wording and what the agency would like to hear us discuss?

Dr. Farley?

DR. FARLEY: Yes. Several folks had approached me about this question informally, and I told them that I would respond on the record, so I will at this point.

Just for the committee's background, what will happen next in the review cycle for this

application is that the applicant and the agency will engage in what's called labeling negotiations. Labeling, including the indication for the product, needs to be agreed to by both parties in order for the drug to proceed to approval should there be no other issues with the approval of the drug, if it's otherwise approvable. So that's what will happen next.

There is not a voting question today. There's actually a harder question for number 1, because what we presented to you is the wording the applicant has submitted for their indication. That's what's reflected in number one and that's consistent with their presentations today, and we're asking you to opine on the overall benefits and risks of an approval for that indication.

Should you feel that the benefits and risks would be positive if the wording was different, that would be super helpful for us to hear because that's why we're bringing the matter to you. We would like you to incorporate that advice in your discussion today. Thanks very much.

DR. BADEN: Thank you, Dr. Farley.

What I'd like to do is -- and Barbara, we'll start with you -- I'd like to open it up to discussion amongst us about question 1. The agency will decide if they want to move forward with approval or not. That's not our decision. We can give them advice as to where we see therapeutic potential or benefit given the totality of the data.

Barbara?

DR. GRIPSHOVER: Barb Gripshover. First, actually, I did want to comment and actually ask a clarifying question, what exactly we meant by designated susceptible microorganisms. So does that mean we know they're susceptible to sulopenem? Do we know that they're designated microorganisms, like they are resistant to everything else; therefore, that's why they're designated? It wasn't clear to me exactly what we mean by designated susceptible microorganisms. Thanks.

DR. KIM: Thank you for the question. Peter Kim, FDA. As Dr. Farley noted, this is the wording

provided by Iterum Therapeutics. I think that's a great question given the uncomplicated UTI is typically treated empirically.

DR. BADEN: And in our discussion, we can discuss what we think would be appropriate.

Dr. Lewis, did you have a clarifying question or are you ready for the bigger discussion?

DR. LEWIS: The bigger discussion.

DR. BADEN: Open the bigger discussion, please.

DR. LEWIS: So I think my colleague to my left just asked the many dollar question. I initially interpreted the phrase "designated susceptible microorganisms" to simply mean microorganisms susceptible to the proposed agent. So with that wording and that interpretation, which may or may not have been intended by the sponsor, I would not support a positive risk-benefit or benefit-risk assessment for that broad class.

It seems to me that the considerations that balance the benefit-risk in a positive direction

rely on identifying a subset of patients who have a low probability of successful clinical cure with accepted first-line agents. That population is ideally defined by a culture that demonstrates resistance to accepted first-line agents, but as I mentioned earlier, in my clinical practice, that's rarely the setting in which I find myself.

I think there is another population of women suffering from the target illness who can be identified as being very high risk for falling into a population that's likely to have a treatment failure with accepted first-line agents, and that can be based not just on traditional demographic features, but also by information, as was mentioned earlier about their prior microbiologic results.

So in my mind, an acceptable positive benefit-risk ratio would require wording that restricts the use to a population at substantially higher risk of treatment failure with currently available first-line oral agents.

DR. BADEN: So to add some more flavor to your comments, Dr. Lewis, I agree; the way it's

currently worded is too broad and too high risk. The challenge before us is to help the one and risk the many. I think the assessment for resistant organisms is not only woefully inadequate, it's absent. I think assessment for resistant organisms is in the GI tract. One may do stool monitoring. There's wastewater monitoring. There are all sorts of creative things that could go on that give us better insight into the CRE burden and the manipulation of that through selective pressure.

But taking a step back from the risk to the many, the benefit to the one, one can imagine -- and many of us, if not all of us, have taken care of patients who have a pan resistant organism that requires IV therapy for which they have yet another UTI, and a tablet instead of home IV therapy or hospitalization IV therapy might be a situation of tremendous benefit for that individual. But that's a fraction of a percent of the potential use of this agent in people with UTI.

That's the reason I think you brought us all together, was to discuss that there may be a

circumstance of true benefit for that patient or that group of patients, but how do we minimize the risk to the rest of us? At some point you can educate us on the tools you have in labeling such as restrictive labeling for a limited population pathway, or there are some other labeling issues that might help, but I still think they're relatively limited in the help that they can provide.

But I think that's the challenge in my mind, is there are certain groups of patients who clearly will benefit, in my view, and then 99 percent won't. But this will be an antibiotic you don't have to think about to order, and the outpatient setting has no controls, unlike the inpatient setting.

So it's a friendly amendment to Dr. Lewis' comment in terms of thinking through where the potential benefit is, but what are the tools to target that benefit and minimize the risk in the outpatient setting? I like to be provocative.

Sally?

DR. HUNSBERGER: I just want to second that because I think if you look at the two studies, you were looking for resistance in the 310 study, and all of a sudden you didn't get any, and we don't know why. We have hypotheses that it's about COVID or whatever, but if you just do your empirical treating, we could be wrong, a lot. So I think we need to have diagnostics. We need to have other ways to do it, and I think the risk-benefit is too much without narrowing this down a bit.

DR. BADEN: Arjun?

DR. SRINIVASAN: Yes. In thinking about the drug -- and I think I heard this from what the applicant was presenting as well -- the ideal audience for this drug -- and I think, Lindsey, you were mentioning this, too -- is a drug that you would think of. This is a good, really desirable option for a person with a resistant organism and/or someone who's failed a first-line therapy. That's where I think I would want to have this option because if you have someone who's got a resistant pathogen and you want to avoid the

hospitalization, I think what's challenging is, as Dr. Kim presented, that's specifically not addressed in the data that's available to us.

So it's hard to say use this in people who have resistant organisms if the data is not there to say we know it's going to be effective in that population, and I think that's the real tension that I find here.

I think, as one of the public commenters was also pointing out that, this is not a life-threatening infection or this is not sepsis. This is not a situation where you cannot get it wrong; you have to get it right the first time every time. This is one where the study showed that either under the best of cases, we get it right about 80 percent of the time. That's the best.

So I do think this option of a salvage therapy or a fallback therapy in situations where there is an initial treatment failure, it is still a reasonable application, but I would want some sort of microbiology to guide me in that direction

because, as we're noting, there are a lot of people who diagnose with UTI who fail therapy, and they never had a positive culture to begin with. So what were the urinary symptoms caused by? I don't know. They're probably not a resistant organism. Over. Thank you.

DR. BADEN: Just one question, Arjun.

DR. SRINIVASAN: Yes?

DR. BADEN: In Study 301 -- I think it was 301 -- they had the MITTR group where it had benefit.

DR. SRINIVASAN: Correct.

DR. BADEN: So my read of these data, which is, I think, one of the tremendous challenges with antimicrobial development, is it's hard to get the right patient in, so you don't know for 2 days, and then you get them in and you have multiple subgroups because what grows/what doesn't. So there at least was some data --

DR. SRINIVASAN: Correct.

DR. BADEN: -- that is on point, even though it's uneven across the other studies.

DR. SRINIVASAN: Agreed.

DR. BADEN: As we give advice to the agency, it's nice for it not to be completely data free, although we always wish there were better data, and that's the problem with antibiotics or the antimicrobial space.

Dr. Green?

DR. GREEN: So this is a follow-on. I live in the world of pediatrics, and I just want to build on what Arjun said about first line and don't have to get it right first. Clinically, your child has an ear infection. They're supposed to be started on amoxicillin. We know amoxicillin's going to fail in a number of children. We know the parents of those children aren't going to be happy because those children who it fails are not going to be happy, and we're going to tell them to wait for 2 or 3 days to see if they respond or not. Ideally, we don't give them an advanced antibiotic, although many parents come in and say, "You can't give me that antibiotic. It never works for my child. I have to have this broad spectrum," and

now we have problems with the broad spectrums not working for otitis media.

So I do want to emphasize that this is an opportunity for urinary tract infection for stepwise approach to therapy. Having said that, as was also brought up by Dr. Kim, we don't have a study that looks at here is the use of this drug versus a comparator in patients who didn't respond to a first-line therapy to answer how well will it work in that scenario. But we do have that option to think about it there, so we don't need to start off with a penem to treat what might be responsive to a first-generation cephalosporin, or to TMP sulfa, or to nitrofurantoin. Thank you.

DR. BADEN: Dr. Joniak-Grant?

DR. JONIAK-GRANT: Thanks. Elizabeth Joniak-Grant. I wanted us to talk a bit more about the, quote/unquote, "risks to the rest of us." There's been a lot of discussion about increasing resistance and some intimations toward the importance of carbapenems, but I think as a patient and for patients that are listening and trying to

understand why does that matter, is there something particular about this class of drugs? Is there something particular about that drug that we need it? And I think having that information out there would be really useful.

DR. BADEN: I'll take the luxury of trying to answer and, again, my imagery of robbing Peter to pay Paul in the sense that there are patients with a resistant -- if we use this drug in the community and develop carbapenem resistance, patients who get septic, who get sick, often are from the flora they're colonized with. And if they're colonized with a carbapenem-resistant organism, that's often an antibiotic we use in a life-threatening situation of sepsis or severe infection.

So the concern is that we will have many of us colonized with a resistant bug, and if we were to get seriously ill, the antibiotics we'd usually use and expect to be the most important in saving people may not work. But we're trading a common event for a rare event, less morbid/more morbid,

and how do we balance that, particularly when there's a patient in front of us with symptoms of a UTI that we can't relieve?

DR. JONIAK-GRANT: Thank you. Understanding that it's related to sepsis makes things a lot clearer, for me at least.

DR. GREEN: And I just want to add one point, if I may. Lindsey didn't put it in the context of we see this every day, but I see this every day that I'm on service when I go to my ICU. So carbapenem resistance is a thing, and it's far worse now than it was 10 years ago. There's a new class of drugs where they add something to the carbapenem to try to overcome that. Oh, by the way, we're seeing resistance to that as well.

So this is the struggle. Just to put it in the context that not only can carbapenem resistance happen, it has happened, and it's broadening, and it's expanding, and now we don't have the next class of drugs after the penems and carbapenems of what we use to rescue. And I've taken care of patients, even last week, that had no drugs that

could be used. Thank you.

DR. BADEN: We're better at antibiotic stewardship at my hospital.

(Laughter.)

DR. BADEN: No, this is a problem of substantive importance that will only grow exponentially.

Dr. Lewis?

DR. LEWIS: Just very quickly, there is a separate group of patients, Dr. Baden, that you referred to, which are the patients who clinically are not ill enough to require hospitalization, but because of their prior organisms they've been infected with, we make a decision to admit them to the hospital because we don't have good access to outpatient IV therapy, and give them a carbapenem in the hospital.

So one of the potential benefits of this agent, as you were alluding to, is to shift the location of the penem administration to being oral at home as to be in the hospital with its associated cost, and convenience and risks in

itself. That difference in treatment option doesn't change the burden of the use of penems across the population; it just shifts the location.

DR. BADEN: Yes, I was careful not to go down that route because we don't have data for that here, and they even pointed out switching from induction with ertapenem and maintenance, or consolidation, if I can steal from oncology, with the oral they didn't study. But that would be a logical extension of these data and of improving the welfare of our patients.

DR. LEWIS: But just to be clear, I was not referring to stepdown; I was referring to first treatment in uncomplicated UTIs in patients who, because of their history of, for example, ESBL organisms, are routinely hospitalized because only IV therapies are available. Thank you.

DR. BADEN: Dr. Perez?

DR. PEREZ: Yes. Federico Perez. I wanted to follow up on that point, I think, just so that I can process it as well, because even though I passionately share the concern for the risk of

sulopenem being a selective agent for carbapenem-resistant bacteria, we have to acknowledge that we just don't know, and of course that's a big risk. But as has been presented by Dr. Lewis, there's also the argument to be made that this isn't actually an ertapenem sparing agent, so the balance of selective pressure may be beneficial if other microbiologic and pharmacology conditions are met. I just wanted to make that point. Thank you.

DR. BADEN: Agreed. There's more we don't know than do know. In fact, the pinhole we're looking through I think is so tiny, but we see something that we think can benefit our community. My concern, Dr. Perez, is the math. For me to give IV ertapenem requires a lot of energy. For me to write a script for an oral antibiotic, I think that will go up several logs.

I think of resistance, and it's my assumption, as a numbers game. How much selective pressure on how much flora equals the risk that eventually something resistant will be selected,

amplified, and transmitted? So I share your sentiment that we don't have the data. I just worry that once we select for CRE, you can't put the genie back in the bottle, and I worry about the math.

Arjun?

DR. SRINIVASAN: Well, to build on that point, we've seen these data, like the IDSA treatment guidelines, that you don't use the drug if the resistance rate is more than 20 percent, or whatever that number is, in some of these studies. Presumably, if this drug were approved for treatment of uncomplicated urinary tract infections, it would become the most recommended agent because it would be probably the only one with resistance rates of less than 20 percent, which would, de facto, mean that it's the primary choice for treatment of uncomplicated urinary tract infections according to treatment guidelines, unless I'm wrong in that.

DR. BADEN: And I guess I worry that I've seen this movie before 20 years ago with

quinolones, and how do we manage -- I think of antimicrobials as a community resource. Even though it's an individual benefit, it's a community resource, and I worry that we can burn classes for limited benefit if we don't position it correctly, and I think everyone's worried about that and sharing in the discussion. But I do think that what we did with quinolones, I don't want that to be a preamble for what happens here because the risk, in my view, is you lose the class of quinolones, and you have the beta-lactams. You lose the class of beta-lactams, and that to me feels like a much bigger loss in terms of how we manage seriously ill patients.

So I have a straw man or spaghetti to throw at the wall of the committee. Given, as already has been stated, the uncomplicated UTI, you don't die in a day, therefore we have time; therefore, should we make antimicrobial testing a requirement? And that may delay it at a day or two.

Now, one could imagine if you were tested a month ago -- you don't have to say it has to be

this minute, but it can't be in someone who has never been exposed; just because I'm 75 doesn't mean I have a resistant bug -- is there a way for us to -- I don't know that the agency has these tools, but I'd like to give them ideas of tools that either they, or CDC, or public health departments can pick up. But the interest in doing diagnostics is going away because the economics are against it. Without diagnostics, we're left with empiric therapy, which will only amplify antimicrobial resistance.

Is this an opportunity for us to make a strong statement about the need for diagnostics? And it's beyond the company, it's beyond the agency, but together we may be able to push the community that this is a kind of agent that really should be used in patients who are at highest risk, i.e., they are colonized with, infected with, and we have evidence for an organism with a resistance that would require this?

I don't know if that can go in the label, but that would then -- because our micro labs are

shrinking. Our micro labs are going to technology, which I think is terrific. The problem with technology is it only detects what you ask it to detect, so if you don't know what to ask it to detect, it's not going to detect it.

Is that a crazy idea to suggest? Barbara?

DR. GRIPSHOVER: I was going to suggest maybe we change it to designated microorganisms are actually resistant to all other oral agents, instead of just susceptible; just throwing it out.

DR. BADEN: Again, I'm trying to provoke more discussion, so it's not any one view. Is this helpful? Is this a distraction? How can we help the company, the agency, the community be more responsible and enable our patients to have access to more medications, but we not lose them for everybody else?

Arjun?

DR. SRINIVASAN: I like that wording that Barbara just mentioned. If it is the designated microorganism, meaning resistance to all other oral therapies, I think that would be a --

DR. BADEN: Plus allergy.

DR. SRINIVASAN: -- yes. And I think that is, as the applicant themselves I think have alluded to, the envisioned kind of niche for this drug, and I think that would be great. It would give people an option, but it would be the appropriate situation where other things were not available.

DR. BADEN: Dr. Patel?

DR. PATEL: No, I think you're on to something there, and I think the agency does have tools to incorporate that into the labeling. I think of this very akin to heavily treatment experienced patients who have HIV, and oftentimes those labels for things like ibalizumab or whatever, it's always about who have limited options. So I don't know if you can take a page out of that book and use that.

DR. BADEN: And I want to help put pressure on our health centers to actually get cultures. Providers and health centers should have an incentive to get cultures in order to have the

information versus over-the-phone prescribing for symptoms, which is important, but then it will lead to widespread use and loss of the class.

Dr. Green?

DR. JONIAK-GRANT: Thank you.

Dr. Joniak-Grant. From a patient perspective, I think doing cultures is a really good idea. I think patients are generally shocked. They're kind of like, "Why am I going to see a doctor and paying for this appointment for them to go, 'I guess this could work.' Why can't I just call him on the phone, then, if we're going to throw things at the wall?" and especially when it involves more money to get more than one prescription.

It can involve more side effects for things, and also in some ways, I think it could help rebuild trust a bit with doctor and patient interactions with them saying, "We don't know what it is, so let's do this test, find out what it is, so we're treating it properly from the get-go," versus it doesn't work the first time, and they say, "Oh, my doctor doesn't know what they're

talking about." I feel like we're in an age where that's happening more and more, so anything that would help reestablish trust with good information would be beneficial.

DR. BADEN: Thank you.

Dr. Green?

DR. GREEN: Thank you. I very much like the idea of an indication that's much more restricted, but I do want to ask the question of what that does to keep the prescriber that Dr. Baden was talking about earlier from just writing the prescription. Stewardship programs have very limited control over outpatient formularies. Third-party payers in fact may say we're going to make you get preauthorization but not always do they do the case.

We had a prep call, and we weren't really allowed to ask very many things, but I did ask the gentleman on the left the question, what does the agency know about restricted formulary by third-party payers? And I was told, the FDA, that's not part of their focus.

So I'm not exactly sure. We can dream and want to get a new diagnostic, and we can want to change care and get a culture, but I'm not sure how we also change practice so that you can't get the drug if you don't meet these criteria once it has an indication and it's licensed.

So just for us to think about it, that's not necessarily the complete control, although I do agree with what's been said, that there is a patient population for whom this is going to be a great drug to have available, but again, it's this calculus that's been described that we have to think about. The applicant themselves acknowledged that use it enough, use it long enough, we're going to have prevalent resistance. So we know that's in the future. The question is how long do we get benefit before that's a reality? Thanks.

DR. BADEN: Arjun?

DR. SRINIVASAN: Thank you. I'm agreeing with you, Michael. I think that is the tension, that just because it's labeled for people with no other resistance to all doesn't mean that that's

going to happen. So that is a major consideration just to say, "Well, we'll just write the script," because let's face it, almost all antibiotic use is off label, so there's nothing that would stop this from going down that exact same road.

The other issue with the antecedent culture recommendations/requirement is it does raise some equity considerations, and we would have to do a better job of understanding what insurance covers. What if you're a patient where either given the type of insurance that you have or if you have no insurance, you have to pay for the culture? If I'm in that situation, if I'm the provider, I'd say, "Well, here. I'm just going to write you the prescription because you don't have $200 to pay for a urine culture. I'm just going to give you this drug." So I think we'd have to really understand what the implications are there for different payers for how this would work.

DR. BADEN: Absolutely, however, I'm not sure we should no longer put pressure on using antibiotics appropriately, so we need to solve

those issues and many more. But without putting pressure on the system, diagnostics are withering and empiricism is blooming, and we need to help the ecosystem get that into a little better balance.

DR. SRINIVASAN: Yes. I just want to make sure the pressure is on the system and not on the patient.

DR. BADEN: No, no, no, no. You're absolutely correct. How this gets translated, you're absolutely correct. These are huge equity considerations that have to be properly vetted and thought out. I just worry a lot that this will be purely empiricism. I don't need to think. All I have to do is just write the script, and we'll have millions of those scripts in a year or two, and we'll all be saying, "Well, they shouldn't have been written; it makes no sense," but the horse is out of the barn. And how do we help our ecosystem be a little more thoughtful in antimicrobial use, which is going to cost money. And we have to make sure that the economics of it fall on the right parts of the system and not on the individual

patient, particularly, as you point out, in what could be very inequitable ways.

Other comments?

(No response.)

DR. BADEN: To the agency, before we go to question 2, are there other aspects of this question that we've not discussed that we should dig into a little more?

DR. FARLEY: Farley for the agency. No. Thank you very much to the committee. This was very helpful.

DR. BADEN: I will do the next question, then summarize.

We'll now move to the final question 2, which is also a discussion question. As Dr. Kim mentioned before, considering the totality of the evidence in this application, discuss considerations that would be important for medical providers to know to ensure appropriate use of sulopenem.

Any questions about the wording of the question?

(No response.)

DR. BADEN: If there are no questions about the wording of the question, we'll now open the question to discussion.

Dr. Lewis?

DR. LEWIS: I have a question for the agency about the tools that they have available, that the agency has available to it, in the postmarketing, post-approval setting. This is going to be a long hypothetical. I apologize in advance.

Suppose, hypothetically, the drug was approved with labeling that dictated it should be only used in women with uncomplicated UTIs who had demonstrated -- or a set of criteria for meeting a category of very high risk, for example, a positive ESBL culture within a month or something like that, and the sponsor was required to do a postmarketing study to demonstrate that the prescribing behavior at some acceptable performance criteria met that restriction. If, following through on the rest of the hypothetical, the postmarketing study then demonstrated that the stewardship effort had been a

failure, at that point, what options does the agency have available to it?

The context for my question is that I have been told informally, in this room and by different parts of the agency, that in fact there's not really a mechanism for withdrawing approval based on postmarketing unless it's a safety concern at the individual patient level.

DR. GOPINATH: Can I have backup slide number 2, please?

DR. LEWIS: If you have a slide that answers that, I'll be very impressed.

(Laughter.)

DR. GOPINATH: No, not specifically, but go ahead, Dr. Farley.

DR. KIM: There will probably be a multi-component response with various media forums involved.

DR. FARLEY: I'm thinking through the question. I think it's a good one. I think what would happen -- I think the agency was going to focus on the tools that we have in the label

itself, but I don't know that that's going to address your question. Your hypothetical is in a postmarket setting. There's a lot of inappropriate use going on, basically.

DR. LEWIS: Yes. My impression, there's a personal impression that the committee is struggling with the ability of protections that are built into the label to protect the community at large against practice that results in the emergence of of antimicrobial resistance, carbapenem resistance. So I'm trying to find out if in fact this plays out that way and we see, yet again, that labeling is ineffective, do we have a way of correcting that error, or is there a lack of an option?

DR. FARLEY: I don't think there's a lack of an option. This scenario is kind of two-fold. The first situation is data that's demonstrating that there's a fair amount of use that most physicians would regard as inappropriate use, and that's scenario one. And I think in that case, we would, first of all, work with the sponsor. The labeling

is a joint process. We have to agree. But they are as committed as we are to ensuring that use is appropriate, and there may be additional changes in the wording of indication, et cetera.

FDA, as well as professional organizations, have the ability to communicate with physicians around that, so that would be something that we could do because I think we're in a setting where I think the general sense of the committee is there is an unmet need for a product like this, so there are some patients that are potentially benefiting. Of course, if we got full resistance throughout the population, that's going to be a different story.

I think the second scenario is if there is microbiologic population data that seems to indicate that the drug is driving resistance in some way, and FDA does regard resistance as a safety concern, so we would have more tools at our disposal at that point, rather than just labeling and communication. Thanks.

DR. LEWIS: Thank you.

DR. BADEN: Ramya, the slide is up if you

wanted to comment.

DR. GOPINATH: Yes. No, I had just wanted to put this slide up to provide the information that some of the potential labeling strategies that are available to us are this, and we have further details if anyone needs it.

DR. BADEN: But I'd like to broaden the discussion a little bit in that the risk to the community we've discussed. There's the risk to the individual. The patients I have who have fluoroquinolone resistance have been on fluoroquinolones, so the population flora of an individual patient may respond, in fact I would argue, has responded, to whatever selective pressure we put them on.

Fortunately, we never measure it, including in these studies, so that we have no way to comment on it, and I think that's a blind spot in these studies in general, and I hope will not be a blind spot going forward in that if you were to move forward and label it, if someone has been on this agent and they come in septic, would you use a

carbapenem or not? What if they were on this agent 5 years ago, 5 weeks ago, 5 days ago, and you never measured any of their cultures because the cultures we're talking about our convenience cultures, not systematic cultures of the induction/amplification of resistance within the given individual.

So I would argue that you actually need stool surveillance in the patients who receive this to understand what happens to their flora. For example, if they're a cancer patient, or a transplant patient, or a patient on immunosuppressive agents who gets recurrent infections and lots of antibiotics, they're not well served if they're colonized with more and more resistant organisms.

So I think there's an individual concern, not just a community concern, but as best as I can tell, there is zero data that we can talk on, so we could say it doesn't exist because it was not measured, which disappoints me in this process because nobody takes the time to measure what happens to people's flora when you put them on a

nuclear bomb antibiotic like a carbapenem.

So sorry for my diatribe, but I just want to bring this back to the fact that it's the individual patient who may actually be at risk and not know it by us changing their flora, and if they're in the middle of multiple high-risk interventions because of comorbid medical illness, we may have done them a major disservice without realizing it. So I would commend stool surveillance and insight into prior use impacting future antibiotic options.

Arjun?

DR. SRINIVASAN: Allow me to expand on your diatribe. I think you're raising a really important point, and it may be good that you talked about the responsibility of the committee to try to pressure the committee. I do think that maybe one of the routes we need to take in that regard is this should become, I think, part and parcel of antimicrobial trials moving forward, assessments of the disruption of the microbiome, which is not that hard to do anymore. It's not the futuristic

quasi-experimental stuff. This is readily doable, done by hundreds of labs all over the country.

I think you're raising an exceptionally important point, that we are intending to think, "Oh, it's the trade-off," and this is the false dichotomy that's raised a lot of ideas. "Oh, well, you have to treat the patient in front of you, and you shouldn't be thinking about societal implications of the patient when you're thinking about the patient in front of you."

But as you're very correctly pointing out, Lindsey, there are significant considerations for the patient in front of you, and how would we feel as providers if we gave somebody courses of a penem antibiotic for a non-life-threatening uncomplicated urinary tract infection, and then a month later, or 2 months later, or 3 months later, that patient gets admitted with sepsis due to a penem-resistant organism and dies from that infection? Because 30-40 percent of people with penem-resistant sepsis are going to die.

It's the same challenge that we have now,

where you're saying those patients who have gotten repeated exposure to quinolones, they come in for a prostate biopsy and they get the prophylactic dose of a quinolone, and it doesn't work, and they get septic. So I do think, perhaps, maybe one of the criterias before the approval is considered here, maybe there should be a request of the company, let's do some studies of microbiome, and let's see what happens with these patients who get this exposure, to give us some reassurance that we're not putting that individual patient at significantly increased risk.

I do think that will have also the benefit of addressing some of this potential implication for the societal impact. How often are we breeding, if at all, these types of resistant infections? So I think you're raising a really important point here, and it may be data -- I would argue it probably is data that should be obtained as part of the package of considering where this drug fits in the armamentarium.

DR. BADEN: Dr. Perez?

DR. PEREZ: Yes. Federico Perez. I think considering the ecology of resistance is fundamental, I think in the spirit of learning more, it should be essential to considering introduction, again, of an oral version of a drug that is so central in our armamentarium, penems, carbapenems. I think careful structure function analysis of cross-resistance between this drug, that after all is a thiopenem, with the carbapenems, becomes then very important.

I think we just didn't learn about what are exactly the mechanisms by which resistance occurs in sulopenem, and what, if any, are the correlates in the other drugs of the same class, and I think that becomes very interesting information. Thank you.

DR. BADEN: Thank you.

Dr. Green?

DR. GREEN: Thanks. I want to just follow on the theme, and I think that this is a great idea, but I want the committee, and the FDA, and probably the applicant to understand the

limitations of what's being proposed.

Earlier in my career, I ran a research clinical microbiologic laboratory, and we did surveillance for resistance in a variety of settings, 5 versus 10 days for ear infections, urinary tract infections. We also did surveillance in the Children's Oncology Group when they started to look at the value of levofloxacin as prophylaxis for patients who were neutropenic with AML, et cetera, and I call on the adult folks to remember the studies in the adult patients when they used levofloxacin in those settings.

I'll tell you, we didn't see the signal in the study, but the problem is that the study's done in a relatively small number. They're powered to show benefit for their endpoint but they're not powered to show will you see resistance emerge when you're doing it. So the limitation of looking for it in the context of trials is that trials are hundreds, maybe thousands, but they're not tens of thousands of patients, so they're not completely reassuring unless the selection process is so easy

that you're going to get it quickly. With these spontaneous selection of 1 to 10 to the minus 8, you may not see it, and that might be reassuring in the moment, but it's not necessarily reassuring long term.

I still like the idea of thinking about it, but I just want us to understand that if we do data on 100 or 1,000 treated patients, I don't know that I would feel comfortable to say, "Well, that means it's not going to happen" because I've participated in the studies that didn't show it, only to see what happens when it's used over time. Thank you.

DR. BADEN: Mike, your point is well taken that it's a dynamic issue, and whether it's endogenous selection -- and my gram of stool may have 1 times 10 to the 13th, so 1 times 10 to the 8th is kid stuff -- the issue is, is it that you induce resistance de novo? Is it that you reduce the resistant flora so I get your bug because I have no flora to resist?

So it may actually be temporally dependent through time, so I don't think any one study, any

one data set resolves this, in any way. I think that the concept that I hope we get more on the table in our community discussion is I would argue microbiome injury, and how do we think of microbiome injury with antibiotic use and the dynamics of that, which is not going to be resolved in any one study, and the tools today versus when you were a fellow, we might have gotten past agar [ph] and might be able to use some other high throughput tools.

But again, I don't want to get committed to any technology or any one time. The concept is we have microbiome injury, whether we induce it, whether we make it susceptible for easy acquisition so that in a community -- and to me the community is not the 75-year-old community, it's the people at the transplant center. It's the people at the dialysis center. It's for this kind of person-to-person set of bugs, as opposed to things that we eat, as opposed to things that we breathe and sneeze. So this has, in my view, a lot more to do with one susceptibility in the community one is

exposed to and how one diminishes your resistance to acquiring a resistance, if I may.

So just amplifying your point that it's complicated and we shouldn't think of any one maneuver as solving it, I hope it is part of the lexicon more rigorously going forward because I think that's what the agency is getting at with their set of questions to us.

Other comments?

(No response.)

DR. BADEN: Not seeing any, again, I will ask Dr. Farley, Dr. Kim, are there other aspects of this that you were hoping we would discuss before I conclude?

DR. KIM: So we're thinking maybe it'd be helpful to talk through some of our labeling tools as well --

DR. BADEN: That would be terrific.

DR. KIM: -- and follow-on to part of Dr. Lewis' question.

DR. GOPINATH: Could I have backup slide number 2 again, please?

So we have a number of different labeling categories that are of use to us. Also, we have included a short slide about LPAD, so I'll turn it over to Dr. Kopack to walk us through this.

Could we have the next slide, please?

DR. KOPACK: Hi. Dr. Kopack, FDA. We use contraindications when there's a situation in which the drug should not be used because the risk of use clearly outweighs any possible therapeutic benefit, and the causal relationship between the drug and the observed adverse reaction is well established. If we don't have evidence that would support a contraindication but would suggest that the use of the drug may be inadvisable, or there's uncertainty regarding its use in certain clinical situations, then a limitation of use may be more appropriate.

So a limitation of use would be presented separately from the indication in the indications and usage section of the labeling, and like I said, we would include this when there's a reasonable concern or uncertainty about the drug's risk-benefit profile and when we think this

information is important for medical providers to know for safe and effective use of the drug.

An example would be identifying a particular patient population in which a drug should generally not be used, or informing medical providers there is a reasonable concern or uncertainty about the drug's safety or effectiveness outside a specific population for which the drug was approved.

We also have warnings and precautions where we would describe a discrete set of adverse reactions and other potential safety hazards that are serious or otherwise clinically significant, as they would have implications for prescribing decisions or patient management. We would include an adverse event, and the causal association doesn't have to be firmly established, just that it's possible.

A boxed warning is used in these situations: if there's a serious adverse reaction, and it's so serious in relation to potential benefit such as a fatal adverse reaction that that must be considered in assessing the risks and benefits; if we have a

serious adverse reaction that can be prevented or mitigated in frequency or severity by appropriate use; if we have a drug that's approved but approved with restrictions to ensure safe use; or if the warning information is particularly important for the provider to know.

Then the labeling categories are different from LPAD. This is an approval pathway, and one criteria is drugs being intended to treat a serious or life-threatening infection in a limited population of patients with unmet needs.

DR. BADEN: So are there aspects of this like the limited use that you want us to opine? Because it looks like the LPAD doesn't apply.

DR. FARLEY: I can respond to that. I think with LPAD, we haven't made a determination whether this would fit into that category and certainly wouldn't be asking about that, and that's something that the sponsor actually has to voluntarily seek. And again, even if they were to seek it, we haven't made a determination whether it really fits with the statutory framework and vision for that. So

no, I think you had earlier asked about labeling options which might be employed now or in the future, and I think that was the purpose of presenting that overview.

DR. BADEN: Because if you'd go back like two slides, the limited use, we didn't use the framing that you have, but I think that's what we've been discussing is --

DR. SRINIVASAN: It's the next slide. It's the boxed warning slide.

DR. FARLEY: There we go.

DR. SRINIVASAN: I guess -- sorry.

DR. BADEN: Please, Arjun.

DR. SRINIVASAN: The question, I think this gets at what Roger was asking, though. The challenge, of course, is there may be a boxed warning on this one because it's a limit, but if people ignore that, there really is, to my understanding, no enforcement mechanism for the providers. If 95 percent of the use is out of labeled indications, what happens? Aside from we're going to keep trying to train people to do

it, right, is there really any way to say, "Look, we tried, but this drug clearly is not being used the way it it needs to be used," then what?

DR. FARLEY: So I think we're worried about an uncertain future, and I think I've done what I can to address hypothetical situations that we've brought up. What I would point out is that labeling is not insignificant. The next month or two, the agency and the sponsor are going to work very hard on that to address what we've heard from you today.

It's not insignificant. The prescribing information that the FDA writes ends up in all sorts of electronic tools that physicians use at the bedside every day. That's where that data comes from. It comes from the label. Secondly, I think with electronic health records system, they are programmed to pop up things that are relevant to the label. For example, if there's a limitation of use that says this shouldn't be used as stepdown for complicated urinary tract infections and somebody is writing that, that's generally going to

pop up in the EHR system to educate physicians on the spot as they're writing the prescription.

So hopefully that helps. I'm optimistic that labeling does make a difference, and that's why we're having this this discussion today.

DR. BADEN: Dr. Lewis?

DR. LEWIS: So it seems to me, conceptually, that we've talked about four different -- and I'll just use a very broad term here -- protections. The first is the limitation of use. We've talked in various ways about limiting the use to patients for whom there's a very high risk of ineffectiveness of a currently available first-line agent. Then if we go to the black box language -- I think it was the third --

DR. GOPINATH: Could we have slide 6, please?

DR. LEWIS: -- it seems to me that much of our discussion has been congruent with the third sub-bullet, where it says, "The drug is approved by the agency with restrictions to ensure safe use because the FDA has concluded the drug can safely

be used only if its distribution or use is restricted." I can see, for example, a boxed warning consistent with that regulatory language, talking about the risks if the drug were used more broadly and not restricted effectively by the healthcare organizations. So those are the two components that are labeling.

I think that we've talked in general about requirements for postmarketing studies that would address some of the outstanding questions, maybe enlarging, I think you called it the pinhole through which we're trying to see the future, and I think that getting greater understanding of both effectiveness and the safety is important.

I think we've talked about the risk to the individual patients about the resistance of carbapenem emergence or colonization of carbapenem-resistant organisms -- apologies to the ID colleagues if I'm not saying this correctly -- and it seems to me that postmarketing studies, as you pointed out, can't eliminate that risk. In fact, I think we all think that will

occur with some frequency, but it certainly could be structured to put an upper limit on what that risk is to help us quantify that moving forward.

The fourth component, which I think came up from Dr. Farley, is this idea that the agency can view population-based increase in the rates of antimicrobial resistance -- for example, the carbapenems -- as being a legitimate safety concern that might trigger regulatory remedies to either restrict or remove for the approval going forward. It seems to me that with a combination of all four of those components together, there may be a way forward in which the overall benefit-risk ratio would be acceptable.

DR. BADEN: Thank you.

Dr. Green?

DR. GREEN: Thank you. So I'd be very surprised if this really was deserving of a boxed warning because we could argue that with each new carbapenem that's approved in the hospital setting, the risk is similar to selecting for carbapenem resistant, and I usually think of that as a

patient-specific safety for that. And I'm not sure that it meets a contraindication either, which sort of puts us between limitation of use and warnings and precautions.

I like the idea of limitations of use. I really like it in the context of inpatient, where this drug wasn't really talked about, but we do talk about giving oral antibiotics in the inpatient setting and where EMRs can be more enforcing to write the order. You get a warning, and then you might also need to call and get an approval.

I'm not sure whether warnings and precautions, how much that impacts the reader, as opposed to maybe limitations of use, and I think you'd be studying how effective using these tools would be to accomplish the goal that even this applicant says they would really want in this scenario. But looking at it, I think limitations of use, and I think in the warnings and precautions, identifying the fact that it didn't succeed, that it was not noninferior as stepdown therapy for upper tract infection or for

complicated intra-abdominal infection, and that there are no data for it on other sites of infection where you might want to use it for stepdown therapy, would probably be of value to emphasize that.

Then, obviously, it would behoove all of us in the community, whether it's the agency, the CDC, the societies, and those of us that do stewardships in our hospitals, to try to achieve that education. It's just not always that easy to do, and some use could be in remote areas, in communities that don't really have a lot of communication with the academic centers where this information might be more amplified and really enforced, but trying to do it certainly would make sense and really trying to highlight that information.

Maybe when the applicant's representatives are talking to people in their office, they could follow the same party line and try to get at it. It's the best that I think we could probably do. Certainly, again, as we've said earlier, I think there are patients who would really benefit from

this. I just think their number might be relatively small compared to the number in whom it would be considered being used. Thank you.

DR. BADEN: Ramya, do you want to respond to that?

DR. BADEN: Okay. Dr. Joniak-Grant?

DR. JONIAK-GRANT: Thank you.

Dr. Joniak-Grant. I think it would be useful to have the limitations of use saying not for complicated, not first line, not part of stepdown. One thing to consider about why those matter would be having the antimicrobial resistance in the warning, as more and more patients are reading the inserts, but at least in my experience with different patient communities, they tend to read the warnings. The limitations of use, they use a lot of semantics. It's not really clear what everyone's trying to say for people that are not used to the language, so that would be a way to maybe have patients help keep some of their doctors a little honest.

With that, I might even consider having in

there some type of warning that's saying that with the use of this drug, you're more likely to have the microbiology failure without clinical symptoms than other drugs, and the significance of this is unknown, so patients might be a little bit more on the lookout for symptoms to be coming back.

DR. BADEN: Thank you.

Ramya?

DR. GOPINATH: Thank you. This is Ramya Gopinath from FDA. I wanted to just provide one point of clarification, and then ask a question. The point of clarification is just to note that there has been a lot of conversation about the microbiologic persistence part of it. And as Dr. Hunsberger pointed out earlier, while the clinical response was very similar across both the studies, I just wanted to make the point that in Study 310, the superiority in the MITTS population was actually driven by the microbiologic response.

I think that's an important point to keep in mind because when we talk about the clinical versus the microbiological responses, there is some

discordance, but in one study, it was detrimental for the applicant and what they were trying to achieve, but in the other one, it actually drove the overall response for sulopenem. So that's number one. I think that was the main point that I was trying to make.

I just wanted to ask a clarifying question for the panel. When you are all talking about the populations of potential patients that should be considered, and we are talking about resistance, just a clarification about whether we are talking about resistance to other first-line agents or whether we're talking about resistance as in ESBL producers, or just a little additional clarification about that point.

DR. BADEN: Anyone want to field that?

(No response.)

DR. BADEN: I think this is such a dynamic issue, so even what we think today may be different a year from now in terms of how we think about resistance, measure it, but I think my sense of resistance, the greatest concern is carbapenem

resistance because this would be selecting for that. But how one thinks about resistance in general may be the trigger to use, while the trigger to withdraw may be carbapenem resistance.

So resistance itself is a dynamic problem that this agent will apply pressure on, so it depends how you're using the resistance concern because I think if it was M [sic - amox] susceptible, why wouldn't you use amox? So it has to have enough resistance to say you should be in this arena. So I think the resistance will be a dynamic sort of question depending on the issue you're trying to resolve.

Barbara, and then we will have to wrap up because it's the magic hour.

DR. GRIPSHOVER: I was just getting back on the labeling things, and maybe a little to what you were saying because I think as a group, we are worried. I think in terms of labeling, we would want -- I hope I'm not speaking for them -- that it would be resistant to other oral options and maybe with allergies. I had it up because I think,

ideally, I would like that to be included in the indication. I think it's great also in the limitations, but I'm afraid people don't always read limitations, so if I had my two cents, I'd put it right up front.

DR. BADEN: Thank you.

Sally?

DR. HUNSBERGER: I think what you said is really important, so I totally agree. The other piece is I think the information that needs to be included is, for 310, there was only 3 percent that was resistant, and I think people need to know that it's not a high proportion of people that you would need to start out with. So I think if you put that information in there about what the proportion is in the population, that should be -- I mean, I'm a numbers person, so to me that would persuade me, but hopefully it would persuade other people, too, that it's a small group that may need it.

DR. BADEN: Thank you.

The hour is late, so if there no other burning comments, then in summary, if I'm taking

the temperature of the committee correctly, overall, I have the sense from the committee that there are certain circumstances where this agent may be beneficial to our patients. There is a high risk of off-label use, significant community risk to amplification of resistance, particularly CRE. There's individual risk to that amplification, not just community risk. Mitigation is likely the center in a timely identification of who's at highest risk, and whatever tools make sense for that, that are available.

Postmarketing surveillance will be essential, as this is a dynamic problem, so the solutions will have to keep up with the evolutionary pressures; and if there is some mechanism for regulatory review with some period of time and some new data with postmarketing studies to be able to further refine the label, and the education, and the optimization of its use. I think that is what I heard as multiple themes from the committee.

If that doesn't provoke questions from the

agency, I think from the committee's discussion, my sense is we share your enthusiasm for new treatments for our patients. We are concerned with how this will fit in so that it doesn't create new problems for us, and we appreciate the agency's hard work in really trying to think this through and get as much input as possible, including from us, so thank you.

Before we adjourn, any last comments from the FDA?

DR. FARLEY: Yes. Thank you to the committee. You did not disappoint in the quality of your feedback, very, very helpful suggestions, and I wish you all safe journeys home tonight. Thank you very much, and it was, again, great to see everyone in person. Thanks.

Adjournment

DR. BADEN: Thank you.

Now, we will adjourn the meeting.

(Whereupon, at 4:08 p.m., the meeting was adjourned.)