ANTI-INFECTIVE DRUG ADVISORY COMMITTEE MEETING

November 19, 2008

DR. RELLER: I'd like to welcome all to the Anti-Infective Drugs Advisory Committee Meeting. We have a full agenda today. And I would like to begin the meeting with the following comments. For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be fair and an open forum for discussion of these issues, and that individuals can express their views without interruption.

As a gentle reminder, individuals will be allowed to speak into the record, only if recognized by the Chair. And I would also add that we have much expertise around the table and we would like full participation. Consequently, please, keep your remarks focused and share the time with all of your colleagues.

In the spirit of the Federal Advisory Committee Act, and the Government and Sunshine Act, we ask that Advisory Committee members take care, that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are

anxious to speak with the FDA about these proceedings; however, the FDA will refrain from discussing the details of this meeting with the media until its conclusion.

Also, I'd like to remind everyone to silence your cell phones, if you have not already done so. And I would like to identify the FDA press contact, Karen Riley. If you are here, Karen -- thank you.

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

We will next introduce the members of the committee and then hear from our designated Federal Official, Dr. Janie Kim, to my right, who will read the conflict of interest statement.

Dr. Kauffman, if you would introduce yourself and your affiliation, and we'll go around the table right to left this morning.

DR. KAUFFMAN: I'm Carol Kauffman, Professor of Internal Medicine at the University of Michigan and Chief of the ID section at the Ann Arbor VA.

DR. GUTIERREZ: Kathleen Gutierrez, Pediatric Infectious Disease Stanford University, Lucille Packard

Children's Hospital.

DR. FOLLMANN: I'm Dean Follmann, Head of Biostatistics at the National Institute of Allergy and Infectious Diseases.

DR. WEINSTEIN: I'm Mel Weinstein, Professor of Medicine in Pathology at Robert Wood Johnson Medical School in New Jersey. I'm the Chief of Infectious Diseases and the Director of the Microbiology Laboratory.

MR. LEVIN: Arthur Levin, Center for Medical Consumers in New York, and a consumer representative.

DR. HILTON: Joan Hilton, Professor of Biostatistics, University of California, San Francisco.

DR. CROSS: Alan Cross, Professor of Medicine, University of Maryland at Baltimore.

DR. STECKELBERG: Jim Steckelberg, Chair of Infectious Diseases and Professor of Medicine Mayo Clinic.

DR. THOMAS: Jeanine Thomas, the patient representative. I'm the founder of MRSA Survivor's Network and the National Spokesperson for MERSA.

DR. BLACK: I'm Henry Black at the New York

University School of Medicine and Member of the Cardiovascular Disease Prevention Program.

DR. CRAGAN: I'm Jan Cragan from the birth defects -- Birth Defects Branch at CDC.

DR. COX: Good morning. I'm Ed Cox, the Director of the Office of Antimicrobial Products, CDER FDA.

DR. LAESSIG: Katie Laessig, Deputy Director, Division of Anti-Infective and Ophthalmology Products FDA.

DR. NAMBIAR: Good morning. Sumati Nambiar. I'm Deputy Director for Safety, Division of Anti-Infectives and Ophthalmology Products.

DR. POHLMAN: There. Now I've got it. Good morning, Janice Pohlman, Acting Medical Team Leader, Division of Anti-Infectives and Ophthalmology Products at FDA.

DR. SHELBY: Good morning. I'm Mike Shelby, Director of the Center for Evaluation of Risks to Human Reproduction at the National Institute of Environmental Health Sciences.

DR. SMITH: Good morning. My name is Mary

Alice Smith. I'm an Associate Professor in the Department of Environmental Health Science. And my specialty is in reproductive and developmental toxicology.

DR. PAGANINI: Hi. Emil Paganini. I'm Chair of the Section of -- Dialysis Section for Extracorporeal Therapy and Critical Care Nephrology. Retired. And now a consultative nephrologist at Cleveland Clinic Foundation, Cleveland, Ohio.

DR. MIRKES: Good morning. My name is Phillip Mirkes, and I'm a Developmental Toxicologist, and until last December a Professor at Texas A&M University.

DR. SEPTIMUS: Ed Septimus, Clinical Professor of Medicine, University of Texas Health Science Center in Houston, and Medical Director for Infection Prevention for HCA Healthcare System out of Nashville.

DR. NELSON: Lewis Nelson. I'm an Associate Professor of Emergency Medicine at New York University School of Medicine and a Medical Toxicologist.

DR. LESAR: I'm Timothy Lesar, Director of Clinical Pharmacy Services, Albany Medical Center in Albany, New York.

DR. BENNETT: Good morning. I'm Jack Bennett. I'm Director of the Infectious Disease Training Program at NIAID and Chief of the Clinical Mycology Section for the Laboratory of Clinical Infectious Disease at NIAID.

DR. LEGGETT: Jim Leggett, Infectious Diseases, Providence Portland Medical Center, and Oregon Health and Sciences University.

DR. FLEMING: Thomas Fleming, a Professor of Biostatistics, University of Washington.

DR. GOETZ: Matthew Goetz, Professor of Clinical Medicine, UCLA, and Chief Infectious Diseases VA Greater Los Angeles Healthcare System.

DR. ALSTON: Kemper Alston. I'm a Professor of Medicine at University of Vermont College of Medicine and Fletcher Allen Healthcare is Burlington, Vermont.

DR. KATONA: Peter Katona, Associate Professor of Medicine and Infectious Disease at UCLA.

DR. REX: John Rex, formerly Professor of Medicine and Infectious Diseases at the University of Texas Medical School at Houston. Currently Vice President for Clinical Infection at AstraZeneca

Pharmaceuticals. As Dr. -- as Janie Kim will doubtless note, my role on the committee today is that of nonvoting industry representative. In this role I represent regulated industry as a whole, rather than AstraZeneca Pharmaceuticals or any other specific sponsor.

DR. RELLER: Barth Reller, Professor of Medicine and Pathology and Director of the Medical Microbiology Program at Duke University Medical Center.

I'm the Acting Chair for this meeting, being asked to do so, having previously served on the committee and chairing the committee.

Dr. Janie Kim on my right, our designated federal official, will now read the conflict of interest statement.

DR. KIM: Thank you, Dr. Reller.

The Food and Drug Administration is convening today's meeting of Anti-Infective Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With exception of the industry representative, all the members and temporary voting members of the committee are special government employees or regular Federal employees from other agencies and are

subject to Federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 USC, Section 208 and Section 712, of the Federal Food, Drug, and Cosmetic Act are being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with Federal ethics and conflict of interest laws. Under 18 USC, Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have potential financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the FDA, FD&C Act, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees with potential financial conflicts when necessary to afford

the committee essential expertise.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 USC, Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents, and royalties, and primary -- or principle employment.

Today's agenda involves a new drug application, NDA 022-153 -- sorry. Excuse me a moment. We -- I need to take a brief break. One moment.

DR. RELLER: While Dr. Kim is retrieving the relevant information, a couple of additional remarks about today's process. Today -- this morning, and this afternoon, and tomorrow morning, we'll have three sponsor presentations, and then full discussion by the committee.

In this open forum, I think it's incumbent upon all of us to recognize how crucial it is to have

openness and fairness. And, again, I ask that the remarks be focused succinct so that we can stay on schedule, and that there is balance in terms of the range of discussions from the many persons with great interest in this -- these topics.

DR. KIM: Okay.

DR. RELLER: Thank you. Dr. Kim. Also, we had a few technical glitches yesterday afternoon in the voting process, and this would provide me an opportunity to refine that process.

We have the three buttons on the lower panel. You'll vote yes, no, or abstain. There will be opportunity, if one hits the wrong buttons, to change it right up and to the point that I say, are there any additional difficulties with the instrumentation? And if not, I'll say the vote is now locked in. And only at that point will the last tap of the button be captured. Then we'll have a display of the results, which I shall read formally into the record.

When we duplicate some of the statements and readings that were made yesterday, it's because each of these sessions is recorded independently and captured for

the record. Electronic advances are marvelous. They're not yet perfect.

I might add as an aside that, this is my first experience, with what I presume is tantamount to a TelePrompTer in front of me so I can see -- when I'm staring down at the floor, it's not owing to lack of interest, it's in trying to preserve the neurological function of my upper body with the twists and turns. But I can see everything that's said, every vote that's captured, right here in front of me on the screen.

DR. KIM: I'm sorry.

DR. RELLER: Dr. Kim.

DR. KIM: I apologize for the interruption.

Today's agenda involves a new drug application, NDA 022-110, Telavancin, Theravance Incorporated, for the proposed treatment of complicated skin and skin structure infection. This is a particular matter meeting during which specific matters related to Telavancin will be discussed.

With respect to the FDA's invited industry representative, we would like to disclose that John -- Dr. John Rex is participating in this meeting as a

nonvoting industry representative, acting on behalf of regulated industry. Dr. Rex's role at this meeting is to represent industry in general and not any particular company. Dr. Rex is employed by AstraZeneca.

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 the FDA participants have a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusions will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have with any firms at issue. Thank you.

DR. RELLER: Dr. Sumati Nambiar will now provide the opening remarks for today's deliberations.

DR. NAMBIAR: Thank you, Dr. Reller. Good morning and welcome to day two of our Advisory Committee Meeting.

In my introductory remarks I'll briefly touch upon some important aspects regulated by ground of Telavancin.

By way of introduction, Telavancin is a

lipoglycopeptide antibacterial for intravenous use. It is produced through chemical modification of Vancomycin, bactericidal, and acts by inhibiting bacterial cell wall synthesis. It's active against Gram-positive bacteria, including methicillin-resistant Staphylococcus aureus. And the formulation contains Hydroxypropyl Beta Cyclodextrin.

The applicant's proposed indication is for the treatment of complicated skin and skin structure infections caused by Staphylococcus aureus, including methicillin-resistant isolates, Streptococcus pyogene, Streptococcus agalactiae, Streptococcus anginosus group, and Vancromycin-susceptible Enterococcus faecalis.

As we discussed yesterday, there are several antibacterials approved for the agent of -- approved for the indication of complicated skin and skin structured infections. Linezolid, Daptomycin, Tigecycline are approved for cSSSI due to MRSA. Vancomycin being an older drug has a slightly different label. The product label states that it is approved for the treatment of serious or severe infections caused by susceptible strains of methicillin-resistant Staphylococci. And it

also has an indication for the treatment of skin and skin structure infections.

On December 19th, 2006, the applicant, Theravance, submitted a new drug application for Telavancin for the indication of cSSSI.

On October 18th, 2007, the agency issued an approval letter, which included the following: Issues identified at the manufacturing facility had to be resolved. And the applicant was asked to better delineate the overall benefit risk profile of Telavancin, taking into consideration the following factors: The decreased efficacy seen in patients with renal impairments, renal adverse events, including changes in renal laboratory parameters, findings of the therapeutic study, and the findings of teratogenicity in annuals.

On January 21st, 2008 Theravance submitted a complete response to the approval letter. An advisory committee meeting had been planned for February 27, 2008 to discuss this application; however, the meeting was canceled as inspection findings at one clinical site and at the contract research organization, raised concerns about good clinical practice violations with the

potential to effect data integrity. So, it was determined that additional inspections were necessary to evaluate the extent of the problem and to rule out a systematic pattern.

On October 24, 2008, we were made aware of a press release by the EMEA stating that Astellas had withdrawn its marketing authorization application for Telavancin.

The Division of Scientific Investigations at the FDA conducted a series of inspections. There were a total of 13 inspections conducted. This included 11 clinical sites, a specific contract research organization, and the applicant.

These inspections were conducted in two cycles. The first cycle was done prior to cancellation of the Advisory Committee Meeting planned for February of this year. In the first cycle, four clinical sites, CRO and the applicant were inspected.

In the second cycle, which was conducted after cancellation of the Advisory Committee Meeting, seven clinical sites were inspected. Additionally, a targeted audit was performed by the applicant.

In the first cycle of inspections, major deficiencies and good clinical practice were noted at one site, identified as Site 38091. Efficacy data from this site were considered unacceptable. The inspection observation suggested that there was inadequate study monitoring. This resulted in an inspection of this particular CRO. And this CRO that served as the monitor for most clinical investigators was inspected, and it was determined that the CRO had failed to implement appropriate corrective actions at this particular site; however, monitoring of the remaining three clinical sites by the CRO were deemed to be adequate.

In the second cycle of inspections, at all level -- at all seven sites, the observed level of GCP compliance supported integrity of data. Major violations with the potential to effect data integrity consisted of ECG data from two sites, where the ECG data were not obtained according to the time frame specified in the study protocols. Study monitoring by the CRO was noted to be adequate at these seven sites.

Theravance, the applicant, had performed a targeted audit from April to June of 2008, which included

inspection of 31 sites, for a total of 24 percent of all sites. And they also performed an audit of the records for 683 patients, accounting for 36 percent of all patients. The site selected for this audit were based on prior monitoring reports to identify those suggestive of significant GCP violations. And this included five of the 11 sites inspected by the agency. Site 38091 was not included in this audit.

I guess it's moving on its own. Study monitoring was noted to be inadequate at two clinical sites, accounting for a total of 22 patients. The applicant concluded that there was no systematic pattern or incidents of GCP violations that could effect interpretation of the reported efficacy and safety data for this new drug application.

So, this is a summary of the overall assessment of data integrity. In the first cycle of inspections, concern was raised regarding data integrity at one of the four clinical sites, and also regarding adequacy of monitoring by the CRO. This necessitated additional inspections and an applicant audit to evaluate systemic problems with this NDA.

Overall data reported in the NDA are -- were considered to be reliable with the following exception: Efficacy data from three sites were considered unreliable, Site 38091, based on inspection findings by DSI; and two additional sites based on the targeted audit performed by Theravance. ECG data from two sites were considered unreliable. And data from these sites are excluded, both from the FDA and applicant analyses.

To give you an overall summary of what the clinical development program for this drug, is specifically for the indication of complicated skin and skin structured infections. There are two Phase 3 trials, with Telavancin 10 milligram per kilogram per day was compared to Vancomycin.

Additionally, two Phase 2 skin and skin structure infection trials were also conducted which used either 7.5 or 10 milligram per kilogram dose.

Two additional trials was a Phase 2 study in patients with uncomplicated Staph aureus bacteremia; and two Phase 3 studies in patients with hospital-acquired bacteria -- hospital-acquired pneumonia. Both of these indications have not yet been reviewed by the agency.

So, the issues that we would like the advise -- the committee members to consider during our discussion this morning, is the overall benefit risk profile of the drug, taking into consideration the following factors. Telavancin is a bactericidal agent with -- and is effective against MRSA. Limited treatment options are available for the treatment of MRSA. The indication studied here is cSSSI, and there are other therapies available for this particular indication.

Safety issues identified with this drug included renal adverse events, the finding of teratogenicity in animals and an effect on QT interval.

Following is the outline of FDA presentations this morning. Dr. Janice Pohlman will discuss the Phase 3 cSSSI trials, both from an efficacy and safety standpoint. And we'll briefly touch upon safety from the HAP trials, based on a safety update that was provided by Theravance.

Dr. Zhou Chen will discuss findings from the nonclinical studies, with focus on the segmental studies in rats, rabbits, and mini pigs, and also in the renal findings.

Dr. Karen Feibus from the Pregnancy Maternal Health Team will discuss the role for Telavancin in pregnant women and will focus on pregnancy risk classification and overall risk benefit assessment.

Dr. Susan Berkman from the Office of Surveillance and Epidemiology will discuss risk management considerations for Telavancin.

I would now invite Dr. Coleman.

DR. COLEMAN: Thank you. Good morning. I'm Rebecca Coleman, Vice President, Regulatory Affairs and Quality.

My colleagues and I are pleased to have the opportunity to describe the data supporting Telavancin as an important addition to the therapeutic options available to treat Gram-positive infections.

The development of Telavancin was a successful result of a discovery program aimed at identifying an antibiotic that has activity against resistant bacteria and that discourages the emergence of resistant strains.

Telavancin has been studied in Gram-positive complicated skin and skin structure infections and in hospital-acquired pneumonia. This morning we will

describe data from the studies in complicated skin and skin structure infections. These datas support the approval of Telavancin for the treatment of patients with complicated skin and skin structure infections caused by susceptible Gram-positive organisms.

Dr. Ralph Corey, who served as the principle investigator for the Phase 2 and Phase 3 Telavancin clinical studies, and whose practice and leadership in infectious disease, provides him firsthand knowledge of the urgency of issues arising in the treatment of complicated skin and skin structure infection, will review the growing need for a new Gram-positive antibacterial agents.

Dr. Stephen Barriere had a medical emergency and will be joining us later this morning. In his absence, Dr. Roger Eckels (ph) will provide an overview of the nonclinical development of Telavancin, and of the clinical studies demonstrating the activity and tolerability of Telavancin in cSSSI. Dr. Anthony Scialli, Tetra Tech Sciences in Georgetown University will discuss the benefit risk assessment for the use of Telavancin in a pregnant woman. I will return to present

our proposed risk management plan. And, finally, Dr. Louis Saravolatz from St. John Hospital in Detroit will provide a treating physician's perspective on the overall benefit versus risk assessment for Telavancin in this indication.

Dr. Corey.

DR. COREY: Thank you, Becky.

Good morning, ladies and gentlemen. It's my pleasure to begin today's session by renewing a call-to-action for all of us entrusted with the treatment and prevention of infectious diseases. We are in the midst of an emerging crisis of antibiotic resistance for bacterial pathogens in the United States and, indeed, throughout the world.

Our focus today is resistant Staphylococcus aureus. Methicillin-resistant Staph aureus, MRSA, was first described in the United Kingdom in 1961, but remained an unlikely pathogen throughout the 60s, 70s, and early 80s. However, over the past two decades, rates of MRSA have steadily increased, and now most US hospitals reports over 60 percent of their Staph aureus methicillin resistant.

In recent years, the problem with MRSA has become more of an inpatient phenomenon. MRSA is now the most common cause of complicated skin infections in our US emergency rooms. This study from 2004, involving 11 university affiliated emergency department, shows that MRSA accounted for 59 percent of purulent skin infections. This publication also demonstrated that Staphylococcus aureus is continuously evolving, since almost all of their isolates for MRSA were USA 300 and contained the Panton-Valentine leukocidin.

To put this into clinical perspective, let me show you a couple of pictures of patients with complicated skin infections. MRSA often starts as what patients describe as a spider bite, which can quickly develop into an abscess, cellulitis, necrotizing fasciitis and even bacteremia .

The importance of MRSA infections is shown here. Dr. Clemmons (ph) stated, from the CDC, demonstrates that MRSA accounts for more deaths in the US than HIV, TB, SARS, and the vaunted bird flu combined.

A very important point is not on this slide, that is cellulitis was the third most common side of

invasive MRSA infection in this study. Six percent of the patients with invasive cellulitis died.

The antibiotics currently approved in the United States for complicated skin infections due to MRSA include Vancomycin, Daptomycin, Linezolid and Tigecycline. Though Vancomycin is the most frequently prescribed antibiotic for patients requiring intravenous therapy, clinicians use all of these antibiotics as their patients and circumstances require. Unfortunately, each of these approved agents has weaknesses, as well as growing resistances, like the Linezolid resistant Staph aureus outbreak in Barcelona recently reported at IDSA. As a result, multiple options are needed to treat serious Staph infections.

Staphylococcus is a continuously evolving organism, becoming more virulent and more resistant. Fortunately, overt resistance to Vancomycin is still uncommon, VRSA. However, VISA, which I consider totally resistant also to Vancomycin, hetero-VISA and MIC creep are increasing problems. Hetero-VISA incidents and endocarditis isolates worldwide is now up to 28 percent. And complication rates in this group are more than double

those of nonhetero-VISA patient -- infected patients.

Similarly, Antonio Soriano and Tom Lodese (ph) have demonstrated that patients with MICs at 1.5 to 2, still within the sensitive range, fair worse than patients with MICs at .5 to 1.

Treatment failure has -- for complicated skin infections has serious consequences. Earlier this year Ellsberg (ph) and Colleagues published a retrospective review of over 47,000 cases of hospitalized patients with complicated skin infections. Nearly 23 percent of these patients had evidence of failure of the initial antibiotic regimen. Treatment failure was associated with three-fold increase in mortality, and a five-day increase in inpatient antibiotic therapy.

MRSA is an evil, clever organism. Two years ago I characterized it as being the Darth Vader of Gram-positive infections -- organisms. And I still stick to that description. It is increasing in incidents. It's increasing in virulence. It's increasing in resistance.

Alternative therapies have significant limitations. We need new, effective antibiotics for our patients with complicated skin infections due to MRSA.

Thank you.

Now Dr. Eckels will present the clinical program.

DR. ECKELS: Thanks, Ralph. Good morning. My name is Roger Eckels and I'm an infectious disease physician and consultant with nearly 30 years experience in antibiotic drug development. I appreciate the opportunity to describe the microbiologic and pharmacologic characteristics of Telavancin, and the design of the complicated skin and skin structure infection studies that demonstrate the efficacy and safety of the medicine.

Telavancin is a novel lipoglycopeptide antibiotic. The drug exerts its antibacterial effects via a unique dual mechanism of action, in addition of cell wall synthesis and disruption of bacterial membrane function.

This mechanism results in a broad Gram-positive spectrum, increased potency, and bactericidal activity. In addition, the dual mechanism may confer Telavancin's activity against isolates of Staphylococcus aureus that are less susceptible or nonsusceptible to

currently available agents, and confer low potential for the emergence of resistance to Telavancin.

In global surveillance studies, Telavancin has shown consistent and potent activity across a wide-range of organisms. This includes both MSSA and MRSA, as well as various Streptococci, which are susceptible to low concentrations.

Additionally, Telavancin is active against Vancomycin-susceptible Enterococci with MICs similar to Staph aureus. In surveillance studies, all proposed complicated skin and skin structure infection pathogens, are susceptible to Telavancin with MIC values of one microgram per ML or less.

This potency is methicillin than other approved MRSA antibiotics. Telavancin is shown by the yellow line to the left of the others, reflective of its greater potency against a collection of MRSA clinical isolates from the United States and Europen surveillance studies compared to Vancomycin, Daptomycin, and Linezolid.

Telavancin is active against Gram-positive pathogens that are nonsusceptible to Daptomycin or

Linezolid as demonstrated by the activity of Telavancin against clinical strains recovered during global surveillance studies.

While folious (ph) Vancomycin resistant strains of MRSA remain rare, as Dr. Corey noted, isolates that are intermediately susceptible, and especially those that are heteroresistant, are increasing in frequency and are associated with Vancomycin treatment failures, particularly VISA and hetero-VISA isolates that are nonsusceptible to Daptomycin.

All of these organisms remain susceptible to Telavancin, and there have been no clinical isolates that are not susceptible. Further, no specific mechanism of resistance to Telavancin has been identified among target organisms.

Telavancin has been studied in numerous models of infection that are predictive of outcome and human disease. In all of these models, studying the efficacy of Telavancin against a variety of organisms, including Staph and Strep, Telavancin was shown to be at least as effective and often more effective than comparator agents, including antistaphylococcal penicillins, against

MSSA, as well as Vancomycin, Daptomycin, and Linezolid against MRSA and VISA.

There have been no resistant mutants discovered in single-step selection or serial passage studies that have been conducted over 10 or 20 days. Isolates tested included strains of Staphylococci, including methicillin-resistant strains, Vancomycin-susceptible Enterococci and various Streptococci. And so far in clinical trials no strains with resistance development has been recovered during Phase 2 or Phase 3 studies in cSSSI or hospital-acquired pneumonia.

The pharmacokinetics of Telavancin are linear, with an elimination half-life supporting once daily dosing. Studies state peak and trough plasma concentrations following a 10 milligram per kilogram IV dose are approximately 90 and 10 micrograms per ML respectively.

Using these data, along with results from a neutropenic-mouse thigh infection model which has been shown to be predictive of outcome with antibiotics in humans, Monte Carlo simulations were performed to assess the probability of attainment of the PKPD target of AUC

over MIC of 219, found to result in one log killing of bacteria in the model.

The results indicate greater than a 99 percent target attainment for organisms with MIC as high as two micrograms per ML. The highest MIC observed to date for all Staphylococci, including MRSA, hetero-VISA, and VISA strains, as well as isolates nonsusceptible to Daptomycin or Linezolid, is one microgram per ML.

These data suggest that Telavancin should have efficacy in the treatment of infection due to pathogens that are unlikely to respond to Vancomycin or other available agents.

The Telavancin clinical development program includes studies in patients with serious Gram-positive infections, with the initial indications of complicated skin and skin structure and hospital-acquired pneumonia. Data from the Telavancin studies and hospital-acquired pneumonia have been submitted to the FDA in the form of a full safety update and have -- and a completed MDA is being prepared for regulatory review.

Over 1,600 patients in each treatment group were enrolled across all of the efficacy and safety

studies. In the complicated skin and skin structure studies there were approximately 900 patients in each treatment group, including 12 percent of patients who have moderate or severe renal impair, and nearly 20 percent of the patients were at least 65 years old.

In the HAP Studies, about 750 patients were enrolled in each treatment group, and as might be expected in this disease state, fully a third of these patients had moderate or severe renal impairment, and over half are greater than 65 years of age.

In cSSSI, the program included two identical double-blinded, randomized and multinational studies with enrollment conducted during 2005 and 2006, reflecting a contemporary patient population. 126 sites in 21 countries enrolled at least one patient. The inclusion and exclusion criteria in these studies were designed to enroll patients with complicated infections. For example, patients with self-limited infections, or infections with high surgical cure rates were excluded.

The studies compared Telavancin at a dose of 10 milligrams per kilogram, IV once daily. With Vancomycin, one gram IV Q 12 hours, the FDA approved

dose, which could, per protocol, be adjusted using site-specific guidelines for body weight and or renal function.

Additionally, as long as the blind was maintained for individuals at the site performing efficacy and safety assessments, Vancomycin serum level monitoring could be performed. It was expected that the patients would require at least seven days of intravenous therapy, up to a maximum of 14 days. Aztreonam and/or Metronidazole could be added for Gram-negative and/or anaerobic coverage respectively.

Approximately 900 patients were enrolled in each treatment group and received at least one dose of study medication. These patients are represented -- represented in the all-treated population. Clinically evaluable or CE subjects were those in the all-treated population who met all prespecified criteria for evaluability included in the statistical analysis plan.

The most common reason for nonevaluability were indeterminate outcome at the test-of-cure visit, the receipt of potentially effective nonstudy antibiotics, and having received less than the minimum specified

duration of therapy.

There are small differences between our CE population and the FDA defined CE population. The primary difference is application of a criteria for having the identification and susceptibility of the pathogen confirmed by the central laboratory. Theravance included patients whose pathogens were identified only by this local laboratory, but only in cases in which the sample was not sent to the central lab or not viable upon receipt.

We included these patients in the evaluable populations because of the observed concordance of local and central laboratory identification of Staph aureus and methicillin-resistance was greater than 95 percent.

The baseline demographic and disease characteristics in the studies were well matched across all treatment groups. Key differences were that there were more patients with severe renal impairment at baseline in the Telavancin group, and more patients in the Telavancin group who are bacteremic at baseline. Primarily with MRSA, which accounted for 40 percent of Gram-positive bacteremic Telavancin patients, and 20

percent of Vancomycin patients with positive blood cultures.

There were numerous characteristics consistent with a population of patients who had complicated infections. The average surface area of the infection site was nearly 20 percent of body surface area, and half the patients had lower extremity infections. There was a high rate of obesity, morbid obesity, and significant incidences of diabetes and peripheral vascular disease.

Approximately 70 percent of patients were hospitalized at baseline. And those who were not were eligible for outpatient IV antibiotic therapy programs. Approximately one-quarter of the patients had failed previous treatment with other antibiotics.

Staph aureus represented nearly 85 percent of the baseline pathogens, and more than 50 percent were MRSA, making this the largest cohort of MRSA complicated skin and skin structure infection studied in a clinical program to date.

The graph in each of the next three slides displays the point estimate of the difference of Telavancin minus Vancomycin for the specified endpoint.

And the bars on either side of that point estimate display the 95 percent confidence intervals around the treatment difference.

Point estimates to the right of the white zero line favor Telavancin. A point estimate to the left of the zero line would favor Vancomycin. The minus 10 percent line is indicated in blue, and none of the yellow lines cross the blue line, demonstrating noninferiority.

This is the all-treated population, which showed cure rates of approximately 77 percent for Telavancin, compared with approximately 75 percent for Vancomycin. The Vancomycin cure rates are similar to those observed in other double-blinded registrational trials, and are consistent with those anticipated in the noninferiority margin determination.

In the clinically-evaluable population, the confidence intervals also did not cross the blue 10 percent line, demonstrating noninferiority. The cure rates in both studies were in the high 80 percents, and were similar for both treatment groups. The Vancomycin cure rates remain consistent with those observed in other double-blinded registrational trials, supporting the

validity of these results.

More than 560 clinically-evaluable patients had MRSA as the baseline pathogen. In the clinically-evaluable population of patients with MRSA, for clinical cure, microbiological eradication, and overall response, the results showed a trend in favor of Telavancin, with response rates of approximately 90 percent for Telavancin, compared with approximately 86 percent for Vancomycin.

Various exploratory post-hoc subgroup analyses were performed on the data sets, primarily to confirm consistency of effect across the subpopulations.

Diminished efficacy in the Telavancin group, as renal function decreased, was observed in the clinically-evaluable population. Because the sample sizes in the moderate and severe renal impairment subgroups are small, we also examined the larger all-treated population.

In the all-treated population, the moderate renal impaired group showed a slightly higher cure rate for Telavancin; however, lower clinical response rates were observed for the Telavancin all-treated patients

with severe baseline renal insufficiency, with creatinine clearance less than 30 MLs per minute, as was seen in the clinically-evaluable population.

These observations were considered important and we worked diligently to understand these differences. However, our thorough assessment of the cause of these differences has been inconclusive.

As might be expected, patients with moderate and severe renal impairment were found to have more comorbid conditions predictive of poor outcome, compared with patients with normal renal function or mild renal impairment. They were older, more frequently diabetic with large lower extremity infections, primarily cellulitis and infected ulcers. In addition, the subset of patients have more cardiac disease, especially congestive heart failure.

Randomization was not stratified by renal function, and there were modest imbalances, such as higher rates of lower extremity infections and bacteremia among the Telavancin-treated patients. But this does not fully account for the differences in the outcome.

These and other variables known to effect

outcome were included in a multivariate logistic regression of the entire data set. The results reveal that numerous factors, such as those noted above, were found to be at least as important as the treatment by a creatinine clearance interaction.

When notable finding was that more patients in the Telavancin arm of the moderate to severe renal impairment subgroup had their treatment prematurely discontinued due to an adverse event, which was not necessarily related to study medication. In the clinically-evaluable efficacy analysis, these subjects discontinued due to adverse events were counted as clinical failures.

We also evaluated the possibility that failure to adequately dose adjust as renal function improved may have been responsible for lower cure rates, but this did not explain the outcomes.

In conclusion, we've explored the differences in outcome between the two treatment groups and the subset of renal impaired patients. From examination of various baseline characteristics and performance of a multivariate regression analysis, no firm conclusions can

be drawn. Treatment outcome in this population is related to multiple patient and disease factors. The proposed label should include the data showing the relationship between clinical response and creatinine clearance so the treating physicians will be able to make an informed decision in determining the benefit risk assessment for each patient.

The complicated skin and skin structure infection studies demonstrated the efficacy of Telavancin as being noninferior to Vancomycin. We note that the cure rates in the complicated skin and skin structure studies were lower in patients with severe renal impairment. Patients enrolled in these studies were representative of contemporary populations with the targeted infections. Efficacy endpoints also demonstrated noninferiority in a large cohort of patients with MRSA infection.

The safety of Telavancin at a dose of 10 milligrams per kilogram IV once daily has been evaluated in more than 1,000 subjects treated in our cSSSI Program. This total includes patients from Phase 2 studies who also receive Telavancin at 10 milligrams per

kilogram. Patients treated with Telavancin 7.5 milligrams per kilogram in Phase 2 and Phase 3 studies are not included in this data set. Parts of this safety presentation will also include supportive data from an additional 751 patients treated with Telavancin 10 milligrams per kilogram in the HAP Program.

Seventy-seven percent of Telavancin-treated patients experienced at one -- at least one adverse event, compared to 71 percent with Vancomycin. The majority of adverse events in both groups were mild to moderate in intensity. The incidences of serious adverse events and discontinuation of study medication due to an adverse event were low in both groups, but slightly higher in the Telavancin group. In the Telavancin 10 milligram per kilogram cSSSI Studies, there were nine deaths in the Telavancin group, and nine deaths in the Vancomycin group that were reported in the prespecified study window. One of the nine patients in the Telavancin group who died was treated with 7.5 milligrams.

The safety data collection window was up until the test-of-cure follow-up visit, or if there was no test-of-cure visit, up to 28 days following the day of

the last dose of study medication.

An additional seven deaths were reported outside the study window, one on Telavancin 7.5 milligrams, and four on Telavancin 10 milligrams, and two on Vancomycin. None of the out-of-the-window deaths were assessed by the investigator as related to study medication.

The most common adverse event was altered taste, which is described as a metallic or soapy taste. Two patients on Telavancin, and one patient on Vancomycin, discontinued for this adverse event. Foamy urine was also reported as a frequent side effect, but it was not associated with proteinuria, nor was it associated with renal impairment, and no patient discontinued study medication due to this side effect.

Nausea and vomiting were common adverse events occurring more frequently on Telavancin. Severe vomiting occurred in 0.4 percent of patients on Telavancin. The incidence of pruritus was higher in the Vancomycin group. And the composite incidents of infusion-related events was 11 percent in Telavancin, and 20 percent in the Vancomycin group.

Two safety issues in particular were further explored based on our clinical experience. The risk regarding QT prolongation and the risk for renal impairment. These are important, since they were suggested in preclinical models, and have been observed in clinical studies.

The effect of Telavancin on cardiac repolarization was extensively evaluated in a double-blinded placebo controlled thorough QTc study comparing Telavancin to Moxifloxacin in 160 healthy subjects. The results showed a mean change of less than 5 milliseconds, and a maximum change between 12 and 15 milliseconds. The study also revealed a nearly flat dose response relationship for Telavancin based on doubling the dose. The 15 milligram per kilogram dose was poorly tolerated due to nausea and vomiting, preventing the assessment of higher doses.

Importantly the mean and maximum changes from baseline were numerically less than, or conservatively similar to Moxifloxacin, a drug generally considered of minimum risk for torsade.

In response to our findings in the Phase 1

study, a thorough evaluation of QT changes was included in the Phase 2 and Phase 3 cSSSI Program. In these studies, compared to Vancomycin, the difference in mean and maximum changes in QTc from baseline were approximately 7 to 8 milliseconds greater in the Telavancin group. From a clinical perspective, examination of outliers of this particular importance in these studies -- in these types of studies. These were identified as either a maximum change from baseline of a 60 millisecond, or a maximum value of 500 milliseconds, or both. Of these two measures, the greater than 500 millisecond threshold is considered clinically relevant for the risk of torsade. The incidences of a greater than 60 millisecond change were 14 patients for Telavancin and 5 for Vancomycin. One in two patients respectively in the Telavancin and Vancomycin arms experienced a maximum value greater than 500 milliseconds.

One patient in the Vancomycin arm showed both a greater than 60 millisecond increase, as well as a maximum value of greater than 500 milliseconds. No patient on the Telavancin arm showed both changes.

A more powerful database to examine QTc outliers is the experience amongst the patients with HAP. In the HAP Studies, there were no numerical imbalances in QTc outliers of greater than 60 milliseconds, or greater than 500 milliseconds.

Cardiac adverse events are presented for both groups. Of greater clinical significance, there were identical numbers of serious cardiac adverse events in the two treatment groups. Two patients in the Vancomycin group experienced cardiac events that led to discontinuation of the study medication. There were similar numbers of patients who died due to a cardiac event. An independent expert cardiologist, blinded to treatment assignment, reviewed the serious cardiac events that led to death and concluded that there were no imbalance in deaths presumed cardiac, with most deaths complicated by a multiorgan failure.

In summary, the thorough QTc study demonstrated that the QT prolonging effect of Telavancin was numerically less than, or conservatively similar to that of Moxifloxacin, a widely used fluoroquinolone.

In the Phase 2 and Phase 3 cSSSI Studies, the

frequency of clinically meaningful QTc outliers was similar in the two treatment groups, as were the incidences of cardiac serious adverse events. Finally, there was no difference in cardiac deaths or total mortality between the two treatment groups.

The totality of the data support a low degree of arrhythmic risk. The risk management plan to be discussed later in this presentation will include labeling and education regarding cardiac risk.

Based on a preclinical signal, and the known renal excretion of Telavancin, the clinical studies included a thorough assessment of renal effects of Telavancin and a further independent blinded expert review of renal serious adverse events.

More patients treated with Telavancin had a renal event, compared to those treated with Vancomycin. There was an imbalance in patients with severe renal impairment at baseline, with more in the Telavancin group. But this does not fully explain the differences in the incidents of events. This difference was also observed for serious renal adverse events and discontinuation due to adverse events.

Event terms listed at the bottom of the slide were pooled and will be referred to as renal event or serious renal events for the remainder of the presentation.

One patient had acute tubular necrosis, but also had renal insufficiency listed as an adverse event, and is included in this analysis.

One patient treated with 10 milligrams per kilogram of Telavancin died in part due to a renal event, as did a patient treated with Vancomycin.

One Telavancin patient treated in the 7.5 milligram per kilogram dose level died from a renal event, as well as sepsis and respiratory distress.

Another Telavancin patient, a 95-year-old man with chronic renal failure at baseline, died outside the study reporting window after refusing medically indicated hemodialysis.

Given the observed risk of renal events, further analysis was conducted to determine the populations most susceptible to developing an event, as well as the magnitude and impact of the risk.

In addition, expert nephrologist, including

Dr. Julie Lewis who is with us here today, were asked to help characterize the risk and provide expert opinion on appropriate monitoring and management.

The patients most susceptible to developing renal impairment were those with risk factors for renal impairment at baseline, such as congestive heart failure, diabetes, and sepsis. If no baseline risk factors were present, the incidents of events was low and similar in the two groups. These findings were corroborated by a multivariate logistic regression, demonstrating that underlying renal dysfunction and cardiovascular disease were at least as important as treatment in predicting occurrence of renal adverse events.

To further assess the magnitude of the renal risks associated with Telavancin, renal events were also reviewed in a hospital-acquired pneumonia studies. These results are informative because the population in HAP Studies is particularly susceptible to renal injury. In the HAP Studies, the same pattern was observed with renal AEs concentrated in patients with baseline comorbidities associated with renal risk; however, in the HAP Studies the relative differences between treatment turned out to

be somewhat less compared to the skin studies.

To determine the clinical impact of renal events that occurred, the reversibility of these events was explored. Sites were queried for additional follow up after the close of the study because the length of the follow up in this study was relatively short compared to the time it might take to fully recover from a renal insult.

The three patients in this table are noted by the FDA to have had a renal SAE, with final creatinine value that remains two-fold higher than their baseline. We obtained additional follow up in two of these three patients, Patient 2099 and 2498, indicating that their creatinine had further decreased and was below the 2X baseline.

For the third patient, no additional information was available.

To further characterize the magnitude of the renal impairment in the cSSSI Studies, clinically meaningful increases in serum creatinine were examined for Telavancin and Vancomycin. These increases were defined as the post baseline serum creatinine of at least

1.5 milligrams per deciliter, and at least a 50 percent increase over baseline. There were more Telavancin patients with creatinine increases than Vancomycin patients, six percent versus two percent. Fifty percent of Telavancin patients have a maximum creatinine value less than 2 milligrams per deciliter. And when the two rows are combined, 85 percent of the patients on Telavancin had maximum values less than 3 milligrams per deciliter, compared with a similar percentage of patients on Vancomycin.

All nine patients with creatinine clearances greater than 3 milligrams per deciliter, from both the Telavancin and Vancomycin groups, are included in the serious renal adverse events.

As shown here, in most, but not all, Telavancin-treated patients who had normal renal function at baseline, but then experienced a potentially clinically significant increase in creatinine on therapy, creatinine was following or had returned to baseline at last patient contact. Similar results are observed for patients with abnormal creatinine at baseline.

One patient stands out here with a high

creatinine value that did not decline under observation. This was a 74-year-old man with tetraparesis, and a chronic urethral catheterization, received a single dose of Telavancin and then was switched to Vancomycin due to mild exanthema.

The day after Telavancin was discontinued, the creatinine remained at baseline level of 0.8 milligrams per deciliter. On day nine, Gentamicin was added to his antibiotic regimen for the treatment of a UTI. His creatinine was 3.0 on day nine, and rose to 4.5 on day 35, which is the last creatinine available. No further follow-up information was available from the study site.

In conclusion, more patients treated with Telavancin had renal events compared to those in the Vancomycin arm. The patient population most susceptible to developing events, included those with pre-existing risk factors for renal impairment, such as CHF, blood pressure abnormalities, diabetes, and sepsis.

Nearly all the patients with sufficient follow up had recovered or were improving, which is consistent with antibiotic induced renal impairment.

An independent panel of expert nephrologists

conducted a blinded review of the renal serious adverse events in support of the conclusion that they were consistent with renal effects observed with other antibiotics commonly used in clinical practice. They also determined the effects would be expected to be reversible.

The risk management program to be described will also address this issue. One component of this program should be the labeling that recommends renal monitoring for all patients, and dosage adjustment based on estimated creatinine clearance.

Another blinded expert panel reviewed the preclinical reproductive toxicology studies to determine the potential risk in humans. Dr. Anthony Scialli led the expert panel and will present the results, along with the basis for the proposed pregnancy C category labeling.

Dr. Scialli. You have to lift this up. Because if you hold it down it here, it doesn't necessarily transmit.

MR. SCIALLI: Good morning. My name is Tony Scialli. And in addition to my clinical and academic responsibilities, I also run a nonprofit foundation

called the Reproductive Toxicology Center. One of the things that we do is to operate an online database called Reprotox that's used by clinicians, obstetricians, genetic counselors, and others, who are interested in learning about the potential adverse human reproductive effects of drugs and other chemicals. So, I've evaluated quite a large number of experimental animal studies very similar to those about which I'm going to tell you this morning.

These studies involve the dosing of usually two species, rat and rabbit, from implantation through the end of formation of most of the major organs, examination of fetal animals near term, and evaluation at doses as high as those producing some degree of maternal toxicity, in order to provide an adequate challenge to the species and bring out potential adverse effects on development.

Now, the studies reviewed were reviewed as part of a program involving another independent expert, Dr. Jeanne Manson. Dr. Manson is a very experienced reproductive and developmental toxicologist who has performed dozens, if not hundreds, of these kinds of

studies over a career spanning more than 30 years.

Dr. Manson and I were sent the study reports, including all of the data tables. We were asked to perform our review independent of one another. We were not told how the data were interpreted by the sponsor, and we did not know how the data were interpreted by the FDA.

At the end of our review, we wrote down our conclusions and then compared them, and our conclusions were identical.

Our conclusions were that the only effects of Telavancin that were clearly demonstrable in these studies were a small but statistically significant decrease in fetal weight at 100 and 150 milligrams per kilogram per day in rats. Now, when analyzed on the more conventional litter basis, statistical significance was only seen at the high dose, at the 150 milligram per kilogram per day dose. The decrease in fetal weight was 6 percent and 8 percent, which is a very small decrease, but it was statistically significant and it counts.

In contrast to the conclusions of our respective colleagues at FDA, we did not find a

teratogenic signal for Telavancin. The limb findings in these studies were mechanistically not similar to one another. In other words, embryologically they were not the same abnormality. They were not reproducible in rats. And they were not attributable to treatment with Telavancin.

I'd be delighted later during the question and answer period to explain in detail how our findings differed from those of the FDA. But at this time what I'd like to do is to focus on the rat study.

Here are the results of the rat study. In rats, the pregnant animals were dosed with one of three dose levels of Telavancin, plus a control. And, as you see here, in two of the control fetuses there was underdevelopment or absence of development of the eye, plus other abnormalities of the head and face. And we see this not infrequently in developmental toxicity studies in experimental animals. Abnormalities occur in isolated fetuses as part of the background in these studies.

In the middle dose and the high dose groups, there was one fetus each evaluated on external exam --

that means looking at the fetus without dissection -- evaluated as having shortening of a limb. However, in that middle dose fetus at 100 milligram per kilogram per day, that limb shortening was not confirmed by skeletal exam. In other words, the skeleton of the limbs was normal. That means that that fetus did not actually have limb shortening.

The high dose fetus was not examined skeletally, because that fetus had been randomized to a visceral examination. And in rat it's difficult technically to do both a visceral and a skeletal exam on the same fetuses.

Now, you may hear from my colleagues at FDA that short limb was not found in the historical controlled database of the contract laboratory; however, if, instead of looking for brachymelia, which was the term used by the contract laboratory, if you look for micromelia, which is the preferred term, you do find it on the historic controlled database of the Mid Atlantic Regional Teratology Association, which maintains probably the largest historical controlled database in the world. So, that micromelia is seen to occur spontaneously in

controlled rat fetuses from time to time. So, I'm not sure whether there were any instances of true limb shortening in this study, but if there were, they were not reproducible.

A subsequent study called a prepostnatal study, involved dosing of pregnant rats during the same period of pregnancy, plus continuing the dosing during the lactation period. The rats were not dissected, but the rat offspring were observed during that lactation period for functional parameters. There were no instances of limb shortening in the several hundred fetuses treated with any of the doses of Telavancin, including the same doses used in the rat teratology study, the 100 and 150 milligram per kilogram per day doses.

There was one fetus in the high dose group -- you'll see that on the bottom line of the table -- who was observed on the 6th and 7th day of life to have limited use of a forelimb; however, that limited use resolved by day 14 and day 21 of life. So, it can't be a birth defect if it goes away.

Now, let me contrast that with findings for

Vancomycin. The Vancomycin studies were published. Vancomycin was also evaluated in rats and rabbits at three doses plus a control. And, although my FDA colleagues may tell you that Vancomycin does not produce malformations in these animals, that's not quite correct. There were two fetuses in the middle dose rat group with abnormalities of the eye. These were isolated fetuses, as happened in the controlled fetuses in the Telavancin studies. There was one multiply malformed fetus, which happens in background and experimental animals, including the one abnormal fetus in the rabbit study for Telavancin.

There was a multiply malformed rabbit fetus with Vancomycin, and a decrease in fetal weight in rabbits at the highest dose group. So, abnormalities such as this happen. However, with these sporadic abnormalities in one fetus here and there, the general conclusion is that we do not have a teratogenic signal.

Now, the FDA has made comments that Telavancin is of concern because the malformations effect the same organ system, that is the limb or the skeleton. But we did not determine that the geographic location of

abnormalities in the limb meant that it was the same embryologic abnormality, anymore than you would conclude that nephrolithiasis and lupus nephritis were the same disease because they both occur in the kidney.

In addition, for Vancomycin we have the same organ system effected in rats and rabbits. And, so, the Vancomycin data set looks very much like the Telavancin data set, and our conclusion for both would be a lack of a teratogenic signal.

We also know that for other antimicrobials -- these are category C antimicrobials -- including these in green which are used for treatment of skin and skin structure infections, the experimental animal studies -- if you look in the right-hand column -- show both malformations and nonmalforming toxicity. So, the presence of developmental toxicity studies that show abnormalities, does not preclude the clinician and the patient from being given the opportunity, the responsibility to make a risk benefit decision when it comes to therapy during pregnancy.

Well, you might ask, is there any benefit to pregnancy? Here are examples of some patients I've seen

in my 30-plus years of obstetrics. Pregnant women get complicated skin and skin structure infections just like all of the rest of us. And when these women have an infection that requires an antibiotic, the presumption that not treating is in the best interest of the fetus, assumes that there's no adverse effect of the untreated disease on fetal development and fetal well being. And that certainly is highly unlikely to be the case.

In addition, when you hear that all of these women can just be given Vancomycin because Telavancin was noninferior to Vancomycin, keep in mind that the study -- the noninferiority study was done on people who had demonstrably Vancomycin sensitive organisms, not Vancomycin resistant or intermediate organisms.

So, our overall conclusions were that the developmental toxicity profile of Telavancin is similar to that of commonly used antimicrobials and other drugs, such as Vancomycin. That the decision to use Telavancin therapy is appropriately left to the clinician and to the patient.

Now, in spite of the fact that Dr. Manson and I did not identify a particular reproductive or

developmental hazard associated with Telavancin therapy, the sponsor has developed a risk management plan that draws attention to management of pregnancy exposure, and that plan will now be presented by Dr. Coleman.

DR. COLEMAN: The demonstrated risks for Telavancin are effects on the QT interval and on the kidney. While there are no human data indicating a risk to fetal development, there were preclinical findings, and it is prudent to caution patients and their healthcare providers about a potential risk.

The Telavancin risk management plan will address these risks to assure the safe and appropriate use of Telavancin. The goals are to minimize the risk of nephrotoxicity and risks related to QT prolongation, and to minimize the exposure of pregnant women to the potential risks of adverse effects on fetal development.

In addition, the plan will gather safety information to further define the risks associated with treatment. To accomplish these goals, we will utilize several tools, including the product labeling or package insert, a program of educational materials and exercises, a focus on initiation in a controlled healthcare setting,

and an enhanced pharmacovigilance program.

The first tool is cautionary statements in the product labeling. The renal risk will be highlighted by labeling that describes the rates for adverse renal events, instructs that serum creatinine should be monitored in all patients, and that the dose of Telavancin should be based on estimated creatinine clearance.

In addition, the product label will describe the decreased clinical response seen in patients with diminished renal function.

The potential risk for cardiac events associated with the QT prolongation will be identified in the product label, which will include a description of the findings of the thorough QT study, and advise caution when prescribing Telavancin to patients taking drugs known to prolong the QT interval. Labeling will also include the information, that patients with congenital long QT syndrome, known prolongation of the QTc interval, uncompensated heart failure, or a severe left ventricular hypertrophy were not included in clinical studies of Telavancin, and advised that the use of Telavancin should

be avoided in patients documented to have these conditions.

Based on the preclinical findings and lack of human data, the proposed designation for Telavancin is Pregnancy Category C. The label will state, there are no adequate and well-controlled studies in pregnant women, and Telavancin should be avoided during pregnancy unless the potential benefit outweighs the potential risk to the fetus.

Findings from the nonclinical studies, including effects on fetal weight and development, will be described in detail.

The risk management plan will include educational strategies targeting treating clinicians that focus on the potential risks associated with use of Telavancin in pregnant women. In addition, the enhanced pharmacovigilance program will include a pregnancy registry.

The education plan will include materials highlighting the appropriate use of Telavancin. These will be distributed to healthcare providers who prescribe, dispense, or administer Telavancin. The plan

will also address hospital formulary and pharmacy and therapeutics committees.

Two ensure that patients are adequately monitored by clinicians familiar with the appropriate use of Telavancin, initiation of treatment will be limited to controlled healthcare settings. This will be achieved by limiting distribution of the drug to wholesalers who primarily supply hospitals, inpatient hospital pharmacies, and home healthcare pharmacies.

All of the systems and activities will be complimented by enhanced pharmacovigilance. In addition to the standard procedures for capturing reports of adverse events under the med watch system, we will use a structured data reporting form for adverse events of a renal or cardiac nature to ensure that evolving safety data are available to the agency in an expeditious fashion. We pledge to report new data to the FDA every three months for the first two years.

Distribution patterns for Telavancin will be reviewed on a periodic basis to verify that the drug is being utilized in controlled healthcare settings.

Finally, we will establish a pregnancy

registry to capture and monitor the course of any woman who receives Telavancin during pregnancy, and the health of their babies.

To ensure its effectiveness, the entire risk management plan will undergo periodic assessments. In order to assure that the educational components of the risk management plan are achieving their goals, Theravance will monitor healthcare provider's awareness of the identified and potential risks of Telavancin, and the incorporation of that awareness into their clinical practice. We will establish a panel of pharmacists from representative hospitals who will periodically track and report the use of Telavancin in their institutions, including profiles of the patients who were prescribed the drug, and their outcomes with regard to safety.

Also we will conduct periodic surveys of physicians to determine their awareness of the renal risks, QTc prolongation, and potential fetal effects of Telavancin. These surveys will examine how this awareness is reflected, both in their intended use of the drug in specific patient populations, as well as their reported actual use.

The assessments will enable ongoing refinement of the plan to both assure its effectiveness and to identify any changes in the safety profile of Telavancin.

Dr. Saravolatz.

DR. SARAVOLATZ: Good morning. I have been in practice in clinical infectious disease now for nearly 30 years in the Detroit area. Our group described the first community-acquired MRSA epidemic in 1982 in the Annals of Internal Medicine. And since that time I've been struck with the increasing incidence of this problem, and more recently with the severity of MRSA infections, as well as the challenge the clinician faces with dealing with a limited number of therapeutic options.

As Dr. Corey emphasized, the methicillin-resistant Staph aureus is increasing as a burden in the management of infections of the skin and skin structures. In fact, in our community 70 percent of community and nosocomial Staph aureus are caused by MRSA. And community-acquired MRSA is the most common pathogen in skin and skin structure infections in the United States today.

The mortality in a surgical infection due to MRSA is increased 12-fold, compared to those who are not infected. And it's increased three-fold compared to those those with methicillin-sensitive Staph aureus infection.

The prevalence of MRSA has made treatment of skin and skin structure infections increasingly difficult. In addition, MRSA has had a significant impact on the course of infection, increasing both clinical failure, as well as reinfection. And, indeed, in the last 30 years the MRSA that we have been treating today is very different, both in terms of virulence, as well as resistance.

Finally, there are, in fact, only four available antiMRSA agents that we have to treat patients with. These are limited to Vancomycin, Daptomycin, Linezolid, and Tigecycline, which are associated with either emerging resistance, toxicity, or both.

For all of these reasons we have an immediate and growing need to have new antibiotics that are effective against MRSA for the treatment of cSSSI.

As an infectious disease clinician, we need

multiple treatment options as we approach patients, in order to optimize treatment for each patient. As we assess patients, we individualize our approach by first assessing the patients extent of infection, the presence of comorbidities, the concomitant medication, prior antimicrobial therapy.

Based upon the severity of the infection, we then determine the need for surgical versus nonsurgical management, as well as intravenous versus oral antibiotic therapy.

We then consider the patient's history and the local epidemiology and we determine the most likely pathogens and then choose appropriate therapy and dosing.

Throughout the course of treatment, we monitor safety and efficacy, adjusting treatment as needed.

Telavancin has several features that make it an appropriate choice to consider for a patient with cSSSI. From a clinical perspective, knowing that a drug in vitro demonstrates a mechanism of action, which is a dual mechanism of action, in contrast to Vancomycin, is an important consideration. Telavancin is bactericidal. It's active against resistant strains, strains with

reduced susceptibility to Vancomycin. And there's a low potential for the development of resistance in vitro.

We know that for skin and skin structure infections, the penetration of the agent is good into the targeted sites as demonstrated by blister-fluid concentrations, and there's an added convenience of once daily dosing.

We know that Telavancin was demonstrated statistically to be noninferior to Vancomycin in the treatment of cSSSI. And a striking feature of these trials was the effectiveness of this agent against the largest MRSA cohort ever studied.

There was no emergence of Telavancin resistancy in these clinical trials. And, finally, it's nice to encounter a lower rate of infusion reactions when compared to Vancomycin.

Based upon the in vitro activity of Telavancin, this drug has the potential benefit of being effective in the treatment of cSSSI caused by VISA and hVISA, as well as strains that are not susceptible to Daptomycin and Linezolid.

This advantage would be expected to translate

into fewer treatment failures, which then would be translated into fewer short -- shortened hospital duration and a need for a shorter duration of intravenous antibiotic therapy. Both have demonstrated the potential benefits of Telavancin outweighs the risks.

Renal events occurred more often in Telavancin, though the rates were similar in patients who did not have comorbidities. Overall these renal events were detectable, manageable, and largely reversible. This is typical of what we see in terms of renal effects with antimicrobials and can be readily addressed through standard monitoring of the serum creatinine. These events do not come close to what we see with aminoglycosides, which are commonly and safely used in clinical practice.

There is a QTc prolongation associated with Telavancin, but it is less than what we see with Moxifloxacin, another drug we safely use in clinical medicine.

The incidences of cardiac toxicity, or serious serious adverse events, mortality, were similar for Telavancin and Vancomycin. This provides added assurance

that Telavancin does not have cardiac toxicity of particular concern.

There has been the observation of reduced litter weights in animals, but we do not have any human experience in pregnancy. When it comes to pregnancy, we must always be careful in our choice of drugs, especially antimicrobials, balancing the benefit to the mother against the potential risk for the fetus. For example, in our community it would require a very critical and careful judgment in treating a pregnant woman with a skin and skin structure infection because of the high rate of MRSA, which is 70 percent in our community, and the high rate of hVISAs, which are 15 percent. In such a patient, we would be concerned about using Vancomycin or Daptomycin because of resistance, and there would be toxicity concerns with using Linezolid, and tolerability concerns with using Tigecycline, especially during pregnancy.

Telavancin represents an important therapeutic option that physicians need to have available in order to optimize care for each patient. This option is particularly important in light of the increasing

prevalence of MRSA in cSSSI, and the growing need for these choices for these -- the growing need for more choices for patients. Telavancin has a positive benefit risk ratio. It is clearly effective against MRSA, and has activity in vitro against VISA, hVISA, and strains that are not susceptible to Daptomycin and Linezolid.

The safety profile has been well characterized with an -- with manageable adverse events.

DR. COLEMAN: Thank you, Dr. Saravolatz.

We appreciate this opportunity to present you the results of our studies demonstrating the efficacy and safety of Telavancin in cSSSI and would welcome your questions.

In addition to the presenters you have heard from, we have four other individuals who are with us today, Drs. Craig Pratt, Julia Lewis, Gary Koch, and Richard Sweet are available for questions in their respective disciplines.

In addition, I am very pleased to note that Dr. Steven Barriere has joined us.

DR. RELLER: Thank you, Dr. Coleman.

We will have questions for and clarifications

by both the applicant and the FDA immediately following the break.

Dr. Janice Pohlman will now begin the FDA's presentation.

DR. POHLMAN: Good morning. It's my job now to present the FDA clinical review of the efficacy and safety of Telavancin for the treatment of complicated skin infections.

Just in terms of a brief overview, I'm going to review the Phase 3 study design and statistical analysis plan, outline the FDA populations and analyses used to determine the benefit to risk of Telavancin for treatment of complicated skin infections, present the FDA clinical and microbiological efficacy results, and review the overall clinical safety, renal toxicity and QTc effect.

I think in terms of the study design in efficacy, there's going to be a lot that overlaps with what Dr. Eckles talked about.

Studies 17 and 18 were two independent studies of identical design. Random -- they were randomized, double-blind, active comparator studies comparing

Telavancin 10 milligrams IV Q24-hours, to Vancomycin 1 gram IV Q12 hours. Adjunctive Aztreonam and/or Metronidazole could be added at the investigator discretion if Gram-negatives and/or anaerobes were suspected.

Treatment duration was to be 7 to 14 days, with duration determined by investigator assessment of clinical status.

The primary endpoint was the clinical response assessed by the investigator at 7 to 14 days after the end of study treatment. Clinical response definitions were as follows: Cure was resolution or improvement in signs and symptoms of infection, such that no further antimicrobial agents were required for the complicated skin infection. Not cured was inadequate response to therapy. And the indeterminate outcome -- I'm going to discuss a little bit further later on -- was defined as inability to determine outcome. The missing, just ignore. I don't -- I'm not quite sure where that came from, whether it was the statistical analysis plan. The -- and I believe the indeterminate outcome was added as it -- part of a protocol amendment to the test-of-cure

assessment, if I'm not mistaken.

The core primary efficacy analyses assessed the difference in clinical response rates for Telavancin relative to Vancomycin, a test of cure, in the alterated and clinically-evaluable populations, with a prespecified noninferiority margin of 10 percent. If both studies demonstrated noninferiority, an additional prespecified goal was to test for superiority of Telavancin relative to Vancomycin in patients with MRSA as baseline pathogen pooled from both studies.

And I just want to go over the FDA analysis populations. We don't purposely try to change the populations, but we do have some definitions that diverge, and I'd like to explain those differences.

The all-treated population is -- consists of all patients who received any study drug. Patients were excluded from the three centers as previously described. And they were also excluded in the Theravance efficacy analyses at FDA's recommendation.

The microbiological all-treated population differs, in that the FDA microbiological all-treated population contains all-treated patients with Gram-

positive pathogens at baseline. Patients with Gram-negative -- only Gram-negative pathogens isolated were not included.

In terms of the FDA clinically-evaluable population, these are -- this group consisted of all-treated patients using original protocol definitions. It's -- in terms I think I'll use the least -- at least five days of therapy, or ten doses of treatment required for patients to be assessed as cures, which sort of fits into a compliance of -- we set limits on compliance typically for clinically-evaluable populations of 80 to 120 percent. So, since it was a 7 to 14 day therapy, you want -- would want them to get at least five days.

We went back to a closer to protocol-defined test-of-cure window, 7 to 21 days, instead of 7 to 28 days.

And, then, in terms of the microbiologically-evaluable population, these included patients in the microbiological all-treated population who were also clinically evaluable and had central microbiology confirmation of identification and susceptibility of

pathogen. On -- this has been done with other antimicrobials in the end assessment of microbiological efficacy.

I mentioned that I was going to go back to the indeterminate outcome assessment. It became apparent in reviewing the case report forms that the investigators were -- some investigators were assessing patients as indeterminate when they were discontinued from study therapy, and the physician considered they couldn't make a judgment at that time because the patient was being discontinued prematurely from study therapy. Patients who were discontinued and were given an indeterminate response at end of therapy, were then -- could be reassessed for efficacy, a test of cure. So that potentially they could receive concomitant nonstudy antimicrobials and be considered to be cures at test of cure. They would be nonclinically-evaluable, but they would be cures in an ITT population.

Additionally, I made two changes. And I know this is a subject that was talked about a little bit yesterday, in terms of when surgical procedures become -- when surgical procedures become important down the line,

in terms of draining -- perhaps draining unnoted abscess from presentation. But I think in terms -- and the protocol specified the patients could have two -- up to two procedures. However, I think there's also a limitation on time beyond operative debridement of necrotic tissue where I think, that if there's reaccumulation of abscesses where -- you know, I think you have to start thinking about clinical failure.

And then the other group that was assessed as clinically -- or clinically-evaluable failures were patients who had amputations. It was often difficult to tell from the limited amount of information on case report forms whether or not the actual area of infection was amputated. And in review of the impact of this overall, it was limited and balanced between arms.

In terms of the baseline demographics, Study 18 there were 862 patients randomized at 40 sites. Study 18, he had 1,035 patients randomized at 89 sites. 73 and 65 percent of the population was from the US for Studies 17 and 18 respectively.

The study populations were balanced for age, gender, and race. Mean age was approximately 48 years,

with a slight male predominance, and 75 percent were white. I agree with the assessment, I think it was 25 percent of patients had been pretreated, had received greater than 24-hours of antimicrobial therapy were considered to be either failures or had pathogens resistant to a therapy they were receiving.

Twenty-five percent had diabetes. 60 to 80 percent received initial treatment in the hospital, which we based on being in the hospital on day two. They could still be subsequently sent home with home IV antibiotics.

Okay. And this was just to outline the major types of abscesses. And I'm not sure I can -- this is the -- here's the laser pointer. All I wanted to point out, actually major abscess was the most common type of infection, 42 to 45 percent, followed by deeper extensive cellulitis, 33 to 38 percent, and wound infections were approximately 15 percent. I know this came up yesterday about others, I just did that to save space. I didn't mean to include ulcers and burns as one category.

And I think this was presented as well, in terms of baseline characteristics for renal function. Approximately 15 percent of patients had either moderate

to severe renal impairment.

And this doesn't show up very well, but in -- this -- these are the results, in terms of the FDA primary efficacy analyses. Study 17, the difference in percent success point of estimate was 1.0 and 1.5 for the all-treated and clinically-evaluable populations respectively. And the lower bound of the 95 percent confidence interval was greater than minus 10.

Study 18, the point estimate for the difference in success was 0.7 and minus 3.8 for all-treated and CE respectively, with the lower bound of the 95 percent confidence interval greater than minus 10.

So, in terms of the efficacy results, due to differences in population definitions and outcome assessments, FDA cure rates differed from those of Theravance. However, the FDA conclusion regarding noninferiority of Telavancin relative to Vancomycin for each study did not differ from that of Theravance.

In terms of the efficacy results of patients with MRSA at baseline, the -- this was the prespecified pooled analysis. It shows numerically a slight advantage to Telavancin, although superiority was not done

demonstrated.

And I just put this up in terms of the clinical -- the MIC is for Telavancin and Vancomycin in the clinical studies of -- I believe this is all the skin isolates, compared to surveillance isolates from referenced microbiology labs of different isolates from different sites. These were specifically -- primarily, I guess, skin. Maybe there might -- were some blood in here. I can't tell. The range was 0.06 to 1 MIC range. And MIC 90 over 1.

And for -- in terms of Vancomycin, clinical isolates for MRSA, MIC range 0.25 to 2, with MIC 90 over 1. And, again, in terms of subgroup analysis, we always like to see how cure rates stack up against each of the types of infection. And, basically, between Telavancin and Vancomycin, similar results in major abscess and in the cellulitis category. Perhaps a slight decrease in wound infections for Telavancin, but the numbers are smaller.

And I think this was nicely presented by Theravance. The -- what we noted, was in patients with -- as renal function at baseline decreased, there was a

progressive decline in efficacy rates for Telavancin, while Vancomycin remained relatively stable. And, like Theravance, I think we were unable to come up with a good explanation. I think it was multifactorial, the different populations that were explored. I think, in terms of the types of infections, and the rationale that Theravance provided I think was a good one, in terms of patient characteristics and infection characteristics.

And this doesn't -- probably doesn't project very well either. This just points out the clinical response by pathogen. Looking at MRSA, the rates actually favor one drug versus the other in one study, and the opposite in the second study. And the converse was true for MRSA. The Streptococcal -- beta hemoglobin Streptococcal isolates were really low in number and hard to make anything out of those cure rates.

In terms of the safety database, at the time of the NDA submission, we had patients who had been treated in the clinical pharmacology studies. There were also 1,221 patients treated in the clinical program with Telavancin, 192 of whom had received a dose of 7.5 milligrams per kilogram, and 1,029 with a dose of 10

milligrams per kilogram.

Additionally, at the initial submission we had some blinded safety data from the HAP trial -- the hospital-acquired pneumonia trials, as well as the uncomplicated Staph aureus bacteremia study. The Staph aureus -- uncomplicated Staph aureus bacteremia was unblinded in the four month safety update for the submission of the original NDA. There were about 30 patients treated with Telavancin. So, there would be 30 more that we would have some details.

In terms of safety, the deaths in all -- all of the clinical skin infection studies, they're complicated skin infection studies. I -- the definitions for disease were slightly different in the Phase 2 studies. And that's why I kind of -- when I say all studies and complicated, it -- the definition just vary minorly -- minor -- minutely.

There were nine deaths in each treatment group during the reporting period. Five additional deaths in Telavancin, and two in the Vancomycin treatment groups were reported after the reporting period.

Investigator assessed death is possibly or

probably related to study medication in four in one Telavancin patients starting each period respectively. And these were the events that the investigator assessed as possibly related the adverse events resulting in death.

In terms of the bottom two, the cardiac events, the ventricular arrythmia occurred in a gentleman who had received one dose of Telavancin, was -- missed a dose on his -- the second day, and essentially was found dead -- an unwitnessed death.

The cardiac arrest on the bottom, the unwitnessed was a woman who would -- had received six days of Telavancin, had slight bump in creatinine. Also anemia was noted. I think she was transfused. Again, that was an unwitnessed arrest. And the only remarkable or notable factor on that, she did have an ECG that showed QTc range -- it went from 450 to 475. And I think I'll just leave the renal for a little bit later discussion.

In terms of the Phase 3 studies, there were 80 serious adverse events reported, 69 out of 929 Telavancin-treated patients, 65 SAEs and 43 of 938

Vancomycin-treated patients. These are all with the 10 milligram per kilogram dose.

The -- and imbalances were noted by system organ class, with renal and urinary system organ class being represented, with 11 Telavancin patients and 2 Vancomycin patients.

Vascular disorders were noted in nine Telavancin and two Vancomycin treated patients, although there was no unifying diagnosis for vascular disorders. There were arterial events, venous events, blood pressure events. The most common adverse events, I believe, were cardiac and respiratory, in terms of SAE reporting.

In terms of discontinuation of study medication, 8 percent in the Telavancin-treated group discontinued due to adverse events, versus 6 percent in the Vancomycin group.

Skin disorders were the most common reason for discontinuation in both groups, about two percent.

There were imbalances noted by system organ class, gastrointestinal disorders, two times in -- Telavancin was two times the rate of Vancomycin, 13 to 6, primarily on nausea and vomiting.

Renal disorders, again, the imbalance is noted, eight Telavancin and zero Vancomycin treated patients.

Infection disorders I think -- or that primarily represented, I think, the largest group, and that was patients with osteomyelitis .

In terms of the common safety adverse events, altered taste was the most common and a discriminatory factor, I think, between the Telavancin and Vancomycin groups, 34 percent of the Telavancin group versus 7 percent in the Vancomycin group.

Nausea was more common in Telavancin, vomiting as well, and the foamy urine that has previously been reported.

In terms of renal adverse events, the SAEs in all of the skin studies -- and this includes the 7.5 milligram per kilogram and 10 milligram per kilogram doses -- in line with the prespecified definition of potential effects on the kidney, which included preferred terms of renal impairment, renal insufficiency or impairment, acute renal failure, chronic renal failure, and increased creatinine, occurred in 14 Telavancin and 4

Vancomycin-treated patients. Three Telavancin-treated patients -- excuse me -- required dialysis. Two had had rising creatinines prior to study, refused dialysis and died.

One of the four remaining -- or one of the four Vancomycin patients was receiving hemodialysis prior to the study and continued. And, as mentioned, the three patients that had incomplete resolution, two of which I -- Theravance has shown evidence of follow up, that this statement was based on the last laboratory assessment that we had at the time.

Six -- and at the bottom, 16 Telavancin-treated patients had study medication, prematurely discontinued, compared to the Vancomycin treated patients, due to adverse events consistent with prespecified renal impairment definition.

In terms of renal laboratory parameters, potentially clinically significant changes in creatinine -- serum creatinine and BUN had been prospectively set to evaluate for these potentially clinically significantly changes.

And this table shows the group with the normal

baseline creatinine. The methods used to define potentially clinically significant were increased to 1.25 percent times baseline, and showed that there were 37 percent in the Telavancin group who reached that definition, compared to 21 percent in the Vancomycin group.

The other -- the next definition was any post baseline creatinine greater than equal to 1.5 milligrams per DL, and at least 0.5 milligrams per DL greater than baseline. Again, there's a three to one higher incidence in the Telavancin-treated arm.

Any post -- and the third definition, any post baseline creatinine greater than 1.5 milligrams per DL. And at least 50 percent greater than baseline. Again, you see the imbalance between the Telavancin and Vancomycin arms.

In terms -- and this just goes through the same thing for patients with abnormal baselines and creatinines. The lower number of patients, 83, that were assessed in the Telavancin arm, 68 in the Vancomycin. Again, you see a difference between the Telavancin and Vancomycin arms. Although, actually, when you get down

to the bottom definition, they tend to look a little bit more equal.

In terms of the QT effect, the preclinical studies had shown an in vitro QT effect; however, the results from a conscious telemeterized dog study did not reveal any treatment related effect on blood pressure, heart rate, or ECG.

In terms of the clinical program, FDA had requested that Theravance conduct this study. And it was based on 2002 guidelines at the time, which was based on a FDA-Health Canada concept paper. 7.5 milligram per kilogram and 15 milligram per kilogram doses were tested. And there's some differences from current QT studies, in that this QT study assessed -- there were three doses of IV Moxifloxacin given, whereas in present day studies one dose of oral comparator is given, rather than three days of dosing. And there's some terms of corrections for baseline -- changes from baseline.

And based on that assessment, the predicted mean change for Telavancin was 12 to 15 milliseconds. The mean change for the IV comparator is 24 milliseconds. And the clinical skin -- or studies

demonstrated that the mean post drug average change, the maximum change from baseline were greater for Telavancin-treated patients, 9.4 and 15.5 milliseconds for Telavancin, and 3 and 8.4 milliseconds for Vancomycin respectively.

Four Telavancin-treated and six Vancomycin-treated patients have cardiac adverse events resulting in a death. Two deaths in the Telavancin group were considered possibly related to study medication. Those were the two patients that I had mentioned earlier.

Thirteen Telavancin treated and 13 Vancomycin treated patients had at least one SAE in the cardiac system organ class, MedDRA classification system. Four SAEs in the Telavancin-treated patients, and two in Vancomycin were considered possibly related to study medication by the investigator.

And as was noted, patients treated with Telavancin had a higher risk of outlier values, the QTc change of greater than 60 milliseconds or absolute greater than 500 -- or a value greater than 500 milliseconds, when treated with medications known to cause QT prolongation than did those treated with

Vancomycin. The risk was low and outlier values were not associated with cardiac events.

In terms of the safety update from the two hospital-acquired pneumonia trials which have been completed, we were able to review summary data on deaths serious adverse events and discontinuations, essentially consisting of tabulations and narratives. 751 patients who have been treated with Telavancin, mortality was 20 percent in Telavancin versus 18 percent in Vancomycin groups. And this is pretty consistent with other trials in nosocomial pneumonia.

The adverse events resulting in death were most frequent in the respiratory and infection category -- the infection category, including sepsis. And they were balanced between the treatment groups.

Cardiac events resulting in death were actually more frequent in the Vancomycin treated group, including the congestive heart failure and ventricular arrhythmias.

In terms of the SAEs, the respiratory infection related events were most common. The SAEs, along with the cardiac SAEs, generally were balanced.

Although there was a finding -- and this is just something that popped up -- was pulmonary embolus in seven Telavancin versus one Vancomycin-treated patient. Although, in terms of reviewing those cases, there's no unifying event that jumps out, although, it was notable.

And in terms of the renal SAEs, there were 25 in Telavancin. Basically I received the table with the 15 -- Study 15 and 19 combined. So, I had received information about 25 Telavancin versus 15 Vancomycin.

When I broke it down by study, in Study 15, there were 17 in the Telavancin group, versus 7 in the Vancomycin group. Study 19 was balanced with 8 and 8.

So, in terms of the conclusions, the Phase 3 studies support the conclusion that Telavancin is not inferior relative to Vancomycin for treatment of complicated skin and skin structure infections.

Telavancin did not demonstrate superiority in treatment of patients with MRSA at baseline.

SAEs discontinuations and predefined definitions of renal impairment were higher in the Telavancin-treatment group, two to three times.

Telavancin does prolong the QT interval.

And GI adverse events were the most common adverse events associated with Telavancin treatment.

And at this point I'd like to turn the podium over to Dr. Zhou Chen, who will be discussing the preclinical pharmacology, toxicology studies.

DR. CHEN: Good morning. My name is Zhou Chen. I'm the pharmacology and toxicology reviewer for this NDA application. And next I would like to briefly introduce teratogenic findings for Telavancin.

The sponsor originally performed the Segment 2 studies, Segment 2 teratogenic studies in rabbits and rats. Because of concerns raised from positive findings seen in these two species, we asked the sponsor to perform a study -- to perform a third study in animal species that is higher on the phylogenetic scale. So, the decision was made to perform the study in mini pigs. So, a total of three species were used for teratogenic evaluation.

First, rat study. Pregnant rats were treated with this control -- placebo control and the Telavancin at 50, 100, and 150 milligram per kilo per day from gestation day 6 to day 17. It's organogenesis duration.

The animals were sacrificed at a C-section on gestation date 20. It's just before the natural delivery. Post maternal fetal toxicities were evaluated.

Toxicology significant offspring, external malformations were noted either 100 milligram per kilo and 150 milligram per kilo doses. This is middle dose and this is a high dose. Brachymelia and the syndactyly were noted in a single fetus in the middle dose group. And the brachymelia was also noted, you know, a single fetus in the high dose group.

Post brachymelia and the syndactyly are not listed in the contract lab's historical control database. In the study report, the contract lab stated that brachymelia (inaudible), middle dose and the high dose groups was treatment related. And syndactyly noted only in the middle dose group was uncertain relationship for the treatment.

Rabbit study. Pregnant rabbits were treated with placebo control. And the Telavancin at 60 or 75 milligram per kilo from gestation day 7 to day 20. The animals was sacrificed gestation day 29 and post maternal fetal toxicities were evaluated.

In the offspring external examination, at a high dose, one single fetus showed flexed front paws, brachymelia, and adactyly. Brachymelia here is not listed in the historical control database from this lab.

In the offspring skeleton examination, there are several positive findings. But, toxicology significant findings are, absent ulna, and the adactyly. These two rare formations were noted, you know, in a single fetus in this group. This fetus is the same one with the external malformations, like brachymelia and the flexed front paws.

Both fetal and the litter incidence for flexed front paw and adactyly are over the historical controls mean variables in this lab listed here.

And this -- the fetal is 0.6 percent, and the litter incidence is 5.3 percent. And the brachymelia and absent ulna are not listed in the historical control database in this lab.

In the final study report from Covance, the contract lab responsible for both rat and the rabbit studies, they concluded that the limb malformations noted mimic or are similar to the malformations of brachymelia

and the syndactyly observed in rats at doses of 150 and 100 milligram per kilo per day respectively.

These findings further support a direct effect of the drug on the developing fetus.

Mini pig study. Pregnant mini pigs were treated with control -- placebo control, and the Telavancin at 25, 50 or 75 milligram per kilo per day from gestation day 11 to day 35. The animals were sacrificed at C-section on gestation day 109 to day 111. The gestation duration for this species is about 130 days. The examinations for both dams and fetuses were conducted.

This mini pig study had some problems. The final pig numbers for evaluation was very low. And also the pregnancy rate was very low. See, only 36 percent is in the placebo and the high dose groups.

The historical control variables is liable for pregnancy rate is about 65 percent to 93 percent. So, the low pregnancy rate effected the final numbers for fetuses evaluated in this study.

Although this study had some problems, but positive findings should not be ignored. This table is a

summary of positive findings in this study. Positive findings are concentrated in low dose and the middle dose groups. These findings include the syndactyly in one middle dose fetus, and the polydactyly in placebo control low dose and the middle dose groups. And -- and the misshapen digit and deformed limb was missing radius in one single middle dose fetus. And for all these positive findings the litter incidence range from 12.5 percent to 37.5 percent. They are all over the historical control variables.

For the high dose group, everything is clean. There are no positive findings. This may be due to the low number for fetuses evaluated in this group. Only 17 were evaluated -- were available for evaluation in this group.

There are several positive findings not listed in the final results because of different reasons, like dams were sacrificed early in the study.

Okay. What this one low dose fetus showed a deformed head and misshapened digit. And the one -- this one -- middle dose fetus show the legs turned inwards. And another middle dose fetus show multiple absent

ossification sites, absent the tarsal bones on both legs. And this high dose fetus had a deformed head, four legs, and a snout. And the -- this high dose fetus had a deformed hind leg.

So, this table just summarize the fetal findings -- from positive findings from all available fetuses, including fetuses from early sacrifice of dams. Because of cannibalism in the adolescents, not all fetal effects were observed in fetus from dams sacrificed early in the study.

I just want to show you in this table, that the high dose group is not clean. There are some positive findings. These findings seem to be dose dependent.

This table does compare plasma exposure to the drug between animals and the humans. The animal doses listed here, they are not (inaudible). Out of these doses, positive teratogenic findings were noted. Okay.

Based on the AUC data listed here, we can find animal over human ratio is between 1 and the 2. So, basically, there's no safety margin between animal doses listed here and the clinically recommended human dose.

So, in summary, we have seen limb malformations in all three animal species (inaudible). In each species the instance was low. However, if we collected all data together, we can find across all three species, this malformations were similar, and that they are all over the historical control database, database variables. So, it is concluded that these malformations are drug related, are treatment related.

The big safety concern, is that this malformations occurred at clinically relevant maternal exposure based on the plasma AUC data.

Because a sponsor has different interpretation for these positive findings compared of this -- compare with the contract lab and the FDA reviewer, the division asked to see their experts from reproductive and the developmental toxicity sub-committee to perform independent review based on nonclinical study data.

The committee concluded that -- it was the consensus of the committee that the limb defects observed in these studies were related to the drug, where the evidence of drug induced limb malformations in each species is weak. The weight of evidence across all three

species strongly suppose that findings are drug related.

Regarding labeling, both committee and the reviewer believe that the positive findings should be detailed in the labeling, and appropriate pregnancy category should be based on risk benefit of profile of the drug, and the risk benefit ratio in pregnant women. The following factors should be considered: Seriousness of indication and the potential for serious complications in pregnancy associated with the indication. Availability of alternative treatments and the teratogenic effects at or near the proposed human dose.

Next I would like to use a few slides just to very briefly introduce renal toxicity noted in nonclinical studies. This sponsor has performed many general toxicologist studies. There is a duration up to six months in rats and three months in dogs. The targeted organs of toxicity are identified as the kidneys and the liver in both species.

In many rat studies renal toxicity was identified by increased serum BUN and the creatinine levels, urinary occult blood, increased kidney weight, and necropsy examination, enlarged renal lymph nodes,

