DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTI-INFECTIVE DRUG

ADVISORY COMMITTEE

Monday, March 6, 2006

8:30 a.m.

CDER Advisory Committee Conference Room
Room 1066
5600 Fishers Lane
Rockville, MD

PARTICIPANTS

James E. Leggett, Jr., M.D., Acting Chair
LCDR Cathy Groupe, B.S.N., Executive Secretary

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Janice M. Soreth, M.D., Division Director
Sumathi Nambiar, M.D., M.P.H. Medical Team Leader
Alfred Sorbello, D.O., Medical Officer
Charles Cooper, M.D., Medical Officer
Peter Coderre, Ph.D., Microbiologist

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order

DR. LEGGETT: We are here this morning for discussion of a new drug application, Cubicin which is daptomycin, by sponsor Cubist Pharmaceuticals for the proposed indication for the treatment of Staphylococcus aureus bacteremia, including those with known or suspected endocarditis caused by methicillin-susceptible and methicillin-resistant strains.

I know some members are late but I heard on the radio this morning that there are lots of traffic accidents today, so why don't we get started with introductions? When you introduce yourself push "talk" and then push it once again to have it stop.

DR. MALDANADO: Samuel Maldanado from Johnson & Johnson, industry representative.

DR. FOLLMANN: I am Dean Follmann, Head of Biostatistics at NIAID.

DR. EBERT: Steve Ebert, Meriter Hospital and Professor of Pharmacy, University of Wisconsin,

Madison.

DR. BORER: Jeff Borer, Professor of Cardiovascular Medicine at Cornell and Head of Cardiovascular Pathophysiology at Cornell.

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

DR. OMEL: I am Jim Omel. I am a family practice physician from Grand Island, Nebraska and the patient representative on the committee.

DR. PATTERSON: Jan Patterson, Infectious Diseases, University of Texas Health Science Center, San Antonio and South Texas Veterans Healthcare System.

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

LCDR GROUPE: Cathy Groupe, acting executive secretary of the committee.

DR. COOPER: Chuck Cooper, medical officer for the Division of Anti-Infectives.

DR. CODERRE: Peter Coderre, microbiology reviewer, Division of Anti-Infectives.

DR. SORBELLO: Fred Sorbello, I am a medical officer, Division of Anti-Infectives, FDA.

DR. NAMBIAR: Sumathi Nambiar, medical team leader, Division of Anti-Infective Drug Products, FDA.

DR. SORETH: Good morning. I am Janice Soreth, Division Director of Anti-Infective and Ophthalmology Products.

DR. GOLDBERGER: I am Mark Goldberger, the Director of the Office of Antimicrobial Products.

DR. CROSS: Alan Cross, University of Maryland.

DR. BRADLEY: John Bradley, Children's Hospital, San Diego.

DR. LEGGETT: At this point, Cathy Groupe, could you please give us the conflict of interest statement?

Conflict of Interest Statement

LCDR GROUPE: The following announcement addresses the issue of conflict of interest and is made part of the record to preclude even the appearance of such at this meeting. Based on the

submitted agenda and all financial interests reported by the committee's participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting, with the following exceptions.

In accordance with 18 USC Section 208(b)(3), the following participants have been granted full waivers: Dr. John Bradley for consulting on an unrelated matter for a competitor. He receives less than $10,001 per year. Dr. Steven Ebert for serving on speakers bureaus for the sponsor and a competitor, for which he receives less than $10,001 per year per firm, and for consulting on related matters for a competitor for which he receives less than $10,001 per year.

In accordance with 18 USC Section 208(b)(1), Dr. Jan Patterson has been granted a full waiver for her spouse serving on unrelated speakers bureaus for two competitors for which he receives from $10,001 to $50,000 per year per firm,

and for her spouse's unrelated consulting advisory board activities for two competitors for which he receives less than $10,001 per year per firm.

In accordance with 18 USC 208(b)(3), Dr. Jeffrey S. Borer has been granted a limited waiver which allows him to participate in the committee's discussion but not vote for serving on a speakers bureau for a competitor for which he receives from $10,001 and $50,000 per year; for consulting on unrelated matters for a university which is supported by a competing firm for which he receives less than $10,001 per year; and for consulting on unrelated matters for two competitors for which he receives less than $10,001 per year from one firm and greater than $50,000 per year from another firm.

Dr. James Omel has been granted a waiver under 21 USC 355(n)(4) for ownership of stock in a competitor. This stock is valued at less than $5,001.

A copy of the waiver statements may be obtained by submitting a written request to the

agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

We would also like to note that Dr. Samuel D. Maldanado has been invited to participate as an industry representative, acting on behalf of regulated industry. Dr. Maldanado's role on this committee is to represent industry interests in general and not any one particular company. Dr. Maldanado is employed by Johnson & Johnson.

In the event that discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvements and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment on.

DR. LEGGETT: Dr. Soreth, could you please give us an introduction?

Introduction

[Slide]

DR. SORETH: I would like this morning to give a brief introduction to the regulatory history of bacteremia and endocarditis, highlighting firstly the drugs and kinds of studies that previously led to an approval for bacteremia or septicemia or endocarditis and, secondly, the evolution of guidance in this area so that we understand the road taken to the design and conduct of the daptomycin trial. I apologize in advance that my talk is not shorter.

[Slide]

If one does a PDR search for products labeled for endocarditis or bacteremia several drugs come up, including imipenem, cefazolin, gentamicin and vancomycin. If you expand that search for the general term of staphylococcal infection or staphylococcal disease, then nafcillin and oxacillin also come to the fore.

[Slide]

Of those drugs, imipenem and cefazolin in this group are the most recently approved in the

'70s and '80s and their labels are the most succinct with regard to bacterial septicemia or endocarditis due to either a list of pathogens or, in the case of endocarditis Staphylococcus aureus.

[Slide]

Going back to older drugs like vancomycin or gentamicin, the indications are worded in a more wordy fashion and the label reads something like vancomycin is indicated for the treatment of serious or severe infections caused by susceptible strains of methicillin-resistant staphylococci. Vancomycin is effective in the treatment of staphylococcal endocarditis. The third bullet point is that its effectiveness has been documented in other infections due to staphylococci, including septicemia, bone infections, etc. when staphylococcal infections are localized and purulent antibiotics are used as adjuncts to appropriate surgical measures.

[Slide]

For gentamicin, it has been found effective when used in conjunction with

penicillin-type drugs for the treatment of endocarditis, in this case caused by group D. strep. Furthermore, gentamicin has been shown to be effective in the treatment of serious staphylococcal infections. While not the antibiotic of first choice, gentamicin may be considered when penicillins or other less potentially toxic drugs are contraindicated and bacterial susceptibility tests and clinical judgment indicate its use, with, at least back then, perhaps more of a marriage with what was going on clinically actually being reflected in the label.

[Slide]

This may not project very well but I put it up there simply to show that the cillins--oxacillin or nafcillin--are indicated for the treatment of infections caused by penicillinase-producing staphylococci which have demonstrated susceptibility to the drug--very broad and general. Culture susceptibility tests should be performed, etc.

[Slide]

I thought it a daunting task to try to summarize in five minutes or less the underpinning studies for all of these drugs. Fortunately, the job was made easier once I looked at the NDA reviews and the summary bases for approval. For the typical study that underpinned the labels that we just ran through read as follows, this is one study: multicenter study of the comparative efficacy, safety and tolerance of drug X compared to drug Y in the parenteral therapy of infections in hospitalized patients caused by susceptible pathogenic bacteria. Imagine now doing a special protocol assessment on that!

So, we have under one clinical trial or study half a dozen infections studied, including lower respiratory--as it was called back then--infections, skin, gynecologic, urinary tract infections, osteomyelitis, septicemia, endocarditis and, necessarily, the treatment duration ranged in this mix from a week or so to several weeks to a month or longer. Experience in bacteremia or

endocarditis, when I reviewed those drugs, was limited at best to a handful of cases, sometimes supplemented with case series or data from an uncontrolled study. So, within a single study there was a mix of half a dozen or so different infectious disease entities. No single study was powered within a given subset like skin infections, or pneumonia, or bacteremia or endocarditis, to permit statistical analysis and the least studied subgroup was typically endocarditis or bacteremia.

As I said this was not a day and age of special protocol assessments. I think it is fair to say that at that point in time in anti-infective drug development there was a greater acceptance within a regulatory framework to do what I believe is routinely done in clinical practice, and that is the use of inferential thinking to inform and to guide drug use.

[Slide]

If we fast forward now to the 1992 Points to Consider document, a guidance written by the FDA, on endocarditis there is a paragraph or two

which says the following: One open trial--read here uncontrolled--of at least 50 patients that establishes a predetermined overall clinical and microbiologic success rate is suggested. If there is not a reasonable mix of artificial and native valve, right and left-sided disease and acute versus subacute clinical presentations, such should be noted in the approved labeling by restricting the labeling in the indications and usage section of the product to just those types of infections and populations actually studied. The trial should involve at least two investigators in different geographic areas, and pathogens listed would be determined on a case-by-case basis.

So, I think the salient features that I wish to note for the standard in the '90s was the expectation that it would be a non-comparative study; a relatively small experience; a mix of patients with diversity in right and left side; native valve, prosthetic valve; acute, subacute presentation. But if a reasonable mix was, in fact, not gathered it would not necessarily be a

barrier to approval but, rather, simply the label would reflect the patient population studied.

I think it is clear, as it is stated in the document, that the Points to Consider document was written to facilitate anti-infective drug development, not restrict it. Specifically, the endocarditis section was meant to outline what would be an acceptable approach or an acceptable minimum that would make it easier for sponsors to move forward in this area. In practice, if one looks at the anti-infectives approved for endocarditis after the '92 guidance, there was nothing. In practice, it seems that what we wrote and thought would be readily doable was a barrier, an insurmountable barrier because nothing came to the fore.

We will shortly hear from Dr. John Edwards and Dr. Henry Chambers who will give us both an overview of epidemiologic considerations of S. aureus endocarditis and bacteremia as well as a review of case management. I think that we recognize that the incidence of hospitalized

patients with bacteremia is on the rise. It is on the rise certainly with regard to gram-positive pathogens. It is on the rise with regard to S. aureus disease. It is on the rise with regard to S. aureus with endocarditis.

With that in mind, we wrote another guidance several years ago for the study of catheter-related bloodstream infections, including those due to S. aureus. Again, however, despite the best of intentions we wrote a guidance that in practical terms did not translate into the conduct of a clinical trial. Several sponsors have come to the fore, telling us of the screening of several thousand patients and enrollment of a handful.

[Slide]

We went back to the anti-infective advisory committee in October of 2004 and we asked what should we do with regard to S. aureus bacteremia as an indication. You advised us to re-write the draft guidance related to bloodstream infections to reflect the current reality of patient and public health needs and resources for

drug development. You advised us further to balance good science with practicalities of clinical trial design and conduct, and to study patients with S. aureus bacteremia, including in a development program patients with defined sites of infection and concurrent bacteremia, as well as those without an identified organ site.

[Slide]

Today we will hear from the sponsor, Cubist Pharmaceuticals, about their design and conduct of a study in the treatment of patients with S. aureus bacteremia and endocarditis. The sponsor and the FDA agreed upon the study design, a randomized, open-label, controlled trial of daptomycin versus standard of care of vancomycin or semisynthetic penicillins in a group of patients who have S. aureus in the blood, some of whom also have endocarditis. The study echoes--no pun intended--what I believe physicians face: the management of patients with staphylococcal bacteremia, including those with endocarditis.

[Slide]

Briefly, after the overview of the epidemiologic considerations and some case management, we will hear the details of the clinical trial as designed, as conducted, as analyzed by both the sponsor as well as the FDA review team. The charge to the committee will be, as it always is, to ask you if the data presented represents substantial evidence of efficacy and safety for daptomycin in the treatment of patients with S. aureus bacteremia, and to also ask you if the data support the approval of the drug with regard to the subset of patients who have S. aureus endocarditis.

I think in a discussion of this trial we will certainly learn more about the activity and performance of daptomycin and vancomycin or semisynthetic penicillins in the treatment of S. aureus bacteremia and endocarditis. We will also learn more, because now we have a trial conducted, about the complexities of the issues associated with S. aureus bacteremia and endocarditis, which will further inform us should other sponsors rise

to the challenge to conduct a study in this endeavor with either already marketed drugs or those drugs which are still in development.

[Slide]

In closing, I think it is noteworthy that the performance of a study like the daptomycin trial is in keeping with or is compatible with the agency's Critical Path Initiative which is an attempt to bring attention and focus to the need for targeted, scientific efforts to address unmet medical need; to improve techniques and methods used to evaluate products for the safety, efficacy and quality of those products as they move from discovery and product selection to trial design, to mass manufacture, as well as to their use. With that, I will close and invite Dr. John Edwards to the podium. Thank you.

DR. LEGGETT: Thank you.

S. Aureus Bacteremia and Endocarditis:
Epidemiologic Considerations

DR. EDWARDS: As Dr. Soreth mentioned, Dr. Chambers and I will split the introduction this

morning. I am going to go over some concepts about the epidemiological considerations for staphylococcal endocarditis and bacteremia and then Chip is going to go through a very interesting discussion that will be a case-based discussion of the complexities of the management of patients with staphylococcal bacteremia and endocarditis.

[Slide]

Before I start, I need to thank a group of people who have helped me put this presentation together, including Vance Fowler for major logistical assistance with the slides, Arnold Bayer, Brad Spellberg and Loren Miller at our own institution who have done a considerable amount of work on staphylococcal infections in general, and Dr. Chambers and Dr. Francoise Remington from San Francisco who contributed a lot of the epidemiology that will be discussed in this brief overview.

[Slide]

In 2003, in The New England Journal of Medicine, Martin published this huge study of 750 million discharges from U.S. hospitals. I can't

even imagine such a thing which included 10 million cases of sepsis. That study went from 1979 to 2001 and showed a significant increase in sepsis in general in our population. This slide shows the increased incidence in both males and females.

[Slide]

But of great interest in this study was something Dr. Soreth has already mentioned, and that is that there was an overall increase or predominance in the gram-positive bacteremias compared to the gram negatives, starting back here in 1979, where that was certainly not the case before, and shows a real emergence of gram-positive organisms here.

Of interest to me on this slide is also the increased incidence of fungal sepsis, if you will. Tying those two effects together, the emergence of the gram-positive organisms and the fungi, if we take a more general perspective on this issue, we are seeing what is happening here as a development of the changes in the epidemiology related to predominantly the modern medical

therapeutic technological advancements which have been made. I will make some other comments regarding that perspective as we go along.

[Slide]

Dr. Carleton, working with Francoise Remington in San Francisco, published in 2004 this study showing a very significant increased incidence or increased number of isolates of MRSA in the San Francisco area. Of interest here was the fact that most of the overall increase in MRSA came from community onset of the infection and the isolation of the organism. There was a bit of an increase in nosocomial and healthcare facility isolates here but the majority were community onset MRSA. This was one of a number of publications occurring at about this time making that point.

Of great interest also was the fact that the majority of these were the type IV SCCmec genotype which was a bit of a surprise, and we will come back to the significance of that in just a few moments.

[Slide]

In the NNIS database we see that by the year 2000 over half of the isolates of S. aureus coming from intensive care units were MRSA and nearly 40 percent outside of the intensive care units were also MRSA.

[Slide]

Now, the next three slides kind of show evidence for the community acquisition of MRSA. This one is from a questionnaire study, which has subsequently been published in CID, and it looks at the bacterial complications in over 6,000 patients who had influenza during the 2003-2004 epidemic. About 2 percent of those patients had a bacterial complication and 30 percent roughly had S. aureus as the complicating organism causing pneumonia during their influenza outbreak. About a quarter of those were associated with MRSA. So, these are non-hospitalized patients getting influenza, getting a bacterial infection, and we are seeing here S. aureus dominating the pneumococcus and a considerable appearance of MRSA.

[Slide]

In this study of community-acquired MRSA, from 116 consecutive isolates of MRSA which were typable--there were actually more isolates accrued in this study but these were the ones which could be typed--of the healthcare-associated, 28 percent were the USA300 strain associated with a Panton Valentine leukocidin genotype, and 20 percent of that strain, which is considered to be more aggressive in general, were from a nosocomial site.

[Slide]

In this study from our own institution, we saw 14 patients with severe, necrotizing fasciitis caused by community-acquired MRSA. Although the mortality was low in these patients, there was considerable morbidity, including the need for surgical resections and other complications of these very aggressive infections. In this group, 100 percent were the USA300 clone, again containing the Panton Valentine leukocidin genotype. Other features of the genotype are listed here.

[Slide]

So in general regarding community-acquired

MRSA, we can say that it is now a common community pathogen in many parts of the U.S. and also in many areas internationally as well. It is clinically distinct in that it is associated with necrotizing pneumonia; has been associated with empyemas, musculoskeletal infections and necrotizing fasciitis now. It is genotypically distinct, with the SCCmecIV genotype and the PVL genotype expressed here.

There is evidence from data that I am not going to show you explicitly that this genotype is evolving in the community due to community pressures and factors rather than as escape from the hospital as feral clones which then proliferate. In fact, there is evidence both from the San Francisco and other groups that the genotype here is arising in the community and then working its way into the hospital setting rather than vice versa.

[Slide]

Now I am going to switch from bacteremia to staphylococcal endocarditis. This pivotal

study, which was just recently published as the international collaboration on endocarditis group, is an effort to re-evaluate the causes and epidemiology of endocarditis.

[Slide]

That publication is one derivative of the study. This is a second one where a subset of the data sets was pooled that focused on native valve endocarditis, and we will come back to that in just a moment.

[Slide]

This group is large. There are 58 sites involved from 26 different countries.

[Slide]

Of great interest to all of us was the fact that over half of the cases of endocarditis now incorporated in this study were due to staphylococcus, in this proportion of S. aureus and this coagulase negative. You can see that the enterococcus portion has gone down considerably here, as has Strep. viridens endocarditis. So, this is a real change now in the fact that the most

common cause of endocarditis basically internationally is S. aureus.

[Slide]

That study was done over 48 months. There were 1,779 patients involved with what was classified as definite endocarditis.

[Slide]

What is also interesting from the study is that there is a geographical difference in the frequency with which S. aureus was recovered. In the United States or North America we see a very high predominance of S. aureus. In South America it is less so, but the overall view of the occurrence of staph. endocarditis again tells us that this increased frequency of S. aureus is most likely related to advances in modern medical care.

[Slide]

Again, from that subset study we see S. aureus accounting for about 30 percent of the overall cases of endocarditis.

[Slide]

The mortality rate of staphylococcus

endocarditis has remained high and is roughly in the ranges you see here, 25-30 percent range. So, it is associated with a high mortality.

[Slide]

This study looks at the Medicare beneficiaries receiving indwelling cardiac devices, and you can see a steady rise from 1990 up to 1999 during the course of the study.

[Slide]

This shows the increasing numbers of cardiac devices which are being implanted, being a considerable increase here. Much of this is due to the cardioverter-defibrillators that are being used at the present time.

[Slide]

It is clear that if a patient has any sort of prosthetic device implanted and then has staphylococcal bacteremia during the course of a hospitalization increased costs are accrued as a complication of that bacterial staphylococcal sepsis.

[Slide]

Is community-acquired MRSA an emerging cause of endocarditis? Again, in these countries we see roughly a 30 percent incidence of community-acquired MRSA.

[Slide]

We know that we have been seeing diminishing susceptibility to vancomycin associated with S. aureus, and we now have developed a classification which separates the various susceptibility profiles. I am sure everyone here is familiar with the reports of vancomycin-resistant S. aureus which occurred mainly in 2002.

[Slide]

But then there is another one from New York City in 2004.

[Slide]

I would like to make these general summary points regarding the epidemiology here. There is an increased incidence of bacteremias in general, particularly in the technologically advanced countries. There is an increased incidence of

gram-positive bacteremias. There is a substantial increase in bacteremia due to staphylococcus. S. aureus now is the most common cause of endocarditis. This increase in staphylococcal endocarditis is associated with modern healthcare advances. There is a highly significant increase in both community and nosocomial sources of MRSA, and really that not only applies to the U.S. but also internationally. There is a developing increased resistance to staphylococcus to vancomycin.

I think if we were to take a broader perspective we could say that in the history of infectious diseases that has preceded us and in the future that is certain to unfold, this organism is another example of an evolving pathogen which has established a different relationship with the host, and has adapted abilities to interact with the host that are in its favor and is adapting mechanisms to resist our therapeutic strategies.

I would like to stop there and ask Dr. Chambers to the podium.

DR. LEGGETT: Dr. Edwards, could we see if you have time for a couple of questions?

DR. EDWARDS: Sure.

DR. LEGGETT: One question, in Fowler's data in JAMA with the 25-30 percent mortality, was that both left-and right-sided, or was that just left? I don't remember.

DR. EDWARDS: Yes, I may ask Dr. Fowler to comment on that, if that is okay.

DR. FOWLER: Good morning. I am Vance Fowler, Duke University. The short answer is yes, that was including both. I should point out the differences in mortality according to the epidemiologic background in which the endocarditis arose. Specifically, for injection drug users the overall mortality rate is substantially lower, on the order of 10 percent. By contrast, in the setting of the healthcare associated endocarditis, which is what we proposed was contributing to the bulk of this emerging infection, the mortality was substantially higher, on the order of 30 percent. This probably had to do in large part with the fact

that these are sicker people that acquired the infection. So, the overall mortality rate, on the order of about 25 percent, is very consistent with prior studies in the area.

DR. LEGGETT: Thank you. Any other questions?

[No response]

Thank you, Dr. Edwards. Cubist Pharmaceuticals has allowed me the opportunity to introduce Chip Chambers to give us an overview of S. aureus disease. Chip is a professor of medicine and Chief of the Division of Infectious Diseases at San Francisco General Hospital.

Cubist Pharmaceuticals Presentation

Overview of S. Aureus Disease

DR. CHAMBERS: Thank you, Dr. Leggett, and good morning.

[Slide]

I wish before starting first to thank the committee for the opportunity to review and discuss the most important and quite serious infection, the problem of S. aureus bacteremia. I have chosen

this morning to use as a point of departure and to put into context for my further discussion in managing staphylococcal infections, particularly bacteremia, two cases that typify the extremes of decision-making that is required in approaching this disease.

[Slide]

The first case is that of a 38 year-old man who had new congestive heart failure due to cardiomyopathy and a hematocrit of 13. He was treated with packed red blood cells, diuretics and afterload reducers and on the sixth hospital day underwent an upper and lower endoscopy in order to determine the source of what was felt to be a GI bleed. Post procedure he had a temperature of 39 degrees and blood cultures were taken. Antibodies were not started at that time and the next day he was afebrile, but those two blood cultures that were obtained were both reported back as growing gram-positive cocci in clusters. He was found to have a right former IV site that was red, tender and indurated, and vancomycin was administered.

The next day the blood culture isolate was identified as a methicillin-susceptible strain of S. aureus and he had further blood cultures obtained on that day, which subsequently proved to be negative.

[Slide]

What are the management issues in dealing with this relatively straightforward case of catheter-associated bacteremia? You need to consider what is the risk of a poor outcome in this patient because that will dictate the aggressiveness of therapy; what antibiotics are going to be used; and how long should the patient be treated.

[Slide]

With respect to the risk of a poor outcome, this pie chart shows what complications are reported in patients who have a source identified as a catheter and associated S. aureus bacteremia. This study is from Sam Raad's group, looking primarily at an immunocompromised patient population but it is fairly generalizable.

I want to point out two features on this slide. First of all, in the blue are patients who do well. They have no complications, and that is about 80 percent. So, you would expect that with removing the catheter and proper therapy the patients would do well in about 80 percent of the cases. However, there is a substantial proportion of individuals who develop early or late complications. These complications are often not present at the time the bacteremia is diagnosed. The early complications are those that occur generally within the time frame of the treatment course that is administered, as I said, which is relatively short. The late complications are, unfortunately, identified after the patient has been treated, sent home and represents a relapse of the infection before it is recognized.

[Slide]

These are two additional and more recent studies also of catheter-associated bacteremia. In the study by Fowler et al., here, this 13 percent rate represents infections that were limited to

endocarditis, arthritis and osteomyelitis, so the more serious metastatic complications occurring from a catheter-associated bacteremia but representing a very serious group of patients and a substantial rate of complication.

The study below from Thomas, in New Zealand, shows a 9 percent death rate associated with this disease and a distribution of early and late complications similar to what I showed on the earlier slide. Again, they found endocarditis, arthritis, thrombosis, pneumonia and epidural abscess.

[Slide]

Now, obviously in managing patients with S. aureus bacteremia it is critical to identify those who are going to do well and those who are not going to do well so the duration of therapy can be extended or expected management can be used in analyzing the patient and then a preemptive identification of a possible metastatic site can be done.

These are four predictors that are

clinically useful relatively early in the course of identification of S. aureus bacteremia that have proven useful in predicting outcome. The most potent by far is a positive blood culture on therapy, generally 48-96 hours into treatment. Now, this is intuitively obvious as a bad predictor, that once antibiotics are started the blood cultures remain positive. That increases the odds of a poor outcome by 5-6 percent.

The second most powerful predictor is community onset disease which has a 3-fold increased associated risk. Persisting fever and skin lesions each double the risk. Those skin lesions are embolic or hemorrhagic skin lesions which are suggestive of an underlying endocarditis. So, we are not talking about a rash; we are talking about stigmata of endocarditis or possible stigmata of endocarditis.

[Slide]

Now, you can use those four predictors to generate a prediction model that helps you assess the likelihood of a complication but, as you can

see, there are red flags. The red flag that I have depicted over the score of 4, which is associated with an 80 percent probability of a complication occurring as a result of the bacteremia, indicates the power of a blood culture being positive on therapy at 48-72 hours. So, if a patient has a positive blood culture into the course of therapy it is highly likely that they are going to have a complicated clinical course. Note that compared to the other predictors, only one point being assigned to each of those, you can have all three other predictors and they do not measure up to the predictive power of this positive blood culture.

But the second red flag I have positioned over the zero score. You will notice that there is about a 15 percent complication rate in individuals who have none of these predictors that are present, indicating an inability to identify these complications at any reasonable time frame before the patient is treated. So, there is considerable uncertainty about the ultimate outcome in a small proportion of patients or patients who have no or

one risk factor. It is not a guarantee of success.

[Slide]

On this slide I have shown the predictors of poor outcome for S. aureus bacteremia summarized from a variety of studies. One is the no-brainer of septic shock, which is never good. Identifying a persistent focus of infection, that is failure to remove the catheter; failure to drain an unrecognized abscess, etc., is a predictor of poor outcome. Having any secondary focus of infection, whether it is identified or not; prolonged bacteremia, as I have mentioned, on therapy; the occurrence of S. aureus bacteremia in an elderly patient given the unfortunate cut-off of 60 years of age; MRSA bacteremia, carrying a substantial risk of a worse outcome; and at the bottom I have listed the two issues of therapy that will be the next point of discussion, the use of vancomycin instead of a beta-lactam antibiotic and short treatment durations, generally in the range of 10-14 days or less than that.

[Slide]

Now, in choosing an antibiotic to treat S. aureus bacteremia there are four criteria which need to be considered. Number one, the drug should be bactericidal. That is because the most feared, serious and a very common complication is endocarditis and antibiotics, in order to cure endocarditis, must be bacteriocidal in their action. That is because there is no host defense at the site of infection that will allow the bacteria to be eradicated and one must rely entirely on the intrinsic activity of the antibiotic.

The second is always that the drug should be non-toxic and well tolerated. Obviously, the nature of the infection is going to allow some latitude in this criterion. Third, the antibiotic should be parenterally administered at least initially in order to assure high drug levels and to assure that compliance is in play early on. Finally, there should be convenient dosing, which is less of an issue while the patient is in the hospital having a parenterally administered drug,

but if one wishes to treat the more uncomplicated patient as an outpatient it is really important to have a drug regimen which is able to be complied with.

[Slide]

Now, what antibiotic should be used? The guidance on this is really shockingly limited. What I have cited here is a quotation from Victor Hugh's textbook, "Antimicrobial Therapy and Vaccines," in which it is cited that if the focus of infection has been properly removed with rapid documented resolution of bacteremia, within 3 days, 2 weeks of antibiotic therapy with a penicillinase-resistant penicillin, first generation cephalosporin or glycopeptide is likely to be enough. Notice the lawyer like wiggle room--no guarantees here, "likely" to be effective. And, under no circumstances should patients simply have a catheter removed without antibiotic treatment.

[Slide]

With respect to what antibiotics should be

used of those three listed, a number of studies--and this is one looking at patients with S. aureus bacteremia from a variety of sources who are treated with a beta-lactam versus vancomycin, those individuals who are treated with a beta-lactam have a better outcome than those who receive vancomycin who have a higher death rate and relapse rate and lower cure rate.

[Slide]

Now, there are two factors driving the institution of vancomycin therapy or that might drive this result. One is using vancomycin instead of a beta-lactam so if a beta-lactam is more effective you would get this result. But, remember, vancomycin is being used to treat methicillin-resistant infections primarily so it could reflect the less intrinsic activity of antibiotics against MRSA in particular. It turns out that both are probably operative. If one breaks out patients in the vancomycin group who could have received a beta-lactam because they are not infected by an MRSA strain, you would get

similar results. So, vancomycin is therapeutically less effective than a beta-lactam and one would prefer a drug with beta-lactam activity if one had one's choice.

[Slide]

Now, this is the list of antibiotics that could be used based on Dr. Hugh's prescription for us and his recommended doses, and I have given you my listing of the pros and cons of each. Nafcillin or oxacillin, 2 g every 4 hours, is highly effective. However, it can be poorly tolerated because of phlebitis from infusion. It is certainly inconvenient, having to be given 6 times a day, and is not a user-friendly outpatient regimen.

Cefazolin at 2 g every 8 hours IV is probably less effective than other beta-lactams. It is definitely a second choice in most people's opinions. It is somewhat more convenient than other beta-lactams because it can be given 3 times a day, but still in dealing with home infusion units it is difficult to have them come in and

agree to administer a 3 times a day regimen, and it would be difficult to have a patient come back 3 times a day to receive this regimen.

Vancomycin, a gram q. 12 hours IV, is generally well tolerated; is more convenient but less effective than a beta-lactam. So, now we are trading off convenience for efficacy--always a difficult choice. My preference in this disease is to shave whenever possible to efficacy.

Finally, at the bottom of the list is a PO regimen that might be used, a dicloxacillin or cephalexin, a gram. It is certainly convenient because it is oral. However, this is of totally unknown efficacy. I, myself, have never used this drug to treat S. aureus bacteremia. There are considerable GI side effects that make you wonder about the people who make these recommendations. If they were to, in fact, take the drugs that they recommend, once their diarrhea ensued, how they would feel about it now. This is not a great dosing regimen to imply compliance in a serious disease. So, I think oral therapy is not ready for

prime time.

[Slide]

With respect to the duration of therapy, the regimens that might be considered are a short course of 7-10 days. However, this is associated in numerous studies with a high relapse and complication rate and I think it is presently not a good alternative. The 4-6 week course of therapy is certainly likely to be effective and is effective in many but not all cases of endocarditis, osteomyelitis and more complicated bacteremia but, again, entails significant difficulty in terms of compliance in completing the course of therapy, particularly if one is not able to give a conveniently administered regimen. The standard recommended duration is 10-14 days, and you saw that Dr. Hugh felt that 14 days was required.

[Slide]

Now, what was done in our patient? A PICC was placed for home infusion therapy. You may be horrified to note that cephtriaxone, which did not

appear on the list, was given at a 2 g dose. This is a high dose of drug. It has good but not great anti-staphylococcal activity. We were simply not able to arrange to give the patient any of the other drugs, and the decision in this case was driven by preferring a beta-lactam antibiotic with a once daily dose for 14 days.

I spoke to the patient last week. He is doing fine 3 weeks after therapy. I intend to follow him up again. This is a regimen, as I say, that was chosen for convenience, hoping to preserve efficacy, but certainly has not appeared on anybody's slides for treatment of staphylococcal bacteremia.

[Slide]

Now let's turn to a more difficult case. This is a 44 year-old man. He presented about a week later to my service. He was homeless and an IV drug user, with fever and back pain but a non-localizing exam. He had no particular laboratory or radiographic signs to point to us where the infection was located at the time of

admission and he had no murmur. He had no stigmata of endocarditis. Vancomycin was administered and 3 blood cultures obtained grew MRSA. A transthoracic echocardiograph was obtained to rule out endocarditis. The patient declined a transesophageal study. An MRI was performed of the spine to look for osteomyelitis. That study was negative. His fever persisted into the first week, and on the third hospital day a blood culture, of three that were drawn, remained positive for MRSA, the same strain that was originally isolated.

[Slide]

Now, what is the risk of a poor outcome in this patient? As I indicated before, community onset disease is a risk factor for worse outcome and this chart demonstrates that. Again, you can expect a majority of patients to do well with S. aureus bacteremia from any source overall, but what we want to drill in on are the individuals who are liable to have endocarditis and osteomyelitis. Both of these are in play in our patient and we have been unable to diagnose either.

[Slide]

Let's go back to those independent predictors of complicated bacteremia that I showed you before. In our patient we have a positive follow-up blood culture on therapy. That is four points. We have community onset disease. That is a total of five points. We have persistent fever at 72 hours. We are up to six points. That is off the scale so I guess this patient has a 110 percent chance of a complicated bacteremia. The only feature we are lacking is skin lesions which would point us to an underlying endocarditis.

[Slide]

These are supposed to be embossed so you can't see them because really the only choice is vancomycin, a gram q. 12. We can't use nafcillin, cefazolin or diclox because this is an MRSA strain. We have to use vancomycin. It is well tolerated and convenient, as I said, but we are concerned that it is less effective than a beta-lactam antibiotic.

[Slide]

What was done? A PICC was placed. We placed the patient on methadone maintenance. We gave him vancomycin a gram or whatever was necessary every 12 hours IV for 6 weeks, figuring we would treat for either endocarditis or osteomyelitis as we did not know which we were treating but hoping we would take care of both. We targeted trough serum concentrations of 15 mcg/ml which is on the high end. In fact, it is about double or 50 percent more than what is generally recommended.

[Slide]

What happened? The patient completed therapy and returned 3 months later complaining of back pain. He is afebrile. He has a normal exam. Blood cultures are negative. The MRI of the spine shows a T-10, T-11 osteomyelitis and discitis. A bone biopsy culture grows MRSA that is the same strain that was isolated before therapy at the 3-month previous treatment course.

[Slide]

What was done? Well, we don't have a

whole lot of choice. A PICC line was placed. He was put on methadone maintenance. We gave him a gram of vancomycin every 12 hours for 6 weeks, and we targeted trough serum concentrations of 15 mcg/ml.

Now, I am not very confident in this course of therapy for this patient because we have "been there, done that," and the patient failed at a time in his therapy when you would expect that, having relapsed, he would only do worse on this course of treatment.

[Slide]

The management issues raised by this case are perplexing. Is this a vancomycin failure? I believe it is but, if so, why did it fail? The isolate was not resistant. There was no change in MIC. We targeted high serum concentrations. Perhaps there was a focus of infection that we missed but we certainly couldn't see it on our imaging studies. The patient relapsed with negative blood cultures so I am not very confident that he had endocarditis although he may have.

What is the risk of a poor outcome now? When you retreat osteomyelitis, if that is what he had to begin with and we don't really know that, the failure rate is quite high, as high as 50 percent. What antibiotics should be used? I don't know. There are antibiotics that I can use but I don't know which should be used, and I don't know how long to treat this patient.

[Slide]

In these two cases I hope I have demonstrated the state-of-the-art--and I use that term advisedly and with a bit of sarcasm--in the treatment of S. aureus bacteremia. Two points, the current armamentarium is inadequate for outpatient treatment for MRSA infections which we are increasingly seeing in the outpatient setting for patients who fail or cannot tolerate therapy, particularly, again, for MRSA infection.

Physicians are left to rely on drugs that are not approved for treatment of complicated staph. infections, or drugs with unknown or poorly documented efficacy, or second-line agents and

combinations of agents of unknown benefit.

I hope I have given you a flavor of the disease that we deal with on a daily basis. I thank you for your attention and that concludes my remarks.

DR. LEGGETT: Thank you, Chip. Any questions for Dr. Chambers?

DR. FOLLMANN: I have one question. On slide C-12 you quoted a paper by Fowler in 1998. You looked at cure rates for beta-lactam and vancomycin which were different. Was this a randomized study?

DR. CHAMBERS: No, there are no randomized trials comparing these two drugs. That is because vancomycin--I am sure you don't remember the earlier slides but vancomycin is only indicated for MRSA infections or the severely allergic penicillin patient.

DR. LEGGETT: Any other questions? Jan?

DR. PATTERSON: Hank, you raised the issue of the management of the last patient and the vancomycin failure. Was it a failure? If so, why

did it fail? Could you elaborate on that a little bit?

DR. CHAMBERS: Yes. First, I do think it was a failure. My suspicion, although I can't prove this, is that there was probably a seeding in the spine that we missed that would explain the back pain. I think the bone penetration of vancomycin is poor, particularly if it was a very early infection and there was not a lot of associated inflammation with breakdown of the blood barrier and the ability to achieve blood delivery. I don't think it was our ability to dose the drug. But I also think it reflects the intrinsic lack of activity of vancomycin in treating these patients, and it reflects the question that was asked earlier about the efficacy of this drug compared to other drug classes. So, all of those I think.

DR. LEGGETT: Great! Thank you so much. It is now about 9:35 so why don't we take a 15-minute break now because we are going to need the extra 10 minutes I think before lunch?

[Brief recess]

DR. LEGGETT: For this next portion of the meeting we are going to begin with Dr. David Manus giving us an introduction.

Introduction

DR. MANTUS: Thank you, Dr. Leggett.

[Slide]

My name is Dave Mantus. I am vice president of regulatory affairs at Cubist Pharmaceuticals. I would like to first, on behalf of Cubist, thank the Anti-Infective Drugs Advisory Committee for the opportunity to present today, and also the FDA's Division of Anti-Infectives for all of their efforts over the past years on what you will see to be a pivotal study of daptomycin in S. aureus bacteremia and endocarditis.

I would also like to take a moment to recognize the investigators, patients and patient families who participated in the study. Their intensive commitment made this unprecedented study possible. The results of the study were part of a supplemental new drug application or SNDA, the subject of today's meeting.

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Cubist is very pleased to have numerous experts here today to help with today's discussions. These include members of the adjudication committee from the pivotal study. This committee provided a blinded, independent clinical assessment of all cases in the study. Dr. Ralph Corey, of Duke University Medical Center, was the adjudication committee chair and he will be presenting later. Also on the committee was Dr. Elias Abrutyn, of Drexel; Dr. Sara Cosgrove, of Johns Hopkins; Dr. Vance Fowler, of Duke; and Dr. Adolf Karchmer, of Beth Israel Deaconess Medical Center.

[Slide]

We also are very pleased to have Dr. Chris Cabell here today, the cardiologist from Duke who provided centralized reads of the transesophageal echocardiograms in the study. You have already met Dr. Chip Chambers, from UCSF. We also have Dr. George Drusano, from Albany Medical College; Dr. Donald Levine, from Wayne State University; and Dr.

Al Sheldon, from Antibiotic and Antiseptic Consultants, Inc. These experts bring between 10 and 30 years or more of expertise in S. aureus bacteremia and its clinical and microbiological consequences including S. aureus bacteremia and endocarditis.

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What is daptomycin? It is a cyclic lipopeptide natural product, originally isolated from soil bacterium. In 2003 daptomycin 4 mg/kg IV once daily was approved in the U.S. as Cubicin for the treatment of complicated skin infections, including those caused by MRSA. Similar approvals followed in Israel, Argentina and, most recently, in the European Union.

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We have over two years of clinical experience with daptomycin and over 150,000 patients have been treated. Post-marketing surveillance has revealed no new toxicities, nor have any been reported to Cubist by FDA. The fact that it is once daily dosing and monotherapy may be

why approximately one-third of daptomycin doses are currently being delivered in the outpatient setting. Ongoing microbiology studies continue to demonstrate the potency of daptomycin versus S. aureus.

It is important to note that physicians are already seeking daptomycin as a treatment for bacteremia but without the guidance of an approved indication. Data on physician usage suggests that approximately one-quarter of daptomycin doses are currently being prescribed for bacteremia. However, half of these are at the 4 mg/kg dose approved for skin, not 6 mg/kg that was studied in S. aureus bacteremia.

[Slide]

Why did Cubist choose to develop daptomycin for S. aureus bacteremia and endocarditis? Dr. Soreth has already pointed out that this was a real challenge as no antibiotic has ever been approved for this specific indication. Daptomycin has some properties that make it a rational choice for development. It is rapidly

bactericidal both in vitro and in vivo. It is potent against both MRSA and MSSA, and now has proven clinical efficacy in skin against both MRSA and MSSA. It also has efficacy in relevant animal models at human equivalent doses for endocarditis. It had the potential for outpatient treatment and we have seen this potential realized in the post licensure experience. This can be important in a serious disease where extended duration therapy is often required. Daptomycin had not only the potential to be a treatment option but one with advantages over current standards of care.

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This was an unprecedented study and an unprecedented indication so FDA and Cubist maintained a constant dialogue throughout development. This dialogue led to agreements on critical aspects of the study. These included its open-label design although Cubist maintained its blind to treatment; the choice of comparator agents; the requirement that all patients enrolled had a positive culture for S. aureus; and the

establishment of a data safety and monitoring board.

As the study progressed additional agreements were reached on the establishment of an adjudication committee, the committee's protocols and procedures, and the primary endpoint, adjudication committee's success at test of cure. We also agreed and discussed the statistical analysis plan prior to unblinding, including methodologies and planned analyses. Cubist first presented the results of the study to FDA in July of 2005. In September the SNDA was filed and in November it was granted a priority review status.

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Consistent with the patient population studied in the pivotal study, the proposed indication is the treatment of S. aureus bacteremia, including those with known or suspected endocarditis. The proposed dose is 6 mg/kg IV once daily for a minimum duration of 2-6 weeks.

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The Cubist presentation is going to

continue today with Dr. Helen Boucher who will summarize efficacy; Dr. Jeff Alder who will present key data on microbiology from the pivotal study; Dr. Gloria Vigliani who will summarize safety at 6 mg/kg; and we are very pleased to have Dr. Ralph Corey, the chair of the adjudication committee, present the overall conclusions to the study.

[Slide]

What will they tell us? Daptomycin was effective in the treatment of S. aureus bacteremia and endocarditis. It was well tolerated for extended treatment durations. In fact, it was less nephrotoxic than current standard of care agents. Daptomycin provides a much needed treatment option for the treatment of patients with S. aureus bacteremia including those with known or suspected endocarditis. It gives me great pleasure now to invite Dr. Helen Boucher to the podium to summarize daptomycin efficacy. Thank you.

Efficacy Results

DR. BOUCHER: Good morning.

[Slide]

My name is Helen Boucher. I am a member of the Division of Infectious Diseases at Tufts University New England Medical Center, and have been a consultant to Cubist for the past few years. I am honored to be here today to present the efficacy data for the pivotal trial of daptomycin as therapy for S. aureus bacteremia and endocarditis on behalf of Cubist.

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This study was three times larger than the Korzeniowski study of nafcillin versus nafcillin and gentamicin, the only other randomized study of S. aureus endocarditis. The S. aureus endocarditis and bacteremia study was a prospective, international, multicenter, randomized, controlled trial. The primary objective was to test the hypothesis that daptomycin is not inferior to standard therapy in the treatment of S. aureus bacteremia and endocarditis as assessed by the adjudication committee outcome at test of cure in the intent-to-treat and per protocol populations.

Like the majority of anti-infective

registration trials, this study was designed as a non-inferiority trial. In determining the sample size, we assumed an overall response rate of 65 percent based on the evolving epidemiology of S. aureus bacteremia, namely, the increase in frequency of MRSA and the low observed success rates in the treatment of MRSA infections. And 180 patients, 90 per arm, were required in the intent-to-treat population. The study had at least 80 percent power to exclude a difference in adjudication committee assessed success at test of cure of minus 20 percent. In order to deem the trial a success the lower limit of the 95 percent confidence interval around the difference in success rates, daptomycin minus comparator, had to be greater than minus 20 and include zero.

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The study included adults who provided written informed consent and had positive blood cultures for S. aureus, regardless of the presence or absence of a source or complication. All-comers with S. aureus bacteremia from any source, with or

without complications, were included, including those with known endocarditis.

Patients were excluded if they had intravascular foreign material that could not be removed; if they had prosthetic heart valves; renal failure; known pneumonia or osteomyelitis; polymicrobial bacteremia or a high likelihood of death in the first 3 days.

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I would like to take a few minutes now to review with you the overall design of the study. Patients entering the study were to have a positive blood culture for S. aureus within 2 days of enrollment. This was an open-label study where patients were randomized to either 6 mg/kg of daptomycin or standard of care. Most of our patients initially received vancomycin. Once S. aureus susceptibilities were known, patients with methicillin-susceptible S. aureus, or MSSA, were to switch to anti-staphylococcal penicillin at 2 g every 4 hours IV unless they had a documented allergy. In addition, all comparator patients were

to receive an initial 4 days of low dose gentamicin.

All of our patients were to undergo rigorous diagnostic evaluation that included daily blood cultures until they had been negative for 48 hours; daily physical examinations; any necessary testing to rule out metastatic foci of infection; and a transesophageal echocardiogram or TEE within 5 days of randomization. This TEE was read locally and used by the investigator to guide his or her clinical care of the patient. That same echocardiogram was sent to the central core echo lab for reading by a single cardiologist, Dr. Cabell, who was blinded to study treatment. This was to ensure consistency of reading and interpretation across the study.

At the end of therapy the investigator made a determination of clinical response. In addition, patients were followed for an additional 6 weeks following the end of therapy to the test of cure visit for another evaluation to capture any relapses. This more conservative assessment was

used to ensure that patients were, indeed, cured.

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Due to the open-label nature of the trial, the heterogeneity of the population and the complexity of diagnosis and outcome assessments of patients with S. aureus bacteremia and endocarditis, we convened an adjudication committee to conduct a clinical review of individual patient data, blinded to treatment assignment, in order to make independent assessments of diagnosis and outcome at selected time points.

Diagnosis at study entry was based on modified Duke criteria and categorized as definite endocarditis, possible endocarditis or not endocarditis. These criteria were used to categorize our patients according to their risk of having endocarditis. Final diagnosis was assessed retrospectively by the adjudication committee based on all available clinical and microbiologic data and included bacteremia that was complicated or uncomplicated, right-sided S. aureus endocarditis and left-sided endocarditis. The committee had to

classify all patients including those initially classified as having possible endocarditis. The adjudication committee assessed outcome at the end of therapy and then again 6 weeks later at the test of cure time point, the primary efficacy endpoint. Our presentation here will focus on the patient groups identified by the adjudication committee.

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The definitions of success and failure used in our study are shown here. The protocol definition of success required more than negative blood cultures. Success was required to be judged clinically cured or improved; to have that negative blood culture; to not receive potentially effective antibiotics that might have impacted on the outcome; and to receive at least a minimum amount of therapy as indicated by the investigator.

On the other hand, there were several reasons for failure and patients failed if they had any one of these reasons. They included persisting or relapsing S. aureus infection; death; if they were judged a clinical failure; if they received a

potentially effective antibiotic; if a patient discontinued prematurely due to clinical failure, an adverse event or microbiologic failure; and if they didn't have documented negative blood culture at the test of cure. For example, a patient could have come back for their test of cure visit and had a physical exam and been well, but if the investigator was unable to obtain that blood culture that patient would still have been considered a failure. So, our study had stringent criteria for success and conservative definitions for failure.

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Now I would like to turn your attention to the results of the S. aureus bacteremia and endocarditis study.

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From August 2002 to February 2005 investigators at 44 sites in 4 countries in the United States and Western Europe, treated 236 patients in our study. This was an extremely resource intensive effort. These patients required

expensive diagnostic evaluation, long courses of therapy and long-term follow-up. Importantly, approximately 20 percent of our population were IV drug users, a population with known difficulty and challenges in adherence to therapy and follow-up, adding further to the efforts required by our investigators to follow these patients.

There was one major change to the conduct of the study. Following review by the data safety monitoring board of the data from the first 30 patients treated in the study, the protocol was amended and patients with known left-sided endocarditis were allowed into the study and were separately randomized to ensure an equal distribution of these severely ill patients in the two treatment groups.

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This flow chart shows the disposition of all 246 patients randomized in the S. aureus bacteremia and endocarditis study. Ten patients did not receive study drug, leaving 120 daptomycin and 116 comparator patients in the safety

population. One patient entered the study with a high likelihood of a left-sided endocarditis before the amendment to allow that and was, thus, excluded, leaving 20 daptomycin and 115 comparator patients in the intent-to-treat population, our primary efficacy population. Then a number of criteria were used to assess adherence to the protocol, leaving 79 daptomycin and 60 comparator patients in the per protocol population.

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This flow chart shows the compliance of all patients in the intent-to-treat population. Patients who withdrew from therapy were followed for further antibiotics and for safety. As shown here, 69 of the 78 patients who withdrew from therapy were followed to completion of the study. On the left side we see that of the 157 patients who completed therapy, 148 met the test of cure requirements. So, overall, 92.3 percent of our patients completed study requirements in this study which dictated long-term follow-up. Given the complexity of our population, it is noteworthy that

so many patients completed the study requirements.

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Patients were well matched according to age, gender and race as well as renal function. Approximately 15 percent in each treatment group had renal dysfunction at baseline with creatinine clearances less than 50 ml/minute.

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Looking next at baseline infecting pathogen, rates of methicillin-resistant S. aureus or MRSA were similar in both groups. Approximately 38 percent of our patients had MRSA and this is similar to rates encountered in several of the recent multinational cohort studies.

The next row of the table shows risk factors for endocarditis in each group. Importantly, this was a severely ill patient population with 75 percent of our patients in each arm having SIRS criteria at baseline. The two study populations were balanced in terms of co-morbid conditions. For example, approximately one-third in each group had undergone surgery in

the month prior to entering the study.

Despite the relative balance between treatment groups according to each individual risk factor, there was a notable difference among the number of risk factors present in each treatment group with daptomycin compared to 13 comparator patients having 4 or more of these risk factors present at baseline. What this means is that a patient could have SIRS, diabetes, be an intravenous drug user and have septic pulmonary emboli all present at the time of presentation.

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In addition to the results of the primary efficacy analysis, I will present several of the additional pre-specified analyses of the primary endpoint, including success in patients with MRSA, success according to entry or final diagnosis, and success at the end of therapy.

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These bar charts show success in the primary efficacy endpoint, success at the test of cure as assessed by the adjudication committee in

both the intent-to-treat and per protocol populations of our patients with documented S. aureus bacteremia.

As seen in the magenta bar on the left, 44.2 percent of the daptomycin patients had success in the intent-to-treat population as compared with 41.7 percent of those treated with comparator, shown here in light yellow. The treatment difference is 2.4 percent and the lower limit of the 95 percent confidence interval around that difference in success was minus 10.2 in the intent-to-treat population.

Response rates in the per protocol population were higher, with a similar treatment difference of 1.1 percent. The lower limit of the 95 percent confidence interval here was minus 15.6. Note that the confidence interval is wider here because the number of patients was smaller in the per protocol population so in both co-primary efficacy endpoints the statistical criteria for non-inferiority were met.

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I would now like to draw your attention to some of the additional analyses of the primary endpoint that were specified in the statistical plan, first looking at success in daptomycin patients and in those who received vancomycin for MRSA or anti-staphylococcal semisynthetic penicillin for MSSA with pathogen specific therapy, For the daptomycin-treated patients success rates were the same irrespective of pathogen, 44.4 percent of MRSA-infected patients and 44.6 percent of MSSA-infected patients treated with daptomycin, shown again in magenta, were assessed as success by the adjudication committee. In MRSA 32.6 percent of vancomycin-treated patients, shown here in green, had success at the test of cure. The difference in success rates between daptomycin and vancomycin persists across all the diagnostic subgroups of MRSA infections, including patients with complicated MRSA bacteremia who presented a particular therapeutic challenge.

Among patients with MSSA infections success was seen in 46.7 percent of those who

received anti-staphylococcal semisynthetic penicillin therapy, shown here in grey, a rate similar to that seen with daptomycin.

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Next I would like to draw your attention to the analysis of success at test of cure according to entry diagnosis. Entry diagnoses as determined by our adjudication committee of the intent-to-treat population are shown in these pie charts. Importantly, 75 percent of our population had known or suspected endocarditis at baseline, and the proportions were well balanced between the two treatment groups.

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These bars show success in the strata of patients with definite or possible endocarditis based upon entry diagnosis on the left and bacteremia without endocarditis or not endocarditis on the right. Overall, 45.6 percent of daptomycin patients and 40.7 percent of comparator patients with known or suspected endocarditis were assessed by the adjudication committee as having success at

the test of cure. As in the primary efficacy endpoint, success was similar between daptomycin and comparator-treated patients when assessed according to entry diagnosis.

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The adjudication committee used all available information blinded to treatment assignment to determine a final diagnosis for each patient in the study. These pie charts show the final diagnosis as ultimately determined by the adjudication committee in the intent-to-treat population according to their treatment group. Proportions of the 4 diagnostic groupings were similar in both treatment groups. Importantly, approximately 25 percent of both groups had a final diagnosis of endocarditis and another 50 percent had complicated bacteremia. Prior studies of S. aureus bacteremia have shown a 12 percent incidence of endocarditis so a finding of nearly 25 percent endocarditis demonstrates that the population was truly enriched for endocarditis.

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These bars show success at the test of cure according to final diagnosis. Looking at success as assessed by the blinded adjudication committee according to whether patients had S. aureus bacteremia that was uncomplicated or complicated or right-sided endocarditis here again the success rates were similar for daptomycin and comparator.

The largest group here is the complicated bacteremia group which comprises 51 percent of the population, with 60 daptomycin and 61 comparator patients. Among these patients with high grade bacteremia and/or foci of infection, success was assessed in 43.3 percent of daptomycin and 37.7 percent of comparator patients at the test of cure.

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Looking next at our patients with right-sided endocarditis, 8 out of 19 daptomycin-treated patients and 7 out of 16 of those treated with comparator had success at the test of cure as assessed by the adjudication committee. Success rates in patients with

right-sided endocarditis were higher according to the investigator, with 63.4 percent of daptomycin patients assessed as a success at the test of cure compared to 50 percent of those treated with comparator. Whether assessed by the adjudication committee or the investigator, successes in right-sided endocarditis included patients with MRSA and MSSA infection.

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A total of 18 patients had a final diagnosis of left-sided endocarditis. While four daptomycin and three comparator patients had success at the end of therapy, only one daptomycin and two comparator patients had success at the test of cure. In addition, no patient with MRSA left-sided endocarditis had a success in the study with either treatment.

We reviewed the reason for failure after a success at the end of therapy in all four patients, the one treated with comparator and the three with daptomycin. In the comparator group, the patient who failed at test of cure developed recurrent MRSA

bacteremia and died. In the daptomycin group one patient died. One failed due to receipt of non-study antibiotics for an intercurrent gram-negative infection and one did well but did not return for the test of cure visit to have the negative blood culture documented. This patient was well when called at home by the physician.

Our review of the remaining left-sided endocarditis patients showed that the failures were largely driven by the lack of necessary valve replacement surgery. These patients were critically ill and only one comparator patient underwent surgery on the study, and two daptomycin patients underwent surgery following completion of the study. Despite these poor success rates, 6 out of 9 daptomycin patients survived compared to 4 out of 9 comparator patients.

[Slide]

Let's now turn to the analysis of success at a different time point, the end of therapy. This is a time point used in many case-control and cohort studies. As assessed at the end of therapy,

success was seen in 61.7 percent of daptomycin and 60.9 percent of comparator patients according to the adjudication committee. Success at the end of therapy is higher than at the test of cure. Although 3 daptomycin and 5 comparator patients experienced a relapse of S. aureus at the end of therapy, the receipt of non-study antibiotics and the absence of a documented negative culture contributed most to lower observed success rates at the test of cure visit. These success rates in the 60 percent range at the end of therapy are consistent with our statistical assumptions and with recent epidemiologic studies of S. aureus bacteremia and endocarditis.

[Slide]

The secondary efficacy endpoint in our study was a time to clearance of S. aureus bacteremia. This Kaplan-Meier plot shows that there was no difference between treatment groups in the time to clearance of S. aureus bacteremia. Overall, the median time to clearance was 5 days for daptomycin and 4 days for comparator. The time

to clearance for patients with MRSA infection was longer in both groups, with a median of 8 days for daptomycin and 9 days for comparator patients who received either vancomycin or semisynthetic penicillin with the initial low dose gentamicin.

[Slide]

In addition to their determination of success, the adjudication committee assessed all reasons for failure in each patient who failed. For example, if a patient had a persistent fever, persistent bacteremia and received additional antibiotics that patient would have been classified as a clinical failure, a failure due to persisting S. aureus infection and a failure due to the receipt of non-study antibiotics.

A similar number of patients failed in each group. When looking at the reasons for failure, more daptomycin patients failed due to persisting or relapsing S. aureus infections, whereas more comparator patients failed due to treatment-limiting adverse events. These included renal failure and allergic reactions.

Over 1,200 S. aureus isolates were collected in this study and were analyzed at local as well as central laboratories. The primary pre-specified analyses were based on central laboratory data. Among the daptomycin patients who failed due to persisting or relapsing S. aureus infections, 6 patients had isolates that developed decreased susceptibility to daptomycin on study, with MIC values rising to 2 mcg/ml or, in one case, 4 mcg/ml at the central laboratory.

[Slide]

Details on the 6 daptomycin patients who developed increasing MICs are presented here. Each of these patients had deep-seated sites of infection, including left-sided endocarditis, complicated bacteremia or right-sided endocarditis with foreign body, large pulmonary emboli, septic arthritis and an undiagnosed retroperitoneal abscess in a pancreas transplant recipient. All of these patients required, but could not or did not undergo necessary drainage, debridement or valve replacement surgery.

[Slide]

Based on the work of George Sakoulas and others demonstrating decreased success in patients with vancomycin MIC of 2 mcg/ml, we looked at all laboratory data, including that collected by our investigators at the local hospital labs, for evidence of vancomycin MICs equal to or greater than 2. Among the vancomycin-treated patients who failed one had S. aureus isolates that developed decreased susceptibility to vancomycin on therapy with an MIC rising to 2 mcg/ml at the central laboratory. Five additional patients who failed had potentially MICs of 2 mcg/ml documented at the local hospital laboratory. Dr. Alder will present data regarding susceptibility to both daptomycin and vancomycin in his talk shortly.

[Slide]

In order to determine the treatment effect or the strength of the treatment effect in the primary efficacy analysis we performed a number of sensitivity analyses. First we examined the contribution of treatment-limiting adverse events

to outcome in the study. When considering patients who failed only due to treatment-limiting adverse events as a success we saw success in 49.2 percent of daptomycin and 48.7 percent of comparator patients. The difference is 0.5 percent and the lower limit of the 95 percent confidence interval is minus 12.3. So, when the toxicity component of the endpoint is removed the results remain consistent with those seen in the primary efficacy endpoint.

[Slide]

With our observation of lower than expected overall success for both treatment groups, we thought it important to analyze the contribution of each individual reason for failure to the overall success in the study. Here each patient is counted only once and reasons for failure are considered sequentially so if a patient fails he or she will drop out of the analysis.

In the intent-to-treat analysis non-evaluable patients were considered failures. There were 9 daptomycin and 14 comparator patients

deemed non-evaluable in the study. If we then look at each reason for failure sequentially and first consider persisting or relapsing S. aureus infection as the only reason for failure, success was seen in 76.7 percent daptomycin patients and 78.3 percent of comparator patients.

If we then add death and consider persisting or relapsing S. aureus infection or death as reasons for failure, success is seen in 71.7 percent of daptomycin and 70.4 percent of comparator patients. If clinical failure is added, 70 percent of daptomycin and 68.7 percent of comparator patients have successful outcomes. When treatment-limiting adverse events are included as reasons for failure, success is seen in 65.2 percent of daptomycin and 58.3 percent of comparator patients.

With the addition of potentially effective non-study antibiotics or PENS, as they are noted here, success rates fall to 51.7 percent for daptomycin and 50.4 percent for comparator patients. Adding not having a documented negative

blood culture as the reason for failure brings the overall success rates to 45.8 percent for daptomycin and 42.6 percent for comparator. Adding the last three patients who discontinued for reasons other than treatment-limiting adverse events, we see success in 44.2 percent of daptomycin and 41.7 percent of comparator patients, or back to the primary efficacy analysis.

Our results remain consistent when the endpoint is analyzed in each of its components. In addition, the overall efficacy was driven more by treatment-limiting adverse events or non-study antibiotics than by persisting or relapsing S. aureus clinical failure and death.

[Slide]

Survival was an important additional efficacy endpoint. Time to death for all treated patients was a pre-specified endpoint in our study. This Kaplan-Meier plot shows survival in both treatment groups and there was no difference in early or long-term survival with approximately 85 percent survival in each group through the study.

Eighteen patients in each group died over the course of the study, with 2 daptomycin and 3 comparator patients dying on study.

[Slide]

In addition to the pre-specified survival analyses, we looked at deaths in two subgroups of interest. We looked at death among patients with endocarditis and those who failed due to persisting or relapsing S. aureus infections. In these analyses we looked at two time points, death by day 42 post therapy and at the end of the study. Day 42P refers to 42 days after the last dose of study medication regardless of the duration of study therapy. Among endocarditis patients, 3 daptomycin and 5 comparator patients died by day 42P and 3 daptomycin and 8 comparator patients died by the end of the study, as shown in the first 2 rows. Among our patients who failed due to persisting or relapsing S. aureus infection, 7 daptomycin and 3 comparator patients died by day 42P, and 8 daptomycin and 7 comparator patients died by the end of the study.

We looked at these analyses and the point estimate of the difference varies in favor of daptomycin or comparator. In every instance the confidence interval includes 1, indicating no significant difference in deaths between daptomycin and comparator.

[Slide]

Finally, I would like to return to our primary efficacy results. The investigator also assessed success for each patient based on his or her clinical judgment at the bedside. These two graphs show that whether assessed by the adjudication committee or the investigator success at the test of cure in patients with known or suspected endocarditis was similar for daptomycin and comparator. These are our patients at highest risk for complications of S. aureus bacteremia, including endocarditis, in whom appropriate therapy must be initiated promptly.

[Slide]

In conclusion, this large prospective, international, randomized study of daptomycin

monotherapy once daily versus standard of care met its primary endpoint in both the intent-to-treat and per protocol populations. Response rates were numerically higher among MRSA patients treated with daptomycin. Results were robust and consistent across the relevant pre-specified subgroups at different time points and according to both the investigator and the adjudication committee. Failures were more commonly due to persisting or relapsing S. aureus in the daptomycin group and treatment-limiting adverse events in the comparator arm. [Slide]

Daptomycin at 6 mg/kg once daily was efficacious in the treatment of patients with S. aureus bacteremia including those with known or suspected endocarditis.

Thank you very much, and I would now like to turn it over to Dr. Jeff Alder for discussion of the microbiology data. Jeff?

Microbiology

DR. ALDER: Good morning.

[Slide]

My name is Jeff Adler. I am the vice president of drug discovery and evaluation for Cubist Pharmaceuticals.

Today I am going to be presenting additional data on a salient issue that emerged during the clinical trial, those isolates that emerged with MIC values of 2 mg/ml or greater while on therapy.

[Slide]

In the analyses of these MIC shifts it is important to note that this trial produced an unprecedented microbiology database. Why is it unprecedented? Because of 1,215 serial S. aureus isolates, most of them collected from the blood and collected from patients under therapy in a controlled clinical trial. This has given us an unparalleled look at how bacteria act and how bacteria react while under therapy in seriously ill patients.

The salient issue that emerged was MIC shifts to greater than or equal to 2 mcg/ml. These shifts were noted in both the daptomycin-treated

and in the vancomycin-treated patients. When considering MIC shifts for daptomycin and vancomycin it is important to note that different susceptibility criteria exist for the two drugs. In order for a S. aureus isolate to be considered resistant to vancomycin it must achieve an MIC value of 32 mcg/ml or greater. That represents a 32-64-fold shift above a typical MIC for S. aureus. That same isolate, in order to be considered non-susceptible to daptomycin, need only achieve 2 mcg/ml MIC or a 2-4-fold shift above a typical MIC value.

Because of these classifications, it is virtually impossible in a clinical trial to isolate a bacteria that would be considered resistant to vancomycin. For these reasons, the data here will be presented in terms of MIC shifts to 2 mcg/ml or greater without classification as to resistance or susceptibility. There is increasing literature on lack of vancomycin efficacy at MIC values considerably lower than 32 mcg/ml, including specifically efficacy and lack of efficacy at 2

mcg/ml.

Well, what was found? Well, we are going to do scientific investigations into the three most important factors in an antibiotic trial: the bacteria, the drug and the patient. With the bacteria surveillance data will be presented to show no trends towards MIC increases. The ability of the drugs and the propensity of inducing MIC shifts in vitro and the magnitude of those shifts will also be presented. Also, genetic data will be presented to show the differentiation between wild-type--and by wild-type I mean non-exposed S. aureus isolates--versus those from clinical trials. From the drug standpoint, modeling will be done to look at exposure and response by MIC. Finally, the most important factor, the patient, will be examined specifically in terms of diagnosis and adjunctive care.

[Slide]

This is a surveillance table showing global surveillance studies. The point of this data is to show that MIC 2 isolates for daptomycin

are part of the wild-type distribution. As shown in the far right-hand column, MIC 2's existed as determined both in small, fairly uncontrolled regional surveillance studies, as well as in more controlled global surveillance studies. MIC 2's were present and part of the distribution well before daptomycin was approved in September of 2003.

When looking at surveillance data it is also important to note the quality and size of the study. The global surveillance studies depicted here from 2002 through 2005 were run by Dr. Ron Jones. For example, the 2005 data has over 6,000 S. aureus isolates collected both in the U.S.A. and globally. Isolates that are at MIC values of 2 or greater are vigorously retested in order to ensure the quality of the data--an important distinction between these large global surveillance studies and smaller studies of a couple of hundred isolates. The point of this slide is that MIC 2 values existed as part of the wild-type, non-exposed distribution of S. aureus to daptomycin.

[Slide]

First looking at the most important factor, the patients, a total of 7 isolates under daptomycin therapy emerged with MIC values of 2 or greater. Dr. Boucher mentioned 6 of these isolates. All 7 patients will be presented here, including the clinical success.

One patient emerged with a S. aureus isolate of 4 mcg/ml, outside the normal wild-type distribution. This patient was a complicated right side endocarditis, large septic pulmonary emboli and, importantly, a tunnel infection in which the catheter was left in place for more than 10 days. This patient was a failure.

Six patients progressed to MIC values of 2. One of these was a success, a complicated bacteremia with vertebral osteomyelitis. Importantly, this patient was debrided twice early in therapy. This patient was a success.

There were 3 additional complicated bacteremia patients that produced isolates of MIC 2. All 3 of these patients were complicated

infections--IV port, septic arthritis and undiagnosed retroperitoneal abscess. All 3 of these patients needed but did not receive adjunctive care--drainage, debridement, surgery. Amongst the complicated bacteremia patients, the 4 listed here, the success rate for daptomycin versus these patients where an MIC 2 was obtained is 1 success and 3 failures. In Dr. Boucher's presentation the overall success rate against complicated bacteremia patients was 43 percent.

There were 2 additional failures with MIC 2 isolates. These were both left-sided endocarditis patients who did not or could not receive valve replacement surgery. As Dr. Boucher indicated, the success rate in left-sided endocarditis patients who did not receive valve replacement surgery was exceedingly low. So, the take-home message from this slide is the lack and need for additional adjunctive therapy.

[Slide]

Very similar trends were noted amongst the vancomycin-treated patients. There was a total of

7 patients that produced MIC 2 isolates and they were all complicated infections where additional adjunctive therapy was needed. I won't belabor the complications here. It is important to note that 2 patients produced isolates of MIC 2 by the central lab testing. One was a success, a complicated right-sided endocarditis. One was a failure, a complicated bacteremia with septic thrombophlebitis.

An additional 5 patients produced an MIC 2 isolate but only by the local lab. There is literature on heteroGISA or small MIC vancomycin increases that are lost between transport from a local lab to a central lab. These 5 patients that registered an MIC 2 by the local hospital test, all 5 failed; all 5 were complicated infections. As one example, there is another left-sided endocarditis patient who did not receive valve replacement surgery and this patient failed.

So, overall for vancomycin there us a very similar pattern. Seven patients progressed to MIC 2 looking at central plus local lab data, and the

success rate amongst these 7 was 1 success and 6 failures. Importantly, the failed patients needed but did not receive additional adjunctive therapy.

[Slide]

Next we are going to look at the bacterial factors and are there interactions amongst the bacteria that would suggest a selection for resistance. This is a serial passage experiment. The point here is to look for both propensity and magnitude of MIC shifts. S. aureus is passaged in the presence of sub-inhibitory concentrations of daptomycin, depicted here by the purple lines, or as a representative fluoroquinalone, ciprofloxacin, by the white lines.

The point here is that under ideal laboratory conditions to select for MIC increases daptomycin, over 16 days, selected for only 1-16 X increase in the MIC. This was literally from a starting point of 1 mcg/ml to 16 mcg/ml. Comparatively, ciprofloxacin, over the same time period, selected for 32- to greater than 120-fold increases in MIC. For comparative purposes,

vancomycin's final result is depicted by the green bar. The vancomycin isolate lines would largely overlay those of daptomycin. Vancomycin produced very similar MIC increases under these conditions.

So, the summation of this slide is that both daptomycin and vancomycin selected for only low level MIC increases. A representative fluoroquinalone selected for large MIC increases. This is what was seen in the clinical trial, both daptomycin and vancomycin, when MIC increases were noted, they were primarily 2 mcg/ml right along the X axis in terms of MIC increases. Neither daptomycin nor vancomycin therapy produced an isolate of, for example, 32 mcg/ml in this trial.

[Slide]

Next we looked for genetic patterns related to the daptomycin MIC increases. The goal is to determine genetic patterns that differentiate wild-type or non-exposed isolates from clinical isolates that underwent therapy. Whole genome scanning of the serially passed isolates, MIC 1 through 16, was used in order to do a whole genome

scanning and then determine patterns of genetic changes that correlate with MIC increases.

The first gene change that was noted is in the mprF. This was seen at an MIC of 2 in the serially passaged isolates. In addition, mprF mutations were seen at MIC 2 amongst clinical use. In all, 7 isolates from the endocarditis/bacteremia study had mprF mutations but, most importantly, mprF mutations were also found in the wild-type MIC 2 isolates. This is to say that mprF changes are a part of the wild-type distribution of S. aureus.

The first unique genetic change that was noted was mutations in yycG. These occur at MIC values of 4 or greater. It was noted in the serial passage isolates, also in isolates from other clinical use at MIC 4 and above. This shows a clear pattern of MIC 2 and below as wild-type and MIC 4 occurring as unique genetic changes not found in the wild-type population.

[Slide]

Next these isolates were examined in models of the drug-bug interaction. The goal here

was to correlate daptomycin exposures that effectively treat or fail to treat these S. aureus isolates as MIC increases. This is showing a response curve in the neutropenic thigh mouse model, the gold standard for pharmacodynamics. What is being shown here on the Y axis is the calculated AUC to induce a 3-log reduction in the mouse thigh. On the X axis are listed the 5 MIC values of the isolates from the serial passage, MIC 1 through 16.

What we see is that MIC 1 and 2 isolates respond to about the same amount of daptomycin in the model, that is, AUC values less than 300. MIC 4 and above required progressively more daptomycin. This correlates back to the genetic data. The isolates that have the yycG mutation are requiring progressively more daptomycin for effective therapy. The MIC 2 and below respond to about the same amount of drug. This also correlates back to the wild-type distribution of 2 and below as wild-type, 4 and above as unique.

[Slide]

Now, the clinical isolates from the trial were then put into the same model, both the baseline and the post-baseline from those 7 daptomycin patients. The data is shown here. The Y axis is once again the AUC value for a 3-log reduction in the neutropenic mouse thigh model. The X axis here has been changed to depict the patient number for the 7 patients that showed daptomycin MIC shifts to 2 or above. The green circles indicate the baseline isolates which were MIC 0.25 or 0.5. The red squares are the post-baseline isolates MIC 2 and 4. All of these isolates responded to AUC values of less than 400, with one exception and that is the isolate from patient 152, this post-baseline, and that has an MIC value of 4 that responded to an AUC of 411.

You saw from the previous slide that the median AUC achieved at the 6 mg/kg dose in this study was 543, which exceeds the value for all of these isolates. However, we don't have to guess as to the AUC values. They were calculated directly for each of the 7 patients, as shown here by the

yellow bars. These are the AUCs achieved in these 7 patients compared to the AUC required to treat those same isolates when put into the neutropenic mouse model.

This data suggests that adequate exposure was obtained in these patients to treat those same isolates in the gold standard mouse model. We will never know the exact reasons for a clinical failure in a patient and the interaction between bug and drug and patient. This data does show that inadequate exposure is unlikely to be a cause.

[Slide]

It is important to note that the mouse thigh model also has a penetration component. In order for a drug to be effective, it must leave the bloodstream, effectively penetrate the abscess and exert bactericidal activity. This is a follow-up experiment to further explore penetration of daptomycin. This is a fibrin clot model in which fibrin vegetations are produced in vitro, impregnated with MRSA that has been genetically engineered to luminesce so long as the bacteria are

alive. These fibrin clots are then implanted in the backs of rats. It is a powerful model in that the vegetations achieved here approximate those of human disease. These are approximately one centimeter across in this case.

The way the intensity of the infection is read is just like tuning into the weather channel and watching the storm. The more intense infections are depicted as red and areas of lesser infection are green or blue. The rat on the left is at 72 hours post infection without therapy. The rat on the right has received a total of 2 doses that simulate the 6 mg/kg dose in exposure. Significant reduction in bacterial burden was achieved in all 6 vegetations. A total of one week therapy achieved significantly greater reduction in bacterial burden within the vegetations.

There are two additional pieces of data that supplement the penetration of daptomycin into the vegetations. One is an in vitro model from Mike Ryback's lab showing that a simulated 6 mg/kg dose produced effective penetration and

bactericidal activity against simulated endocardial vegetations.

A second study, from Claude Carbone's lab utilized C-14 labeled daptomycin and that showed both effective therapy and homogeneous distribution throughout the vegetations. All three of these pieces of data together show effective penetration and bactericidal activity of daptomycin into fibrin vegetations.

[Slide]

Lastly, we looked again at surveillance. This is surveillance data primarily from Dr. Ron Jones' service from 2000 through 2005. It is important to note that each of these years has over 2,000 isolates of S. aureus and the 2005 data has over 6,000 isolates. What is being shown here is the incidence for any particular MIC category. Over 90 percent of the isolates of S. aureus have MIC values of 0.5 or 0.25. The isolates at the edge of the distribution curve, MIC 1 and 2, and 0.12, are hugging the X axis--very low incidence of anything other than 0.25 or 0.5.

A one-year pattern was noted in the year 2004 with an increase in the 0.5's and a corresponding decrease in the 0.25's. This pattern largely reversed in 2005. In addition, Dr. Ron Jones followed up on this observation. What he found is that for a period of 18 months, from September of 2003 through April of 2005, lots of media were released which were low in calcium. Daptomycin in vitro activity is dependent upon calcium and the CLSI guidelines indicate that the calcium concentration should be at 50 mg/l. The calcium concentrations in the media lots were approximately 40 percent low over that 18-month period.

In addition to the pattern reversing in 2005 for MRSA, very similar patterns were noted for MSSA and for coagulase-negative staph., including both methicillin-susceptible and methicillin-resistant coagulase-negative staph. It is exceedingly unlikely to get this kind of pattern in four independent bacterial species and have it be anything other than a testing issue.

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In summation, we undertook additional investigations because of the MIC 2 isolates that emerged during therapy and because of the high failure rate in these isolates. Three main factors were investigated, the bug, the drug and the patient.

What was found? There were no decisive bacterial or drug factors that would explain the propensity for MIC increases. There was no trend in surveillance for increasing MICs to daptomycin. In vitro it is difficult to induce large MIC increases to both daptomycin and vancomycin. In addition, that is what was seen in the clinical trial. The MIC values were primarily to 2 mcg/ml. For daptomycin that is on the edge of but part of the wild-type distribution curve. Genetic data shows a similar split with MIC 2 and below as part of wild-type. MIC 4 and above accumulate unique genetic changes never found in wild-type isolates. Modeling has shown favorable exposure and penetration for daptomycin against isolates of MIC

values 2 and below.

Where does that leave us? It leaves us with the most important factor, the patient and patient-specific factors. What can be said for these patients that showed MIC increases is that the infections were complicated and additional adjunctive care was needed but not received. Similar trends were shown in the vancomycin patients. Seven vancomycin-treated patients produced isolates of MIC 2 or above.

We will never have complete knowledge of the reasons for clinical success or failure in any particular patient, however, in the bug-drug-patient interaction the most important factor in this trial by far appears to be the patient and the adjunctive care. Thank you.

I would now like to invite Dr. Gloria Vigliani who will be presenting the safety data. Gloria?

Safety Results

DR. VIGLIANI: Good morning.

[Slide]

My name is Gloria Vigliani. I am the vice president of medical strategy at Cubist, and I am pleased to be here today to present the safety data from this important trial.

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Daptomycin has been on the market for the last two years and the approved indication is for the treatment of complicated skin and skin structure infections. The approved dose is 4 mg/kg intravenously once daily. The dose used in the S. aureus bacteremia and endocarditis trial was 6 mg/kg once daily.

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During marketing use over 150,000 patients have been treated. During this time there have been no safety signals indicating new toxicities associated with daptomycin's use. The major adverse effect in the clinic of daptomycin is on skeletal muscle, with CPK elevations sometimes associated with musculoskeletal symptoms. Based on this, the current product labeling recommends monitoring for the development of muscle pain or

weakness, as well as weekly monitoring of CPK levels. In addition, consideration should be given to discontinuing the use of statins.

The primary data in the supplemental new drug application at 6 mg/kg were derived from data from the S. aureus bacteremia and endocarditis study. However, additional supportive data at 6 mg/kg was provided from 15 other trials. This included trials in both volunteers and patients in other indications where a total of 414 patients or subjects received a dose equivalent to or higher than the 6 mg/kg dose studied in the bacteremia and endocarditis trial. Importantly, no new safety issues were identified in this population.

[Slide]

Careful safety monitoring was undertaken during the S. aureus bacteremia and endocarditis trial. All patients had a comprehensive baseline evaluation and then were monitored daily during therapy and at the key study visits--end of therapy, test of cure and post study. At each visit investigators collected adverse events, labs,

concomitant medications, and all diagnostic and therapeutic procedures. CPK was monitored a minimum of 3 times per week during treatment as well as at the end of therapy and test of cure visits. This was done to assess the incidence and magnitude of the elevations, as well as the time course and resolution of any CPK elevations. Patients prematurely discontinuing study medication were followed for safety until completion of all study visits. A data safety monitoring committee reviewed safety data, blinded to treatment group, 6 times during the course of the study and found no findings related to safety, allowing the study to continue to completion.

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In this pivotal study there was a total of 120 daptomycin patients and 116 comparator patients that received at least one dose of study medication. This comprised the safety population. The mean duration of study drug treatment was 17.7 days in the daptomycin arm, with a maximum duration of therapy up to 74 days. In the comparator group

the mean duration was 19.7 days with a maximum duration of 57 days. Ninety-three percent of comparator patients received initial low dose of gentamicin in accordance with the protocol for a mean duration of 4.4 days.

[Slide]

I would like to begin with a high level overview of adverse events. Most patients in the study experienced at least one adverse event, over 90 percent. There was a similar incidence of events considered drug related, both severe and serious. There was a similar number of deaths between the two treatment groups and a similar number of adverse events leading to premature discontinuation.

[Slide]

This table displays the most common adverse events, here defined by those occurring at greater than or equal to 10 percent incidence in either treatment group. The most common adverse events observed were gastrointestinal in nature and consisted of diarrhea, nausea, vomiting or

constipation. Other adverse events observed at an incidence of 10 percent or greater included anemia, hypokalemia, peripheral edema, headache and arthralgia. All of these common events were seen at a similar or lower incidence in the daptomycin group relative to the comparator.

[Slide]

Overall, there was a similar rate of discontinuations due to adverse events, 16.7 percent in the daptomycin arm and 18.1 percent in the comparator arm. Focusing on drug-related adverse events leading to discontinuation, we find 10 daptomycin patients and 13 comparator patients. In the daptomycin group the patients discontinued due to rash, and 3 patients discontinued prematurely due to elevations of CPK.

In the comparator arm we saw more rashes and hypersensitivity reactions occurring in 9 patients. If we look at the vancomycin-treated patients, this included 1 patient with erythematous rash, 1 patient with a report of a severe red man syndrome and 1 serious anaphylactic reaction. In

the semisynthetic penicillin group there were 4 rashes and 2 reports of drug fever. In addition, 4 comparator-treated patients discontinued due to renal failure adverse events, 2 each in the vancomycin and semisynthetic penicillin groups.

[Slide]

If we look at the incidence of skeletal muscle adverse events, we find here a similar incidence of adverse events in the musculoskeletal and connective tissue systems. If we look at the individual adverse events we see similar or higher rates in the comparator group. There was 1 report of rhabdomyolysis in a daptomycin-treated patient. This was a patient who had a heroin overdose in the hospital and fell and had a maximum CPK of 847. There were no clinical details in this case to support a diagnosis of true rhabdomyolysis.

[Slide]

If we look more closely at the maximum CPK post baseline and focus on those patients who had a CPK level of 500 or more what we find is that there were more daptomycin than comparator patients who

experienced an elevation of their CPK to 500 or greater. There were 11 such patients in the daptomycin group and 2 in the comparator group. In the daptomycin group the CPK ranged from several hundred to several thousand, with the majority being less than 2,000. The highest CPK on study was 5,548. The majority of these CPK elevations occurred within the first 2 weeks on treatment.

We also looked at each of these cases for return of CPK to baseline. In all but one we had data available which showed resolution during treatment or following treatment, and one patient had no follow-up data available. The time course and reversibility of the CPK elevations is consistent with our prior understanding of this effect.

[Slide]

We also looked at CPK elevations in association with any reports of skeletal muscle adverse events in the daptomycin group. Here we found 3 patients. Two patients had plausible alternative etiologies for their musculoskeletal

symptoms. One was the heroin overdose patient who fell.

The second was a patient who had osteoporosis and was on chronic steroids, who presented with lower extremity weakness and was found to have a spinal cord compression. This patient entered the study with a baseline CPK of 833 and their maximum CPK on study was 5,548. This was the highest CPK that we observed on the study.

In the third patient there was no obvious alternative etiology for the patient's CPK. This was a 55 year-old female with a history of diabetes and an extensive cardiac history, including hypercholesterolemia, who was on simvastatin. She had a normal baseline CPK and had a CPK rise to 853 on day 15 which was associated with bilateral upper extremity weakness. A myocardial infarction was not suspected and no EKG or isoenzymes were done. Daptomycin was discontinued and the maximum CPK went to 2,977 3 days after discontinuing and was normal by one week following discontinuation of therapy.

What we can conclude from this study is that while CPK elevations may occur, they tend to be reversible and the incidence of daptomycin-related skeletal muscle adverse effects was low at the 6 mg/kg dose.

[Slide]

I would like to turn now to an important and unexpected finding related to renal impairment in the comparator group in this study. When we looked at all adverse event terms indicative of renal impairment and then looked at the incidence of these terms within the two treatment groups we found that there was a higher incidence of renal impairment adverse events in the comparator group. This was true whether we looked at all adverse events, serious adverse events, drug-related adverse events or discontinuations due to adverse events. Most marked was the difference in renal impairment adverse events in patients aged 65 or greater where more than 30 percent of comparator patients had a renal impairment adverse event. These differences were highly statistically

significant, with the exception of the discontinuations. Of interest, we found that the rates were similar when we separated comparator out to the vancomycin and semisynthetic penicillin groups.

To better understand this issue we looked at a more objective measure of renal impairment, that of laboratory evidence of renal impairment since frequent serum creatinine levels were collected during the study.

[Slide]

This Kaplan-Meier curve displays the time to decreased creatinine clearance by treatment group. Since the finding of renal impairment was unexpected, a pre-specified analytical approach was not defined for looking at renal impairment. However, after consulting with several nephrologists, we came up with a definition of what we would consider a significant decrease in creatinine clearance. For the purposes of this analysis, we defined a decrease in creatinine clearance as any treatment-emergent decrease in

creatinine clearance to less than 50, or if the patient entered the study with a creatinine clearance of less than 50 then a further decrement of 10 ml/minute was required.

In this Kaplan-Meier curve you see that there is a statistically significant difference that occurs early in treatment. This corresponds to the timing of initial low dose gentamicin which was administered to more than 90 percent of comparator-treated patients. We analyzed renal function in a number of other ways, including looking at mean changes in creatinine and creatinine clearance as well as shifts in creatinine clearance from one category of function to another. What we found were similar findings irrespective of how we analyzed the data.

[Slide]

Since patients may require extended courses of therapy in the treatment of S. aureus bacteremia and endocarditis, typically 4-6 weeks, we looked for any differential safety issues in patients treated with longer courses of therapy.

Displayed in this table is the incidence by system organ class of adverse events in patients treated 28 days or longer. We had 27 daptomycin patients and 20 comparator patients in this category.

What we see is that where differences of at least 10 percent exist a higher incidence of adverse events was observed in the comparator group. We also looked at patients treated for 42 days or longer, where we had 8 daptomycin and 12 comparator patients, and found a similar trend favoring daptomycin. Importantly, there were no elevations of CPK observed with these longer durations of treatment.

[Slide]

I would like to now summarize the findings of safety at 6 mg/kg in this study. Daptomycin was well tolerated at a dose of 6 mg/kg administered once daily in patients with S. aureus bacteremia and endocarditis. Skeletal muscle effects were uncommon, reversible and can be monitored using CPK. Comparator agents were associated with clinically and statistically significantly more

renal toxicity than was daptomycin. Importantly, no new safety issues were identified with the dose of 6 mg/kg once daily for treatment courses up to 4-6 weeks.

I would like to now turn the podium over to Dr. Ralph Corey who will discuss the overall conclusions with the study. Thank you very much.

Overview of Benefits/Risks

DR. COREY: Good morning.

[Slide]

My name is Ralph Corey and I am a professor of medicine at Duke University Medical Center.

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I really appreciate the opportunity to talk to you today about two serious infections, S. aureus bacteremia and S. aureus endocarditis and about a very interesting trial concerning their treatment with daptomycin. There are several reasons why I was asked to talk today. First of all, I have spent 20 years of my life, two decades, studying my nemesis S. aureus and S. aureus

bacteremia and endocarditis. Second, as chair of the adjudication committee I personally reviewed all 236 patients enrolled in this study and, therefore, feel that I have a unique position to comment on the results. But, most importantly, as a practicing infectious disease specialist, I encounter serious, often life-threatening S. aureus infections every day and truly understand the importance of a new effective anti-staphylococcal antibiotic.

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In June, 2004 the Infectious Disease Society of American began a campaign entitled "Bad Bug--No Drugs" to educate the public about the seriousness of resistant organisms and the lack of antibiotics in the pipeline. S. aureus was the number one villain in this rogues' gallery of bad bugs. Why? S. aureus is unique.

[Slide]

As you can see here, S. aureus can enter the bloodstream through any crack and, once into the blood stream, starts creating toxins, as you

can see on the right, here. This would cause septic shock. More importantly, however, staph. contains attachment proteins on the surface, as you can see all throughout here. These attachment proteins are extremely important since they allow the organism to attach and invade any tissue--bone, joint, heart valve, brain, spine, whatever. Once invading, it causes destruction.

[Slide]

As a result, patients with S. aureus at Duke hospital have a mortality of 24 percent. All-comer mortality is 24 percent. One in four die. This is a serious infection. Imagine your father coming into the hospital for his elective cholecystectomy, getting a S. aureus infection through the IV site--imagine the consequences! Metastatic infections occur in 1/3 patients; endocarditis occurs in 1/8. No wonder I think of S. aureus as the Darth Vader of gram-positive organisms.

[Slide]

Not only is staph. a unique organism, but

it is also increasing in frequency. Methicillin-resistant S. aureus is increasing in all our hospitals and the community-acquired methicillin-resistant S. aureus is increasing in our communities. Indeed, right now my daughter has a staph. infection on her right cheek. She is two years old. This community-acquired S. aureus can invade the normal host causing serious skin infections, pneumonia, bacteremia and death.

In addition, S. aureus is increasing in complexity. We are putting more and more devices into patients. We are putting pacemakers into them. We are putting artificial hips into them. We are putting all kinds of hardware into them and S. aureus loves to attack hardware and attach to them. As a result, we are seeing more and more device infections and this results in enormous morbidity and mortality for our elderly population. Finally, S. aureus is becoming resistant to all available antibiotics. New options for therapy are badly needed.

[Slide]

Daptomycin is a new option. It is a new antibiotic that has been approved for skin and skin structure infections, especially those caused by S. aureus. Unfortunately, now that it has been approved, 25 percent of its use is off-label for the treatment of S. aureus bacteremia. Why is this? Well, I am not sure but I think it may be due to physician frustration with our present therapy for S. aureus bacteremia and endocarditis.

[Slide]

Staph. now is being tested in patients with S. aureus bacteremia by clinicians in a non-structured setting. We needed a structured bacteremia trial but there are difficulties in designing one.

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First, there is not an overall indication for S. aureus bacteremia and endocarditis available. The FDA guidance focuses on catheter-related bloodstream infections and includes all these wimpy organisms--Strep. viridans, coagulase-negative staph--nobody cares.

It also includes the mean player, S. aureus, which everyone cares about because of its 24 percent mortality. We also know how difficult these trials in catheter-related bloodstream infections are to complete. Vicuron screened 2,639 patients to enroll 75 patients, only 23 of whom had S. aureus. The trial was never completed. In fact, no antibiotic, as Dr. Soreth showed, has been approved for catheter-related bloodstream infection since this guidance was issued.

[Slide]

Focus on catheter-related bloodstream infection ignores several important facts. First, the most important I think is that S. aureus is a unique organism. It is not the same; you cannot lump it together with these wimpy organisms like Strep. viridans.

Second, focus on catheter-related bloodstream infection ignores the fact that we don't know what infection we are dealing with upon first seeing the patient. Staph. is sneaky. It can be just in the bloodstream; we have no other

indication and four days later we get a follow-up blood culture, which we have learned is the most important predictor of badness, and it is positive. We know we are in trouble and we have no idea where that bug is hiding. The poor clinician trying to enroll a patient or trying to treat a patient, either one, needs time to identify the extent of the infection.

The focus on catheter-related bloodstream infection also ignores that the origin of infection does not predict the outcome. It does not predict the metastatic potential of this organism. Okay? We have well shown that with Dr. Fowler's data from Duke.

Finally, the focus on catheter-related bloodstream infection ignores the fact that 40 percent--40 percent of 559 patients in the international collaboration on endocarditis group developed their endocarditis in the healthcare setting. The IV drug user is no longer the poster child for S. aureus endocarditis. We, the medical community are partially responsible for the

problem.

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Similar to catheter-related bloodstream infection, trials in endocarditis are very difficult. There has been no randomized trial in endocarditis completed in the last 20 years. The last trial was Korzeniowski's study, published in 1982 and it included only established therapies, nafcillin versus nafcillin plus gentamicin.

Dr. Soreth has very carefully reviewed all the drugs that are approved for endocarditis. Let's just take one, imipenem. I have never used imipenem for endocarditis. I don't know, maybe somebody in the room has but I haven't had the opportunity. It was approved for endocarditis based on a retrospective review of 11 patients, 6 of whom had S. aureus.

Now, I did some calculations just looking at the 1992 guidance where we need 50 patients, all-comer endocarditis patients, for approval under this guidance or some semblance thereof. Now, if 40 percent of endocarditis all-comer patients have

S. aureus then what we need are 20 S. aureus patients. Is that right? And, if we factor in native valve and then we look at just right-sided patients we need 5 patients with S. aureus right-sided endocarditis for approval under the 1992 guidance--interesting data!

[Slide]

As you can imagine, there are many challenges to undertaking a trial in staph. bacteremia and endocarditis. First is the design. Because of the disagreement between the importance and practicality of differentiating primary from secondary infection design becomes a nightmare.

Enrollment--enrollment in a trial like this is very difficult, especially for a new antibiotic untested in bloodstream infections. Retention of patients in an open-label trial with a long follow-up of an often difficult population can be a real problem and lead to lower than expected success rates. Inter-observer variability in the reading of echocardiograms and in the adjudication process, in outcome determination, make these

important points that we must address when we design such a study.

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Finally, these trials require vigilant, experienced clinicians such as Don Levine or Chip Chambers. For instance, is the patient's back pain due to the hospital bed or is it due to vertebral osteomyelitis? Ninety-nine percent of the time it is due to the hospital bed; one percent of the time it is due to new vertebral osteomyelitis.

It also requires experienced teams of physicians--cardiologists, cardiovascular surgeons, along with infections disease specialists--to make the tough decisions about valve surgery--when it should be done; if it should be done.

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Given all these difficulties, I think it is impressive that anyone would undertake a trial in S. aureus bacteremia and endocarditis. I wouldn't. Fortunately, the FDA provided significant encouragement, support and guidance throughout the process of this trial.

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Let's take a minute to look at some of the results that Dr. Boucher presented. Here I would simply like you to look at the number of patients with endocarditis. There were nearly 25 percent of patients with endocarditis in this study, and I would have expected from our data that only 12 percent of the patients would have had endocarditis. This is obviously an enriched population.

[Slide]

Success at the end or therapy and test of cure is shown here. Look at the remarkable similarities of the two groups. This is the ITT population, the gold standard.

[Slide]

Finally, I like to look at the MRSA subgroups since that has been my main focus of attention for the last several years, and 44 percent of the patients with MRSA treated with daptomycin were cured as opposed to 33 percent in the comparator group. This is not statistically

significant but this is an attention-grabbing difference in trend.

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Finally, the adjudication committee adjudicated not only success and failure but, as you have heard before, reasons for failure. Overall failure was similar in the two groups but the reasons for failure were different. Persisting or relapsing S. aureus infection occurred more frequently in the daptomycin group while discontinuation due to an adverse event occurred more frequently in the comparator group. Six of the 9 patients in the daptomycin--19 patients in the daptomycin group who failed due to persistent or relapsing S. aureus infection developed decreased susceptibility to daptomycin. One patient in the vancomycin group who failed due to persistent or relapsing S. aureus infection failed due to decreased susceptibility to vancomycin.

I think the most important point is one that has been made several times previously. The vast majority of these patients who failed due to

persistent or relapsing S. aureus infections had sequestered foci of infection that were not attended to. They had pus that wasn't drained and antibiotics cannot solve that problem.

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What are the strengths of this trial? First, it was well designed by some of the best experts in the world--I wasn't part of that--in conjunction with the FDA. These experts wisely ignored the source of bacteremia inclusion criteria. They understood that S. aureus is unique. They understood that they didn't care where it came from. The clinicians don't care where it comes from. If your ankle is infected and your bloodstream is infected nobody cares which one came first. You have to treat both and you have to look for other sites of infection. It is as simple as that.

[Slide]

What are the other strengths of this trial? Well, the experts realized that real-world enrollment was very important and that we needed to

enroll a wide variety of patients to make the study practical and make the results generalizable. New antibiotics must take on all-comers. These experts also realized that the standard of care in the United States for S. aureus bacteremia is combination therapy. It just is. Whether it is right or not, it just is. Including gentamicin in the comparator group set the bar as high as possible for daptomycin. These experts also realized that there is immense variability in the reading of echocardiograms from site to site. As a result, the establishment of a core echocardiogram lab was essential. Finally, these experts realized that only with a blinded, independent external adjudication committee could the results be believed.

Let me talk a little bit about that committee. The important word here is the first word, "blinded," a status we rigorously maintained throughout the process and only in this way could we maintain the integrity of the results of this trial. We were blinded to therapeutic groups.

The second important word here is "independent." The only input Cubist had was to provide us with the data. "External" and "consensus" are two other very important words. We had five external adjudicators, Dr. A. W. Karchmer, here, from Harvard, Dr. Eli Abrutyn from Drexel, Dr. Sara Cosgrove from Johns Hopkins, Dr. Vance Fowler from Duke and myself.

We formed two teams plus a chairman to adjudicate the patients. If a team agreed upon patients and I agreed with them we were done. If a team did not agree upon the patients or I did not agree with them, then the other team adjudicated the patient as well, and we discussed the patient as a group. All five members must agree on the final result before we were completed. In addition, we adjudicated all 236 patients with pre-specified criteria.

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What did we find? We found that daptomycin at 6 mg/kg daily is safe and effective in the treatment of S. aureus bacteremia and

endocarditis. We also found that daptomycin is statistically non-inferior to comparator therapies and numerically better for patients infected with methicillin-resistant S. aureus.

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Other important findings--as we clinicians know, persistent S. aureus bacteremia means there is an inadequately attended to focus of infection. We also found that if you have an inadequately attended to focus of infection you had a chance of having decreased susceptibility to either daptomycin or vancomycin. What does this mean to us, clinicians? Well, I think it means that we must remember that staph. is not only a vicious bug but it is also sneaky. Find it and drain it. At the same time, recheck your susceptibilities.

[Slide]

My conclusions and summary, let me tell you those. First of all, S. aureus infections are serious and an increasing problem worldwide for patients and physicians. We, clinicians, urgently need a new option in our fight against S. aureus

bacteremia and endocarditis and we need it now. Daptomycin provides us with such an option. Thank you.

Committee Questions for the Sponsor

DR. LEGGETT: Thank you. I think we will open up here for a few questions from the committee. Jan?

DR. PATTERSON: I had some questions for Dr. Boucher. Thank you for a very clear presentation. I had a question about the protocol. For the comparator, for the anti-staphylococcal penicillin was the option for continuous infusions, which some feel is advantageous? Was that an option for administration or was it just q. 4?

DR. BOUCHER: Dr. Patterson, it was an option to have continuous infusions and there were some patients who went home with a pump and had continuous infusion of semisynthetic penicillin. As that was part of the trial, that actually facilitated the discharge for some patients.

DR. PATTERSON: Okay. Then can I ask you about those two cases of left-sided endocarditis

that had the increasing MICs? I understand the point that there was a lack of valve replacement surgery in those instances, but what was the indication for the valve replacement surgery? Was it persistent bacteremia or metastatic foci? And, why wasn't the surgery done? Were they intravenous drug users or were there contraindications for surgery?

DR. BOUCHER: I am happy to address that. I think I may even have narratives on those two patients but, just briefly, one of the patients had a stroke at the time their left-sided endocarditis was diagnosed so they were deemed not a candidate for surgery. Do we have a narrative on patient 037?

DR. LEGGETT: Given the time--

DR. BOUCHER: We have it.

DR. LEGGETT: That is okay. I think we will skip the narrative and we can come back to that later. We are already half an hour late. Any more, Jan?

DR. PATTERSON: Actually, I did have one

more, if I may. Then, along the same line as those increasing MICs, I am interested in that because we have seen that phenomenon too. There were three complicated bacteremias, the IV port infection, septic arthritis and retroperitoneal abscess and there were 23 complicated bacteremias that were successfully treated with daptomycin. The definition of complicated bacteremias was that they had metastatic foci. So, did the other 23 receive some kind of adjunctive therapy or did some of them have less complicated metastatic foci? What was the difference between these three and the others do you think?

DR. BOUCHER: That is a very important question that we spent a lot of time analyzing. We went back and looked and found that, indeed, a lot of patients who succeeded did have interventions. I think if we look at the patients with bone and joint infection, as an example, that provides some instruction. So, in the complicated bacteremia group patients most often had high grade bacteremia, that is, positive follow-up cultures,

and a focus of infection.

[Slide]

This is looking at a subgroup of patients, 21 daptomycin and 11 comparator patients, who had bone and joint infections. This included vertebral osteomyelitis and a prostate infection for example. Of those, 11 daptomycin or 50 percent compared to 9 comparator or 80 percent had some intervention on therapy. Despite that, success at the end of therapy was seen in 47.6 percent of daptomycin compared to 27.3 percent of comparator, and then at the test of cure 38 percent for daptomycin and 18 for comparator. So, there were patients who succeeded with and without interventions with daptomycin.

DR. PATTERSON: Thank you.

DR. LEGGETT: My understanding is just having MRSA also made you complicated. Is that correct?

DR. BOUCHER: That is correct.

DR. LEGGETT: So, you wouldn't have had to have left-sided--

DR. BOUCHER: Dr. Leggett, just to clarify, when we looked at the patients we looked at them according to whether they had high grade bacteremia or whether they had a focus. All but 4 in each group had both.

DR. LEGGETT: Steve?

DR. EBERT: Also for Dr. Boucher, the patients who were considered failures because of persisting or relapsing S. aureus or because they had treatment-limiting adverse effects, were they allowed to switch to alternative antibiotic therapies? If so, how did they respond?

DR. BOUCHER: I would be happy to provide you with follow-up data on the patients who failed due to persisting or relapsing S. aureus. Just to clarify, when that occurred patients were discontinued from the study. We followed them for subsequent antibiotics until they completed them.

[Slide]

So, if we look first at the group who had decreased susceptibility to daptomycin, these are the 6 patients that we presented initially. What

we see on the left side of the slide--I apologize, it is a little bit busy--is that at the top are our two left-sided endocarditis patients who did not undergo surgery. Both of them died.

Then if we look at the complicated right-sided endocarditis patient who had the PICC line infection and the PICC was left in for 11 days before being removed, after that was removed they received doxocillin and gentamicin and completed therapy.

Our port infection person ultimately got some debridement, received vancomycin and completed four additional weeks of therapy.

The arthritis patient was diagnosed 20 days following the end of therapy, received vancomycin and cephtriaxone and ultimately completed 66 days of therapy.

Finally, the pancreas transplant patient, who is extremely complicated, was ultimately diagnosed with a retroperitoneal abscess, and they attempted a CT-guided drainage but weren't sure how effective that was. He received linezolid and

vancomycin and finally completed antibiotics 60 days later.

DR. LEGGETT: Alan?

DR. CROSS: I was curious, how comparable were the evaluations both in the echo and microbiology between central labs and local labs? It looked like there was some discrepancy. In terms of the generalizabability of the data, how much difference was there?

DR. BOUCHER: Dr. Cross, I will be happy to answer the first part of the question about the echocardiograms. We have Dr. Cabell here with us and I would like him to address the central versus local echocardiogram question. Then I think Dr. Alder will address the central versus local microbiology question.

DR. CABELL: Thank you. My name is Chris Cabell. I am a cardiologist at Duke, and provided all of the readings of the echocardiograms for this trial. Overall, there were 23 patients that we identified where there were discrepant readings between the centralized reading and the reading

done by the local physicians. In 5 of those 23 readings the echocardiograms at the local sites were identified as being positive and we did not see evidence of endocarditis on the tape sent to us. In 3 of those 5 we just had chest wall echocardiograms, not transesophageal echocardiograms. Each of those patients was an intravenous drug user.

As you probably well know, it is difficult to diagnose endocarditis on a centralized echocardiographic read because you may be limited in terms of what data was sent to you. Echocardiograms are a dynamic study. Many of the things that you view on an echocardiogram you view during the study and that may or may not be reported on a tape that may be sent to a centralized facility, and our sense was that some of those tapes that were sent to us may be around that reason.

In addition, 2 of the 5 had significant valvular abnormalities. So, although we didn't identify vegetation on centralized echocardiograms,

the patients had significant valvular or heart disease that likely put them at risk to have difficulty related to endocarditis.

We did identify several cases in which we were able to see evidence of endocarditis that weren't identified by the sites. Most importantly, sites tended to not record other types of infections or evidence of infection, for instance, perforation, abscess, vegetations on pacemakers or ICDs, vegetations on catheters and even vegetations, say, on the superior vena cava. Each of those things we were able to identify on the centralized echocardiographic evaluation that weren't identified by the site investigators.

So, there was some discrepancy, but it may have been that we were looking much more broadly at evidence of endocarditis that was somewhat different than just reporting presence or absence of vegetation at the site.

DR. LEGGETT: Go ahead.

DR. ALDER: There was a microbiology correlation. Daptomycin was tested only centrally

so there is 100 percent correlation. For vancomycin, however, there was less precise correlation. That is simply a function of the local hospitals using whatever methodology they had, E-test, automated susceptibility, broth dilution. That is why we used a central lab in order to correlate all the isolates in the same time frame, same testing methodologies.

DR. CROSS: While you are up there, Dr. Alder, it looked like there was one comparator that also had increased daptomycin MICs. Was that also the mprF genetic change?

DR. ALDER: That isolate increased daptomycin MIC of 2, while on vancomycin therapy it did not have an mprF mutation.

DR. CROSS: Do you, guys, test that? Are you sure that MIC actually was 2?

DR. ALDER: We test that, yes.

DR. CROSS: I thought so.

DR. LEGGETT: Joan?

DR. HILTON: I had a couple of study design questions for Dr. Boucher. The first is

just to clarify for my sake, are the methicillin-resistant patients all on vancomycin if they are randomized to the comparator treatment?

DR. BOUCHER: They should have been. That was the goal. Everybody was to start--most of our folks started on vancomycin because we didn't know what they had, if they had MRSA or MSSA. It turned out that one patient was misidentified or was missed. They had methicillin-resistant S. aureus and they were on a beta-lactam for 9 days. That is why we presented the pathogen specific therapy data today. That excludes that one patient. That was Everybody who got daptomycin or vancomycin for MRSA.

DR. HILTON: It seems to me there are two trials within one trial because there are two major comparator groups. So, this strong difference in efficacy results for the methicillin-resistant patients versus the methicillin-sensitive patients seems to be associated with which drug was the comparator.

DR. BOUCHER: I think I understand your

question. If we look at the overall results, because there was a comparator including both agents--if we look at the slide from the main presentation by pathogen specific therapy, we did see a higher success rate--we saw a larger--excuse me-- treatment difference in the MRSA patients between daptomycin and vancomycin.

[Slide]

We also saw a similar treatment effect between daptomycin and semisynthetic penicillin, 2.1 percent. So, I think the conclusion is that there is efficacy in S. aureus including methicillin-resistant and methicillin-susceptible S. aureus in the study.

DR. HILTON: But in these two figures the comparators are almost completely associated--

DR. BOUCHER: They are different. That is correct.

DR. HILTON: To me, that is really important. The second study design question I have is you have an assumption of a success rate in the control group and the comparator group of 65

percent. Was that an end of therapy event rate or was that a test of cure event rate?

DR. BOUCHER: Well, that is a very important question. The assumption was based on current studies or available studies, none of which were controlled and most of which were not randomized. In fact, they are based on end of therapy success rates. What we saw is that the end of therapy success rates were comparable. So, I think that is the conclusion there.

DR. LEGGETT: A follow-up to that quickly, if you looked at that group that was re-adjudicated as possible endocarditis that then went back to the bacteremia group, were there equal numbers of those re-adjudications between the beta-lactam and the vancomycin group? In other words, could it have been that the beta-lactams were actually much, much better and the vancomycin ones much, much worse so it evened out? That is sort of a follow-up of her question.

DR. BOUCHER: When we looked at the difference between entry diagnosis and final

diagnosis we did see that many of the possible endocarditis patients at entry ended up having complicated bacteremia. They were evenly distributed between vancomycin and semisynthetic penicillin.

DR. LEGGETT: John?

DR. BRADLEY: A related question on the study design, knowing that you had 44 sites and 4 countries, when you first enroll someone in one of these studies you start them on either comparator or the daptomycin and then you find out that they have staph., and then you get the susceptibilities and, clearly, once they are identified the comparators get vancomycin. My question is in that first day or two after you sign them up and you have your blood cultures, before you have your susceptibilities, did any of the sites who placed patients in the comparator arm start MRSA patients on penicillin rather than vancomycin so that during one or two days before they actually got appropriate comparator therapy they had a couple of days of MRSA to sort of take hold?

DR. BOUCHER: That is a very important question. Our patients were all treated according to their local site standards.

DR. BRADLEY: Right.

DR. BOUCHER: We went back and looked and we found that only one patient was inappropriately treated with semisynthetic penicillin. Everybody else was on vancomycin for about two days before their first dose of study drug.

DR. LEGGETT: Dr. Borer?

DR. BORER: Thank you. I have a few questions I think primarily for you, Dr. Boucher, but you may want to triage them. First of all, just to clarify for myself, the diagnosis of endocarditis at entry could have been definite or possible. At conclusion it could only be definite. So, it doesn't sound as if anything happened by using a more rigorous definition at the conclusion of the study. If that is so, is it possible--and I am asking because I just don't know--is it possible that some of the people who at the conclusion of the study were listed as having bacteremia,

complicated bacteremia, whatever, actually had endocarditis that was cured by study drug so that there was no additional evidence and, therefore, they couldn't be considered to have definite endocarditis at conclusion of study? Is that correct?

DR. BOUCHER: Let me try to address that. I think I can clarify a couple of points here. At study entry the diagnosis was made based on modified Duke criteria and included the initial transesophageal echocardiogram. So, that data was used to make that initial diagnosis. What happened between the beginning and the end is that we found 7 percent more patients with endocarditis. If I could have the slide up, please?

[Slide]

So, in this table the first row is the entry diagnosis as defined by the modified Duke and on the bottom is the final diagnosis. What we see is if we look at the first column is that we found 6 additional patients with left-sided endocarditis, here, and 10 additional with right-sided

endocarditis. These were found based on follow-up echocardiograms, people who came back with a relapse and were found to have a myocardial abscess for example. So, there were two separate time points used for these diagnoses and two separate sets of information. The entry diagnosis is all we had in the first 5 days. The final was made retrospectively by the adjudication committee with everything, all the follow-up data.

DR. BORER: Right but, again, something else happened between the beginning and the end. The people were treated. It seems to me not unreasonable that some patients who came in with possible endocarditis might have had endocarditis and might have been successfully treated and, as a result, had no additional evidence and, therefore, at the conclusion with all the data available could not have been given a diagnosis of endocarditis by the committee.

DR. BOUCHER: I think that is a very fair statement and this was our best attempt to stratify--

DR. BORER: Yes, I don't blame you; I just want to clarify for myself. Second--and, again, there is no value judgment here--I would like to understand a little bit better how the delta of 20 percent was selected. I can well accept the idea that if these people had been treated with nothing almost all of them would have been dead so I am not so concerned about the lack of a putative placebo, but how was 20 percent selected as the delta?

DR. BOUCHER: There were a number of factors that contributed to the selection and the decision to pursue a non-inferiority margin of minus 20 or 20 percent in this study at the time the study was designed between the designers and FDA. They included certainly the notion that this is a disease with a very low to negligible placebo rate. It also included an understanding that the overall efficacy of the study was going to be driven by the totality of the efficacy data, so not just the primary statistical analysis but all the supportive analyses--the weighted analysis, the pre-specified analyses by the diagnostic subgroups,

the pre-specified diagnoses according to time of diagnosis according to both evaluators, the investigator and the adjudication committee. The final thing that I think was part of that decision had to do with an understanding, again, that the success of the study would include a risk/benefit assessment so that, for instance, this finding of a safety problem in the comparator group that was not expected that may preclude some patients from receiving comparator might enter into the overall assessment of the study results.

DR. BORER: Okay. Two other, one quickie. You showed slide C-51 and then C-52 and C-52 shows that the daptomycin was substantially more successful than the comparator for MRSA and approximately the same for MSSA, whereas the overall success was pretty much similar between the two--pretty much--but the numbers don't seem to add up. Maybe I missed it somewhere. I don't know how we have 48 successes with the comparator in ITT and now we are down to 42 in this slide for the comparator. What happened to the other 6?

DR. BOUCHER: I will be happy to address that question. This comes back to the methicillin-resistant versus methicillin-susceptible S. aureus and the actual drug received for therapy. If we could have the slide up, please?

[Slide]

On the left here, and this is this slide we showed in the main presentation which looks at patients with MRSA who just got vancomycin and patients with MSSA who just got semisynthetic penicillin. It turned out that one MRSA patient inappropriately got beta-lactam and 10 comparator patients received vancomycin therapy. Six out of those 10 succeeded. Most of them were allergic to beta-lactams. So, that accounts for the difference in numbers and the success rates in the two pathogens are shown according to whichever comparator received on the right side of the slide.

DR. BORER: Okay. And one final question, I found your sensitivity analysis to be very illuminating and very helpful, and I am glad you

showed it but I didn't totally understand it and I would like you to go over the methodology once more and also tell me one other thing, did you do an analysis of the study completers irrespective of whether at the completion of their therapy they had all the blood cultures done, or whatever? Did you do a long-term analysis of the study completers? I saw the death analysis. That is comforting. But even if they didn't have a blood culture drawn at the end of therapy, if six months later the patients were walking and talking I would be pretty happy. So, I am wondering if you did an analysis of the study completers, and I would like to know how you did that sensitivity analysis.

DR. BOUCHER: I am happy to address both issues. First lets start with the sensitivity analysis.

[Slide]

That is shown here as in our main presentation. The idea here was to look at the contribution of each reason for success to the overall observed success rate in the study. So, we

started with the three things we thought were clinically the most important, namely, persisting or relapsing S. aureus, death and clinical failure.

I will just direct your attention. When those three reasons for failure were imposed we saw success rates of 70 percent for daptomycin, 68.7 percent for comparator. We then went on to add treatment-limiting adverse events, the potentially effective non-study antibiotics, no blood culture and those last few discontinuations to march back down to the primary efficacy endpoint.

DR. BORER: Okay, so you made no assumptions about what would have happened to the people who were eliminated at each of these steps. You just eliminated them.

DR. BOUCHER: Exactly. If we turn our attention to the completers, we looked at success among patients who completed therapy, both according to the adjudication committee and the investigator. If we could have the slide up?

[Slide]

This is looking at success in patients who

completed therapy, at the end of therapy on the left and test of cure on the right. This is the adjudication committee assessed success. What we see is that at the end of therapy 87.5 percent of daptomycin and 89.6 percent of comparator patients were assessed as a success. At test of cure it was 62.5 and 61 percent.

[Slide]

Then if we move on, according to the investigator's assessment of completing therapy, success at the end of therapy was 96.2 percent for daptomycin and 96.1 percent for comparator.

DR. BORER: That is very helpful. The only reason I am asking these questions is that there were a number of unevaluable patients and the unevaluable subset was unbalanced and, you know, who knows what happened to them but all these analyses are very helpful, convincing me that that is not an important factor. Thank you.

DR. LEGGETT: Dean?

DR. FOLLMANN: Yes, I have a few questions I guess related to study design. First of all, I

understand this is an unblinded study so the treating physician knew what therapy the patient was on. Then, a part of the endpoint for failure is treatment-limiting toxicities. Was that decided by the treating physician who was unblinded or was that decided by the blinded adjudication committee?

DR. BOUCHER: It was both. The investigator decided to discontinue the patient because he or she thought therapy had a treatment-limiting adverse event, like developing a rash for example. The adjudication committee decided whether that was a reason for failure or one of the reasons for failure.

DR. FOLLMANN: A second question I guess builds on what Dr. Borer commented on, the final diagnosis group. That is not really a subgroup that is defined using baseline measured variables. It depends on what happens to the patient during the course of follow-up. So, to my mind, it is not very helpful to present data broken down by the final diagnosis group. For one reason, these groups are no longer assured to be equivalent by

randomization and, for a second reason, I guess a treating physician has to make a decision based on what is available at baseline, not what might be available later. So, I tend to discount these analyses done by the final diagnosis subgroups.

But my question now has to do with the entry diagnosis subgroup. Was this based on just pre-randomization baseline data? I am thinking this was also based on post-randomization data because you use a transesophageal echocardiogram. Is that right?

DR. BOUCHER: It is correct that the entry diagnosis was based on the available information in the first few days of the study. We knew what pathogen they had and how they were clinically. The echocardiograms were done sometimes right before they entered, sometimes in the first few days after the patients entered.

DR. FOLLMANN: Another question, this intent-to-treat analysis really excludes 11 patients who were randomized but didn't get study drug. I was wondering what happened to them, and

did you run analyses which included these 11 which, to my mind, would be the proper intent-to-treat cohort?

DR. BOUCHER: I hear two parts to your question so I will answer the first part first. Those 10 patients who weren't treated, many of them were transferred for surgery or had other sort of operational type issues, and a few did die.

To answer the second part of your question, we went back and did conduct an analysis of all randomized patients. If I could have the slide up, please?

[Slide]

This is looking at all randomized patients. That would be 124 daptomycin and 122 comparator patients. Success was seen at the end of therapy in 59.7 for daptomycin and 58.2 for comparator; 42.7 at the test of cure for daptomycin and 39.3 for the comparator. Thank you.

DR. FOLLMANN: I had two other questions. One has to do with the analysis of the safety database. You mentioned there were 150,000

patients in your expanded safety database and there were "no new toxicities." I was wondering if there was a signal in terms of rhabdomyolysis in that extended safety cohort. Did you have any cases of rhabdomyolysis in that group?

DR. BOUCHER: I will address your question regarding post-marketing cases of rhabdo. We have had in post-marketing reports of CPK elevations and in certain cases there reporter has also reported rhabdomyolysis. There are inconsistencies in clinical definition of rhabdomyolysis, with true rhabodmyolysis having marked CPK elevations, renal failure, myoglobin in the urine. Could I have the slide up, please?

[Slide]

We had a total of 61 reports in post-marketing of CPK elevations and an additional 14 reports in which CPK elevation was reported as well as the term rhabdomyolysis was used. In order to evaluate these cases we came up with a definition based on the literature of what rhabdomyolysis would be, and evaluated each of

these cases against that.

[Slide]

So, our definition in evaluating these post-marketing cases was that there needed to be a marked elevation of CPK, typically greater than 10 times the upper limit of normal--this is based on guidance for statin evaluation--and that a creatinine elevation should be evident within two weeks of the onset of symptoms. Here it was defined by a 0.5 mg/dl increase if the creatinine was less than 3, and 1 mg/dl increase if the creatinine was greater than 3. Then we also attempted to collect information on whether or not the patient had elevated serum or urine myoglobin or brown urine.

[Slide]

Based on this, we found that of those 14 cases there were 5 that met the definition of rhabdo., with some of the cases having marked elevations, in the 20,000 range, associated with some elevation. At least one patient was on statins. Based on this, we have added the specific

term "rhabdomyolysis" to our product labeling.

DR. FOLLMANN: Did you have any data using other clinical trials where we could compare the two groups for this?

DR. BOUCHER: In terms of CPK?

DR. FOLLMANN: CPK and rhabdomyolysis. This is, you know, uncontrolled data and it is hard to interpret the rates.

DR. VIGLIANI: Could I have slide 199, please?

[Slide]

When we look at the complicated skin/skin structure infection studies, we had two Phase III studies at 4 mg/kg, what we found there was patients with elevated CPK adverse events, 2.8 percent in the daptomycin group and 1.8 in the comparator, and less than 1 percent discontinuation rate, in the S. aureus bacteremia and endocarditis trial the data presented have demonstrated a higher rate of adverse events of CPK elevations, 6.7 percent in the daptomycin group and a slightly higher rate of discontinuations, 3 patients

discontinuing.

When we look at the other studies--I mentioned we have additional studies looking at patients treated at the equivalent of 6 mg/kg, we saw a similar rate of adverse events to what we saw in the S. aureus because study with 5 percent having adverse events of CPK elevation and about 2 percent of patients discontinuing due to CPK events.

DR. BRADLEY: One last, very quick question. On slide C-60, back to Dr. Boucher, the time to clearance of S. aureus bacteremia, although the median between dapto. and the comparator was very small, 5 versus 4 days, actually the revealing aspect is that MRSA was 8 days with dapto. and 9 with the comparator, suggesting that MRSA not only is more resistant but it may have other virulence factors, as alluded to in the first presentation. Actually, community-associated MRSA may be a completely different organism in terms of how we look at cure compared to something like Strep. pneumo. where there is resistance but not increased

virulence. Can you comment on the large differences between days to clearance of the MRSA and the MSSA?

DR. BOUCHER: That is a very interesting question, Dr. Bradley. You know, when we looked at these data and we found it particularly impressive that we saw this difference given that the comparator patients got 4 additional days of gentamicin. I think we might ask Dr. Chambers if he might like to comment as an expert on sort of the larger picture here.

DR. LEGGETT: Chip, that was going to be my question too. The other one is how many of these folks were community acquired versus hospital acquired and, you know, what is going on in terms of that?

DR. CHAMBERS: Yes, you put your finger on a very key issue in terms of microbiologic response. Let me say first that I am not certain that it is entirely due to virulence accounting for it, although it well may. I think it probably reflects more what one may see--and it might partly

explain why vancomycin compared to beta-lactams is inefficacious relatively speaking, as I alluded to. In microbiology and treatment of infectious diseases even if you have organisms that look susceptible to the same drug, organisms that tend to fail and are resistant generally have a higher failure rate associated with them and a resistance that you probably cannot measure.

So, I think that that is what we are starting to unveil now that we have a comparator to vancomycin, that this is a group of organisms that are MRSA but they are drug resistant in terms of their biology, and they are probably resistant to a variety of drugs that, were we able to test them in a model like this model infection system, we would be able to reveal that resistance.

With respect to the community MRSA data, I don't know that vancomycin is any different with respect to inpatient or outpatient, and I am certainly not able to speak to the isolates in the study.

DR. VIGLIANI: I would like to ask Dr.

Alder to address the issue of community MRSA, but I wanted to also clarify one point about the rhabdo. because I didn't fully answer your question. There were no reports of rhabdomyolysis in any of our other clinical trials, in answer to your question. Also, the patient in the S. aureus because and endocarditis trial, although the event was reported as rhabdo., this patient had a normal serum creatinine and no evidence of rhabdomyolysis.

DR. ALDER: Part of the question on community MRSA was potency and efficacy against these types. Within the clinical trial itself and the pre-specified design we have not yet delineated community MRSA versus hospital acquired, although the study itself was certainly designed to enrich for hospital acquired. We do have a number of follow-up studies looking at agr, PVL, etc. We do have two pieces of data, however, that show that daptomycin is equally potent and effective against community MRSA. Slide up, please.

[Slide]

This is a surveillance study of 200

community MRSA S. aureus isolates. What is being shown here is that daptomycin still maintains potency and potency range equal to that of the hospital-acquired MRSA or any other S. aureus, for that matter, with 100 percent of the isolates considered susceptible even under the current susceptibility guidelines.

[Slide]

In addition, when we further delineate by confirmed virulence factors, and the key one is PVL positive as well as agr, daptomycin maintains potency by both MIC-50's MIC-90's and cidality. In addition, from the core presentation that we gave with the serially passaged isolate and the response in animal models, that was community MRSA, mw2 strain.

DR. LEGGETT: By the say folks, I know you are all getting hungry but I figured if we asked the questions now it will make the afternoon go shorter, but we will go on break before the FDA presentation. Alan?

DR. CROSS: I have two fast questions.

The first one is for Dr. Vigliani. I noticed that about 7 percent of the comparators did not receive gentamicin. Although it is probably a very small number, I was just wondering did they have equally adverse effects in terms nephrotoxicity.

DR. VIGLIANI: Thank you. Could I have the slide up, please?

[Slide]

You are right, there were 8 patients who did not receive gentamicin in the comparator arm. We looked specifically at adverse events of renal toxicity in the patients who did receive gentamicin and those who didn't receive gentamicin.

On the right-hand side what you see are the 100 comparator patients who did receive gentamicin, and on the left the comparator patients who did not receive gentamicin. When you look at adverse events of renal impairment, we found that 21 or 19.4 percent of patients on comparator who received gentamicin had a renal impairment adverse event in comparison to none who did not receive gentamicin.

We also, interestingly, looked at success at test of cure because while this was not a comparative study to determine the efficacy of comparator agents with and without gentamicin, we did have 8 patients that we could observe. What we found was that 2 patients who did not receive gentamicin, or 25 percent, had success at test of cure in comparison with 46 or 42.6 percent of patients on comparator who received gentamicin. So, there was a higher efficacy with the combination of gentamicin.

To further answer your question, there was also one patient who received gentamicin who also received daptomycin because, as part of the left-sided endocarditis amendment, gentamicin was allowed for patients also in the daptomycin arm who had left-sided endocarditis. Next slide, please.

[Slide]

It turns out that one patient who received concomitant gentamicin with daptomycin did have a renal impairment adverse event and was also the one success.

DR. LEGGETT: A follow-up to that real quick, the renal impairment pre-study definition was what? I assume it was post hoc nephrology that you showed us with the Kaplan-Meier curve.

DR. VIGLIANI: We looked at patients based on their baseline renal function and divided them into categories of greater than 80, 50-80, 30-50 and less than 30.

[Slide]

If we look at those categories and then look at the shifts in creatinine clearance on study--this is a somewhat complicated table but on the left you have the daptomycin and comparator patients who started at baseline greater than 80, 50-80 or 30-50--remember, patients less than 30 were excluded, just to correct myself--and then comparator patients, and we looked at patients who shifted to a worse category of creatinine clearance. What you see is that 11 daptomycin patients versus 23 comparator patients shifted from a normal, or greater than 80 category of creatinine clearance to a lower category of 50-80. You can

see the corresponding other changes. For patients starting at 50-80, there were 5 daptomycin patients versus 14 who went to 30-50. In addition, of the patients who started in the worst category of creatinine clearance, 30-50, there was one daptomycin patient who went to less than 30 and 7 comparator patients who went to less than 30.

DR. LEGGETT: Alan?

DR. CROSS: So, if I could ask my second question, Dr. Boucher, in the documentation that we received ahead of time there was reference to a Phase II study of daptomycin in bacteremia looking at three different doses of the drug. The study was halted because of slow enrollment. There is no indication of how many patients were there. But there was some statement as to which dosage groups did as well as comparator and which ones didn't. In that paragraph it states that the group that received the 6 mg/kg every 24 hours did not do as well as the comparator--again, assuming that we are dealing with small numbers. What happened between that Phase II study and this study that made you

fix on the 6 mg/kg dose?

DR. BOUCHER: Thanks, Dr. Cross. There are a couple of points to be made about that Phase II study. The groups were very small. There were three different doses tested, and the number of patients with bacteremia was small. The analysis of the failures in that study showed that there were a number of complications, including surgical disease that wasn't adequately addressed.

A number of things added to the dose rationale to proceed with 6 mg/kg both from an efficacy and a safety perspective. The data was that 6 mg once a day was likely to be safe. Dr. Alder will comment on the preclinical data that really supported the 6 mg/kg dose as the appropriate dose for endocarditis.

DR. ALDER: There was a variety of interlocking data that led us to the 6 mg/kg dose: Preclinically the rapid cidality and penetration; efficacy in a number of animal models that simulated 6 mg/kg exposures; and then a variety of pharmacodynamic models, including one that I will

show here, which is an in vitro pharmacodynamic model. Slide up, please.

[Slide]

This is from Mike Rybak's lab. The power of this model is that it simulates human Cmax, AUC and half-life in a biochamber in which a simulated endocardial vegetation is immersed. So, it is about as close as one can get to human endocarditis but using pumps and chambers rather than the body.

The doses that were simulated were 4 mg/kg, 6 mg/kg and 8 mg/kg with corresponding Cmax's of about 58, 95 and 120 8-hour half-lives in each case. What is being shown is the log CFUs recovered from the simulated vegetations on the Y axis. So, we start out at about 106 CFUs per gram of vegetation, and an untreated progresses to about 108 over 4 days. At 4 mg/kg there was a rapid fall-off in CFUs. Again, that is an overall exposure of just over 400 mcg/ml. But then there is some regeneration of S. aureus isolates. To anticipate another question, no, these isolates did not have reduced susceptibility. They still had

the original MIC value of 0.5. At 6 mg/kg and 8 mg/kg there was complete eradication to the limit of detection and there was no additional benefit at an 8 mg/kg dose, for example, compared to a 6 mg/kg dose. At the time that this study was designed in conjunction with the FDA, we had human data up to 8 mg/kg but not beyond. The 6 mg/kg dose was based on efficacy and safety together.

DR. LEGGETT: Go ahead, Alan.

DR. CROSS: Just to follow-up on that slide, the limit of sensitivity of that test was 100 CFUs?

DR. ALDER: 100 CFUs per simulated vegetative--

DR. CROSS: Okay.

DR. BRADLEY: Another quick question about the CPK elevation and safety. Certainly, the rate of CPK elevation doesn't appear too much greater than the background, but for those people who ended up having CPK elevations, as you showed on slide C-102, the elevation seems to be fairly high as though there is some underlying genetic factor or

co-morbidity or predisposition to those who are susceptible to an elevated CPK actually having this side effect. I am certainly used risk/benefit assessment, and this is certainly a severely ill population, and we certainly take more risks in this particular population. If I were to have to use daptomycin for Dr. Corey's two year-old child I would like to be able to explain to him the mechanism of CPK elevation. Do you have any insight into what molecular events are occurring to cause this?

DR. VIGLIANI: On a molecular basis, I may actually ask Dr. Oleson to comment and then I am going to ask Dr. Drusano, who has done some independent work looking at risks, PK/PD risks for CPK elevation, to comment further. Thank you.

DR. OLESON: My name is Dr. Rick Oleson, and I am vice president of non-clinical development at Cubist Pharmaceuticals. While we haven't identified exactly what the putative target is in terms of the skeletal muscle effects, what we do know is that the effects are very specific to that

type of muscle, skeletal muscle. Because of a lot of studies we have done--nd this is a large molecule, as you know, a 13 amino acid cyclic ring molecule as Dave Matthews showed initially, it does not appear to penetrate inside mammalian cells. So, its effect, we think, is related to an interaction with the cellular membrane and it is specific to skeletal muscle since we see no effect in any other type of muscle such as cardiac or smooth muscle, particularly in terms of histology. There are a number of animal studies up to six months in duration.

There is a basis for why we think this, as data shows across animal studies as well as humans in terms of CPK increases and what we consider the mild rhabdomyolysis in that the rhabdomyolysis is reversible very readily once a patient is taken off therapy. That is because this interaction with the membrane is likely to be mediated through a repair process which has now been identified to be important in muscular dystrophy patients, which is called the membrane patch repair process. It is

highly effective and highly able to cause that interaction to be reversed and repaired.

DR. DRUSAON: Hi. Dr. Bradley, we did some looking in a pharmacodynamic sense at the concentrations of daptomycin. Because of some previous work by Dr. Oleson and Dr. Talley that looked at scheduled administration, they could show quite clearly that once daily administration caused less damage than twice a day administration of the same total daily dose, indicating that it was likely that trough concentrations or time above a certain level would be the thing that would be driving this particular type of adverse event. Could I have my slides, please? There are only two.

[Slide]

The first thing that we did was to take a look at the actual observed trough concentration data. We looked with a recursive partitioning algorithm and identified a trough concentration of less than 25.7 or greater than or equal to 25.7 as putting patients into different risk categories.

We looked at it continuously in a logistic regression. We looked at it categorically in a logistic regression. We looked at it continuously in a Cox model and this one picture is in a stratified Kaplan-Meier, and what one can see is that once one is above 25.7 or equal to that there is a much different risk of having a CPK elevation and the time to CPK elevation is much shorter in this circumstance.

To then put it into further perspective in terms of dose since that did come up as a previous question, what we did is we took all of the available daptomycin concentration time data from the trial. We performed a population pharmacokinetic analysis using a non-parametric adaptive grid type approach. We then took the mean parameter of that covariance matrix and we did a number of different Monte Carlo simulations. If you could put the next slide up, please?

[Slide]

So, we looked at 4, 6, 8, 10 and 12 mg/kg. In the middle column, where it says Cmin, what you

see is that this is the rate at which drug concentrations would be predicted to hit or exceed 25.7, and you can see that at 4 it is about 3.7 percent; 7.3 percent at 6; up to 16 at 8; almost 25 at 10; and almost 33 percent at 12. We then had the probability of a CPK elevation so we corrected the number of patients that would get a Cmin exceeding or equal to 25.7 into a probability and so it was 6 percent at the 6 mg/kg dose, which correlated nicely with the observed findings. At 8 it goes to 9 percent; at 10 it goes to almost 13 percent; and at 12 it goes to 16 percent.

And, 4 mg/kg was simulated to provide some kind of external validation. What we see is a probability of 3.7 percent at 4. When you look at the published complicated skin and skin structure study from CID, what one sees in this circumstance is that overall 2.8 percent of patients actually wound up having CPK elevations, lining up reasonably well with the predicted 3.7. We actually can predict the amount really due to CPK as being about 1.4 percent at a dose of 4 and that,

again correlates quite nicely with the 2.1 percent daptomycin treatment emergent drug-related CPK events in the skin and skin structure study. So, this provides at least a little guidance as to what kind of safety burden one takes on as the doses go from 6 to 12.

DR. BRADLEY: Thank you very much.

DR. LEGGETT: Dean?

DR. FOLLMANN: Dr. Alder presented a slide, C-80, which looked at the wild-type distribution of staph. isolates and he concluded that there was a very low percentage, 0.06 percent, that had MIC greater than 2. Later on you talked about how the reagents were varying at some point in time and this caused a dip in your trend plot. I was wondering if thought had been given to whether those 17 could really be just false positives. Was there replicate testing done of these isolates, or were they genetically sequenced, or was something else done, or could these be false positives?

[Slide]

DR. ALDER: In total I think your question relates to the reliability of the data, especially around the MIC 2's. I will specify that the bottom half of this table, global surveillance studies, especially from 2002 through 2005, are extremely high quality, high numbers in which the MIC 2's are retested and reconfirmed.

Now, the testing media issue that I talked about occurred for about 18 months, encompassing the back half of 2003, all of 2004 and media lots in the front half of 2005. However, for those folks who run clinical micro. labs, you know those lots of media will hang around much longer than just the release date. Media with 40 percent decrease in calcium was apparently enough to trigger a shift within the middle of the distribution curve and not a distinct pattern but a pattern in which the 0.5's and the 0.25's--there is a corresponding decrease in the 0.25's and an increase in the 0.5's. This is the same data cut for MRSA from the surveillance. So, there was low calcium from the back half of '03 through the front

half of '05 and that registered most prominently here, in the middle of the distribution curve. The testing was still within QC but on the very high end of the QC. That is what led Dr. Jones to re-investigate. The MIC 2's down here, the green diamonds, are prosecuted vigorously. Any time an isolate registers a 2 it is retested in defined calcium media. So, we have high confidence in the proportion of MIC 2's.

DR. LEGGETT: Steve?

DR. EBERT: A follow-up question for Dr. Alder, you mentioned that there were some mutations that occur that result in elevated daptomycin MICs. Do you have mutational frequency on some of those?

DR. ALDER: Yes, I have to clarify that what we have at this point are mutations that are associated with MIC increases. We do not have cause and effect. For example, with the mprF mutation we do not know if that results in any up-regulation or not at this point although we are prosecuting that.

What we do know from in vitro selection

studies is that the single pass resistance incidence is extremely low for daptomycin and, basically, at 4 times the MIC to less than the limit of detection, 108, 109, 1010, basically to the limit of the number of bacteria that can be assayed.

DR. EBERT: The reason I ask is that for the AUC MICs that you looked at, the target value was aimed at a 3-log reduction in CFUs, if I remember correctly. I am wondering if the presence of some of those resistant subpopulations is lower than that and whether that would be a sensitive enough measure. You are looking at it from a different outcome measure as opposed to emergence of resistance.

DR. ALDER: Could you clarify your question? I am not following you.

DR. EBERT: Well, your data with the AUC MIC of 540--

DR. ALDER: I think you were saying it wasn't sensitive enough?

DR. EBERT: Right. It was looking at a

3-log reduction, 99.9 percent kill. If, on the other hand, your subpopulation of potentially resistant organisms is maybe 1 in 106 there still may be a potential for emergence of resistance that would not be detected by animal studies that use a much lower inoculum.

[Slide]

DR. ALDER: This is the data shown in the core presentation. The point here is this is the mw2 serially passaged strain. So, this is genetically consistent from the MIC 1 through 16, and by whole genome scanning there are two or three changes in this population, mprF mutations at low level MICs; two, yycG that begin at 4 and above; and then what I didn't talk about but at very high MICs there can be rpoB in conjunction with rpoC mutations. That has happened only in the lab. In fact, those isolates with the double mutation become crippled for growth and virulence, which may represent a biologic gap on MIC increases.

So here, with the MIC 1's and 2's, they were treatable at AUCs less than 300. We chose a

3-log reduction as a more stringent criterion. Most often one will see static response or in some cases 80 percent of Emax, which varies over the board here. We wanted very stringent criteria. But we have seen a very unique pattern at the higher MICs where linearly more drug is needed. MIC 2, 1 and in fact lower than 1 from the clinical data are all treated at about the same AUC. Now, as far as selection rate, within these populations that is an unknowable.

DR. EBERT: The other question, hopefully, will be a little easier. There is a lot of concern, of course, about using drugs like vancomycin and the fact that there may be some down-regulation of autolytic capacity which may lead to tolerance. So, my question really is directed towards not the static effects of these agents but their bactericidal nature. Did you track either with daptomycin or vancomycin, either with the strains that had the elevated MICs or other isolates whether there was a diminished cidal capacity for either drug?

DR. ALDER: We did do bactericidal activity assays on the isolates from these 7 patients, both baseline and then post baseline. Slide up, please.

[Slide]

This is the same format as the mouse thigh experiment, except here this is purely in vitro at 8 mcg/ml. Why 8? Because that is approximately the trough level in most patients, although in these 7 patients they tended to have higher AUCs and troughs than the norm. The rule is that one must achieve greater than 3-log reduction within 24 hours to get classified as bactericidal. Daptomycin did achieve bactericidal activity, not in the 24 hours but in the 4-hour time frame. So, daptomycin maintained rapid cidality against these isolates, both baseline and post baseline, more than 3-log reduction.

For vancomycin we haven't followed up for those MIC 2 isolates, but vancomycin in a typical cidality curve will perhaps just cross 3-log reduction at 24 hours at 4- or 8-fold the MIC.

DR. EBERT: Thanks.

DR. LEGGETT: Thank you. I would like to thank all the presenters this morning. Let's go to lunch and try to make it back by 1:15. Thank you.

[Whereupon, at 12:25 p.m., the proceedings were recessed for lunch, to reconvene at 1:15 p.m.]

A F T E R N O O N P R O C E E D I N G S

DR. LEGGETT: As sort of the way I would like to handle this afternoon for those members of the committee that have to leave early, the voting members, I am going to turn the discussion a lot around--there are obviously other things to discuss, but a lot around the questions that we are going to be asked at the end which we are going to have to vote on. So, when people have things to discuss, the ones who need to leave early, you can sort of front-load what you have to say so that you can mark down your votes or pass them to Cathy if you need to go. But I am hoping that we can end on time today.

In view of that, I would like to read the open public hearing script. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes that it is important to understand the context of an

individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Is there anyone interested in presenting at this public session? If not, why don't we proceed with the FDA presentations?

Food and Drug Administration Presentation

Efficacy Results

DR. SORBELLO: Good afternoon.

[Slide]

I am Fred Sorbello. I am a medical officer working at the FDA in the Division of Anti-Infective Ophthalmology Products. I am going to present some of the findings and observations of the FDA review team in terms of the efficacy data for this supplement.

[Slide]

In terms of overview, my comments will be related to the all-comers population, the endocarditis experience and some comments on mortality data.

[Slide]

So, I would like to first begin with some comments on the all-comers population. In terms of the all-comers, there are several issues to note.

[Slide]

It is important to keep in mind that the target population is really pathogen driven and that patients were enrolled in the study having at least one positive blood culture for S. aureus. This was really irrespective at enrollment whether

they had endocarditis or other underlying clinical entities. The statistical approach to the study was powered solely for the all-comers population and was not powered with respect to the final diagnosis, clinical subgroups or the endocarditis experience.

In terms of risk factors and baseline disease characteristics that were identified, there were two that were considered important, very important in terms of the FDA review team. One was the high frequency of infections in both treatment groups within 30 days of enrollment which was approximately 74 percent. The second was the high frequency of surgery in both treatment groups within 30 days of enrollment which across both groups averaged about 36 percent.

The reason that the review team had concerns about these two risk factors is that they seemed to provide evidence of an underlying heterogeneity in this all-comers population in terms of potential inciting infections for staphylococcal bacteremia, potential portals of

entry for staph. to gain access to the bloodstream, and the potential role of some of the surgical infections or surgical procedures to really serve as forms of adjunctive treatment which could have implications in terms of prognosis for patients and the all-comers, and certainly as you get into the clinical subgroups.

[Slide]

Some comments in terms of the final diagnosis assessments, as we heard earlier today, these were determined by the IEAC in a blinded and retrospective fashion but, again, it is important just to note that the IEAC did have access to results of central echocardiography and these results were not available to the investigators who were prospectively managing the patients. Also, there was no requirement for systematic assessment of all patients for evidence of metastatic foci of infection. The investigators were certainly trained to look for metastatic foci and be vigilant for them but there was no requirement to do any type of diagnostic imaging scans. The decision was

really made on an individual basis by the investigator, and the extent of that type of evaluation was also at the discretion of the individual investigator.

[Slide]

I wanted to make some comments next about the approach to characterization of the all-comers population. As was discussed earlier this morning and as was shown in the pie diagram of the slide, the all-comers population was assessed in the sense that each patient's likelihood of endocarditis was assessed using modified Duke criteria. In this manner, the all-comers population appeared relatively homogeneous in that about 77 percent of the subjects had either definite or possible endocarditis.

But as I alluded to earlier, in terms of looking at the original case report forms, going through the patient profiles of this all-comers group, again, it became evident that there was heterogeneity and, again, many patients had infections within 30 days of onset of the

bacteremia. They could have served as a potential portal of entry for staph. to gain access to the blood and really served as a basis for the review team to do a post hoc analysis just to see what potential portals of entry could be identified because this information was not compiled in a prospective manner in the course of the study.

Based on our post hoc analysis, about 54 percent of patients had at least a potential portal of entry. The two largest groups involved either skin and soft tissue infections or catheter-related infections. The other 46 percent either had no portal identified or there was insufficient information for us to make a determination of what the portal might be.

[Slide]

I wanted to move at this point to some comments about the efficacy data. What I have tried to summarize in this table is sponsor's efficacy data in terms of the IEAC success rates at test of cure in the all-comers population and then in the final diagnosis clinical subgroups.

I just want to bring up a couple of issues. In terms of sample size, the all-comers was fairly sized with 235 subjects in the ITT split into the two treatment arms. But when assessed in relation to the clinical subgroups, these final diagnosis subgroups, there is a progressive decline in the number of cases when you go from bacteremia into the endocarditis experience.

In terms of the endocarditis experience, the size of the left- and right-sided IE subgroups tends to be a limiting factor in attempting to really understand the performance and efficacy of study drug. There is insufficient statistical power to draw any meaningful inferences regarding the performance of either drug in those subgroups. The other issue to note is that the overall success rates, both in the all-comers population and in the subgroups themselves, were low.

[Slide]

In follow-up to the efficacy data, the team took a look at some data on failures and on reasons for failure in the all-comers population to

see if we can gain further insight into the performance of the study drugs. This table summarizes a compilation of the IEAC reasons for failure. Of the 111 failures, subjects who failed in this study, there were 229 reasons and obviously some patients had multiple reasons for failure identified.

But among those reasons for failure, the review team wanted to focus upon a topic that has already been discussed earlier today which is persistent/relapsing staphylococcal infections. In the analysis that was described earlier this morning there were 30 patients with persistent or relapsing PRSA infections, 19 in the daptomycin group and 11 in the comparator group.

[Slide]

As a follow-up to the sponsor's data on failures that we looked at, the FDA review team conducted its own analysis of the failures due to persistent/relapsing staphylococcal infections in this all-comers population. In the daptomycin arm two additional patients were identified in the

course of the FDA review. One was a 27 year-old male with a history of drug use who experienced a relapse at day 85 post end of therapy. The second was a 54 year-old Caucasian male who was deemed a clinical and micro. failure by the investigator after having 6 days of persistently positive blood cultures.

But there are a couple of important trends that I wanted to point out from this table. First, the total magnitude of PRSA infections in the daptomycin group was almost twice that of the comparator, and the frequency of persistent/relapsing staphylococcal infections, when stratified by clinical subgroup, revealed that among patients with endocarditis there were more cases of persistent/relapsing infections in the daptomycin group, and among patients with bacteremia there were more persistent and relapsing infections amongst patients in the daptomycin group.

Finally, when this data is assessed in terms of the oxacillin susceptibility of the

baseline pathogen, the frequency of persistent and relapsing staphylococcal infections in the daptomycin group was similar among subjects whose isolates were either methicillin-susceptible or methicillin-resistant, 12 and 9. Whereas, in the comparator arm most of the persistent and relapsing staphylococcal infections were confined to patients with methicillin-resistant staph. infections, 9 cases versus 2.

[Slide]

Another issue of concern to the review team was the issue of patients who developed increasing MICs or shifting of MICs from baseline to higher levels during the course of treatment with study drug. This table summarizes the patients in each treatment group with blood culture isolates that exhibited increasing MICs from baseline during therapy, along with the outcome at test of cure by the IEAC, which is the primary efficacy endpoint for this study.

There are a couple of observations that I wanted to point out from this data. There were 96

patients in the comparator arm for whom full MIC central data was available and 4 of them had isolates of S. aureus that exhibited increasing MICs to either vancomycin or daptomycin. Three had a highest vancomycin MIC of 2 and one had increasing MICs to both drugs from baseline. Of those 4 patients, at test of cure there were 3 successes and 1 failure. Among the 113 daptomycin-treated patients for whom there was full central MIC data, there were 9 subjects for whom their baseline S. aureus isolate exhibited a shift when increasing MIC to either vancomycin or daptomycin or both during the course of the study. Three had increasing MICs to vancomycin and 4 had increasing MICs to daptomycin, and 2 patients had increasing MICs to both drugs.

Of note, of the 9 patients, there was only 1 success and 8 failures at the test of cure. This included all patients in the daptomycin-treated arm whose isolates exhibited increasing MICs to daptomycin while receiving daptomycin therapy.

Thus, among all subjects for which we were

able to discern full MIC data that was available through central lab and whose S. aureus isolates exhibited increasing MICs to study drug during the course of treatment, the treatment failures at the primary efficacy endpoint at test of cure were predominantly limited to patients treated with daptomycin, and particularly involved subjects who developed increasing MICs to daptomycin during the course of daptomycin therapy.

[Slide]

I want to just summarize a couple of points about the all-comers before I move on. First, it is apparent that there was significant heterogeneity amongst the subjects in the all-comers population. Second, when the all-comers population were assessed in terms of the clinical subgroups, the final diagnosis subgroups, the small sample size, the insufficient statistical power and the low efficacy rates make evaluation of the performance of study drug problematic.

In terms of PRSA infections, they accounted for more failures among

daptomycin-treated than amongst comparator-treated subjects and the all-comers population, and this included more persistent and relapsing staphylococcal infections in the daptomycin arm among subjects with bacteremia and among subjects with endocarditis.

The finding of staph. isolates that exhibited shifting to increasing MICs from baseline, increasing MICs to daptomycin, particularly patients who received daptomycin therapy, was associated with failure at the primary efficacy endpoint at test of cure.

[Slide]

I would like to shift with a few comments about the S. aureus experience.

[Slide]

I will begin with a table which summarizes some of the sponsor's efficacy data in terms of the ITT and per protocol for subjects who were identified by the IEAC as having S. aureus endocarditis. There were 53 such subjects in the ITT and 33 in the per protocol population.

From this table I just wanted to point out a couple of issues. First, when assessed in terms of left- versus right-sided disease, the overall total number of subjects in each group is small. The point estimates for success are low and there is insufficient power to make any statistically meaningful conclusions about study drug performance.

Then, when right-sided endocarditis is assessed in terms of complicated and uncomplicated disease, those subjects consist of fewer patients. There are 6 or less observations in each cell in terms of success for those 2 categories. Again, the small sample size and lack of statistical power make it difficult to make any meaningful inferences about the performance of study drug in those subgroups.

[Slide]

I wanted to make a few comments about echocardiography because echocardiography was performed in almost all patients in the study, except one patient who left against medical advice

after two days and did not have an echo performed. As was described earlier, the echocardiograms were performed locally and then they were sent for re-interpretation to the central echo lab for review and interpretation and possible re-interpretation.

This slide depicts a schematic to allow you to track some of the echocardiography results as interpreted by the central and the local echo labs. Again, there were 53 subjects who were identified as having endocarditis and of those 53, 34 had a positive central echocardiogram; 18 had negative central echocardiograms; and then there was the one where it wasn't performed.

Of note, of the 34 patients with a positive central echo, 10 had correspondingly negative local echo interpretations and this included 8 subjects with left-sided endocarditis. The reason this is important to keep in mind is because part of the protocol-specified definition of left-sided endocarditis was that patients had to have positive echocardiographic findings involving

aortic or mitral valves, but that requirement was not established for right-sided disease. Of the 18 subjects with a negative central echo, 8 of them had correspondingly positive local echo interpretations.

So, these discrepancies in the interpretation of the same echocardiogram by the central and the local lab raised concern amongst the review team about the specificity and even the reliability of the endocarditis diagnosis and some of the patients that were included in the endocarditis experience.

[Slide]

As a follow-up to that schematic, it creates some issues as far as trying to interpret the efficacy of drug. This table summarizes the IEAC success rates at test of cure by various echocardiographic findings. The first row is the 53 patients identified by the IEAC who had a diagnosis of endocarditis and the success rates at the test of cure were 36 percent versus 32 percent in comparator and daptomycin respectively.

In trying to analyze and understand the endocarditis experience, the review wanted to try to see if we could delineate a subset of those patients who had echocardiographically demonstrable either valvular vegetations and/or perforations that would be attributed to endocarditis. As you see in the table, depending on whether you use central echo lab results or local echo lab results or a combination, you see both a drop in the number of patients from 53 and a drop in the success rates, but you also see contrasting success rates. If you utilize all subjects with a positive central echocardiogram regardless of how the local was interpreted, you are down to 34 patients from the original 53 and the success rates at the test of cure were 35 percent versus 28.6 percent in favor of comparator. On the other hand, if you utilize all positive local echocardiograms regardless of the central interpretation, you get a contrasting conclusion in the sense that the comparator was 36.8 and daptomycin was 10 points better at 46.1. So, again, it created some difficulty and problems

in trying to interpret the endocarditis experience.

[Slide]

I would like to just move on with a couple of mortality-related comments.

[Slide]

This is a table which depicts all-cause mortality, a summary of that for the all-comers stratified by the time points of deaths up to 42P, which would be 42 days after end of therapy so basically 6 weeks after end of therapy as a time point, then all the deaths to the end of the study, and stratified by clinical subgroups.

I just wanted to point out again a couple of things. Number one, the overall percentages of deaths in each treatment arm at both of the time points were similar. But when you focus on the clinical subgroups what you find is that there are more deaths in the daptomycin treatment arm at both time points in subjects with bacteremia, whereas there are more deaths in the comparator group at both time points in subjects with endocarditis.

[Slide]

As a follow-up to the data previously presented about patients experiencing shifting MICs and increase in MICs from baseline to higher MICs during the course of treatment with study drug, we wanted to try and take a look at the relationship of increasing MICs to the issues of persistent and relapsing staphylococcal infections and death. It is noteworthy that only among daptomycin-treated subjects whose staphylococcal blood culture isolates exhibited shifting and increasing MICs to daptomycin, vancomycin or both drugs we observed persistent and relapsing staphylococcal infections and in some cases death. In particular, of the 6 daptomycin-treated patients whose blood culture isolates exhibited increasing MICs to either daptomycin or to daptomycin and vancomycin, all those patients developed persistent and relapsing infections and there were 2 deaths.

In contrast, in the comparator-treated subjects who had blood culture isolates that had increasing MICs to daptomycin, vancomycin or both drugs, none of those subjects developed persistent

or relapsing staphylococcal infections and there were no associated deaths.

I just wanted to make one final mortality comment in terms of crude mortality. The review team conducted several exploratory analyses looking at mortality data to try to determine what was the risk for death among subjects who failed study treatment due to persistent/relapsing infections in both treatment arms.

[Slide]

This table summarizes the crude mortality rates for both treatment groups which is based on the all-cause mortality rates that we saw earlier and proportionate mortality rates associated with PRSA in the two treatment groups. Of note is that although the proportionate mortality rate associated with PRSA is higher in the daptomycin group, the risk of death in terms of crude mortality rate associated with persistent and relapsing staph. infections in the population was similar to that of the comparator, with a relative risk of death of 1.1.

We did a follow-up assessment where we looked at age-adjusted mortality rates and we saw again similar risks of death associated with PRSA even after controlling for age.

[Slide]

So, in summary some observations and findings from the FDA review of the efficacy data.

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First with respect to the all-comers population, it is important to remember that the study was powered to demonstrate efficacy based on all subjects having one or more positive blood culture for S. aureus, and that the generalizability of the efficacy performance from this all-comers population to the endocarditis subgroup was problematic. It really related in part to the underlying heterogeneity of the patients, different pathophysiologies related to the infections that they had, the potential role of surgery as adjunctive treatments and, obviously, the impact of both the pathophysiology and the surgical interventions on the prognosis for

patients within the different subgroups. It is clear that the heterogeneous nature of this all-comers population warrants further characterization and, again, the overall point estimates for success were low.

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In terms of the endocarditis experience, again the endocarditis experience was a small subpopulation of the all-comers. There was insufficient power to make any statistically meaningful inferences about study drug performance within the endocarditis subgroup. There were difficulties in establishing the specificity of the diagnosis, and this was contributed to by the contrasting interpretations of local and central echocardiograms. And, overall the efficacy rates in both treatment groups were low, particularly in left-sided disease.

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In terms of persistent and relapsing staphylococcal infections, they were more frequent among failures in the daptomycin group, including

patients with bacteremia, patients with endocarditis and really irrespective of the oxacillin susceptibility of the baseline pathogen.

Finally, in terms of patients who had shifting and increasing MICs, particularly the daptomycin during the course of daptomycin therapy, this was associated with an increased likelihood of failure at the primary efficacy endpoint of test of cure. There was also an association of patients who go on to develop persistent and relapsing staphylococcal infections and in a few cases subsequent death.

I think at this point I am going to turn the podium over to Dr. Coderre who is going to provide some information on the microbiology aspects.

Microbiology

[Slide]

DR. CODERRE: I am Peter Coderre. I am the microbiology reviewer for the Division. Dr. Sorbello has addressed the efficacy concerns regarding daptomycin. I will address the

microbiology concerns regarding daptomycin, particularly the observed increase in MICs during therapy.

[Slide]

These increasing MIC's have been documented in vitro, in vivo, in the literature and during this clinical trial. It is important to keep in mind that at the present time S. aureus isolates with an MIC less than or equal to 1 mcg/ml are considered susceptible to daptomycin. However, at this point we do not have break points for intermediate and resistant isolates.

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We asked the question what are the implications of increasing daptomycin MICs during treatment with daptomycin for infective endocarditis and bacteremia in patients with persistent or relapsing bacteremia, S. aureus demonstrated increasing daptomycin MICs during or after therapy with the drug.

[Slide]

This table is taken from the FDA analysis

and it shows MIC data from patients with relapsing or persistent bacteremia. The table shows clinical failures associated with methicillin-sensitive and methicillin-resistant S. aureus MICs equal to or greater than 1 mcg/ml and MICs that increase by more than or equal to 2-fold dilutions. Data from this table indicate that patients with relapsing or persistent bacteremia in the daptomycin arm were more likely to have pathogens with an MIC greater than or equal to 1 mcg/ml and demonstrate a 2 or more increase in MIC dilution steps than relapsing or persistent bacteremia patients treated with comparator.

[Slide]

Data from patient report forms were used to construct the following table. This table presents the MIC distributions by dilution for patients with bacteremia or endocarditis in the ITT population according to clinical outcome. Data from this table indicate that there were more patients with daptomycin MICs greater than or equal to 1 mcg/ml among clinical failures than among

clinical successes. Six patients with complicated bacteremia, one patient with complicated right-sided endocarditis, and four patients with left-sided endocarditis had pathogens demonstrating MICs greater than or equal to 1 mcg/ml. Six patients who were clinical failures developed non-susceptibility during treatment with daptomycin. These data indicate that greater than 10 percent of clinical failures had an MIC of 2 mcg/ml or greater.

[Slide]

This table was constructed from patient report forms and shows more detailed data from the patients in whom isolates developed at least a 2 dilution step increase in daptomycin MICs among clinical failures. Notice that all cases demonstrated an MIC step increase of at least 2 steps with the exception of 2 patients. All cases demonstrated a highest level of MIC of at least 1 mcg/ml, and 6 of 8 patients had MICs of 2 mcg/ml or greater.

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The sponsor has provided patient report forms that contain MIC data from the central laboratory for patients given daptomycin or comparators to treat endocarditis or bacteremia. This table is constructed to show the numbers and percentages of patients in both study arms, showing number of patients with increases in daptomycin and vancomycin MICs and those who developed daptomycin non-susceptibility or vancomycin resistance.

The data from this table show that patients in the daptomycin arm, whether they were clinical successes or clinical failures, were more likely to demonstrate increased MICs to daptomycin than patients in the comparator arm. Also, patients in the daptomycin arm that were clinical failures were more likely to develop non-susceptibility to daptomycin than clinical successes or patients treated with the comparator. The data also show that increases in daptomycin MICs and daptomycin non-susceptibility are not correlated with increases in vancomycin MICs or vancomycin resistance.

[Slide]

The sponsor has provided an overview of isolates with treatment-associated decreases in daptomycin susceptibility following commercial availability. This table shows that 15 patients developed MICs to daptomycin greater than or equal to 1 mcg/ml since daptomycin was approved by the agency. Of these 15 patients, 9 patients had S. aureus isolated from blood. Of these 15 patients, 10 patients demonstrated a 3-step increase in daptomycin MIC. This led us to ask the question are there reports of daptomycin resistance in the literature since the submission of the original NDA?

[Slide]

Eight publications from recent literature report resistance or non-susceptibility to daptomycin in clinical isolates from patients on therapy. Two isolates were E. faecium, 2 isolates were E. faecalis and 4 isolates were methicillin-resistant S. aureus. Five isolates were identified in patients with bacteremia. One

was febrile neutropenia, one osteomyelitis and one fever. All samples were from blood and dosages ranged from 4 mg/kg to 8 mg/kg. The highest MIC obtained ranged from 4 mcg/ml to greater 32 mcg/ml.

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The sponsor's data from surveillance studies in North America and Europe from 2000 to 2004 are shown in the following table. Percentages are calculated for each MIC step for each study year in order to compare the MIC distribution. When the percentages of isolates for each MIC dilution are calculated, the data show the percentage of isolates with MICs of less than or equal to 0.12 mcg and 0.25 mcg decreasing over time. The percentage of isolates with MICs of 0.5, 1 and 2 mcg/ml increased over time in these particular studies. The observation is evident in both the methicillin-susceptible and the methicillin-resistant isolates of S. aureus.

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The following data were taken from Focus Technologies. Between 2004 and 2005 the percentage

of MICs with an MIC less than or equal to 1 mcg/ml decreased from 99.1 percent of isolates to 96.7 percent of isolates. Also during this time, the percentage of MICs with an MIC greater than 1 mcg/ml increased from 0.9 percent of isolates in 2004 to 3.3 percent of isolates in 2005. This represents an increase of more than 3-fold.

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The sponsor has presented data from a number of animal models, including rabbits, rats and mice, that include bacteremia, endocarditis, fibrin clot, hematogenous pneumonia and experimental meningitis. In published studied daptomycin was shown to be more efficacious than comparators in the rabbit model of endocarditis. Silverman et al. showed that 2 of the 16 animals yielded organisms resistant to daptomycin, 1 organism at a 4-fold rise in MIC and another at an 8-fold rise in MIC.

Thus, while daptomycin was more efficacious than vancomycin diminished susceptibility developed during therapy. The

investigators theorized that the resistant organisms were selected for by sub-inhibitory concentrations of daptomycin deep within the vegetations. The investigators also warned that extensive clinical use will be required to establish whether resistance to daptomycin will be a major clinical problem, but their findings in the rabbit animal model raise concerns regarding this possibility.

[Slide]

In this application the sponsor has noted that spontaneous mutations leading to daptomycin resistance are rare in gram-positive bacteria and that there are no known transferable elements that may confer daptomycin resistance. Liebowitz has shown in a study that no spontaneously resistant mutants were obtained from any clinical or laboratory isolates after a single passage in daptomycin. However, stable resistant organisms have been isolated after multiple passages in liquid media containing progressively increasing concentrations of daptomycin and following chemical

mutagenesis. Kaatz showed in another published study that daptomycin-resistant mutants were not found to be resistant to vancomycin or ampicillin, as would be expected because of the differences in their mechanisms of action. However, cross-resistance to nisin, which is an antimicrobial similar in structure and possibly mode of action to daptomycin, was found.

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Evidence for pathogenesis of biofilms in infective endocarditis is strong. Sixty percent of daptomycin penetrates into vegetations, and 90 percent of daptomycin is protein bound. Therefore, we would expect less than 60 percent of the daptomycin to penetrate into vegetations. Once developed, vegetations manifest biofilm-like antibiotic resistance that cannot be completely explained by poor penetration of antimicrobials. Studies show that the composition of valve biofilm has direct bearing on clinical outcomes. Taken together, these experiments demonstrate an association between the biofilm composition and its

clinical manifestations, and support the concept that infective endocarditis can be manipulated by targeting biofilm development.

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In summary, patients with relapsing or persistent bacteremia were more likely to have increased MICs if treated with daptomycin rather than comparator. This was irrespective of whether S. aureus demonstrated oxacillin susceptibility or resistance.

Patients treated with daptomycin for endocarditis or bacteremia caused by S. aureus who were clinical failures are more likely to exhibit isolates with increased daptomycin MICs.

Surveillance data shows some MIC dilutions increasing and others decreasing over time. The literature reports instances of non-susceptibility or resistance.

In a rabbit model of staphylococcal endocarditis daptomycin was more efficacious than vancomycin, but diminished susceptibility developed during therapy. Investigators theorized resistant

organisms were selected for by sub-inhibitory concentrations of daptomycin within the vegetations. The investigators in this study warned that extensive clinical use will be required to establish whether resistance to daptomycin may be a clinical problem.

In vitro studies have demonstrated that bacteria can develop resistance to daptomycin when subjected to sub-inhibitory concentrations of daptomycin, such as may be found in endocarditis vegetations. Daptomycin did not exhibit cross-resistance to vancomycin or to ampicillin, but did exhibit cross-resistance to nisin.

At this time, Dr. Cooper will further explore the safety concerns in the next presentation. I thank you for your attention.

Safety Results

DR. COOPER: Hello.

[Slide]

My name is Chuck Cooper. I am a medical officer in the Division of Anti-Infectives.

[Slide]

I am just going to touch on a few safety issues that came up during the review of this NDA. In particular, I am going to start with infection-related serious adverse events, renal toxicity and the CPK analysis.

[Slide]

This graph shows all serious adverse events for comparator versus daptomycin. You can see that there are increased numbers of patients in the daptomycin arm who had osteomyelitis, sepsis and staph. bacteremia. That led us to look at infection-related serious adverse events in particular. When we did that we saw that there were more infection-related serious adverse events in the daptomycin arm than there were in the comparator arm.

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Trying to figure out what was driving this difference, we looked at these infection-related serious adverse events by preferred term, and you see again osteomyelitis, sepsis and staph. bacteremia. However, you also see that at the

bottom there is a case of klebsiella infection and enterobacter bacteremia. Because of those two, we looked in particular at gram-negative-related infections that caused serious adverse events.

[Slide]

This is a slide that shows what we found when we looked at gram-negative infection-related serious adverse events by preferred term. Actually, for sepsis a patient had 2 separate events so this could be 7. In addition, we looked at gram-negative bacteremias that were reported as adverse events but were not coded as serious. When we did that, we found 4 additional gram-negative bacteremias in the daptomycin arm and, again, zero in the comparator arm.

[Slide]

Moving to renal toxicity, this is a graph that shows non-serious renal events in blue and serious renal events in red. You can see that there are increased numbers of serious and non-serious renal events in the comparator arm compared to the daptomycin arm.

[Slide]

However, there is some difficulty in trying to understand the renal adverse events. It became clear that there wasn't really standardization in terms of what was a renal adverse event and what wasn't a renal adverse event, which became an issue because of the open-label design and because it could be presumed that there was an expectation of renal toxicity in the comparator arm but not necessarily in the study drug arm and the potential for comparator-treated patients to possibly be treated longer.

[Slide]

Here is an example of some of the inconsistencies that we found. In the comparator-treated patients we see a patient who had acute renal failure with the corresponding creatinine increase. In the daptomycin arm we see patients who had similar or greater increases in creatinine that weren't called adverse events. In the comparator arm there also were patients who had increases in creatinine that weren't called adverse

events. So, it is just inconsistent and made it difficult for us to really understand what was going on in terms of the renal toxicity.

[Slide]

For that reason, we conducted an analysis looking at identifying renal toxicity cases. We identified patients who had an increase in creatinine of 25 percent or more while on therapy or within 30 days after the last dose and whose peak creatinine was over the upper limit of normal, 1.5. We used this definition because of the discussions that we had with Dr. Pelayo, who is a nephrologist at the FDA and has experience in assessing drug-related nephrotoxicity.

When we did this analysis the results were that there were greater numbers and a greater percentage of patients in the comparator arm who had renal toxicity using this definition than in the daptomycin arm.

[Slide]

However, we had some difficulty with interpretation there also because the treatment

arms had differences with regard to age and treatment duration. In particular, we found that patients who were 60 years or older and who had longer duration of treatment, specifically greater than the median, had the highest rate of renal toxicity, and there were more of these patients in the comparator arm than there were in the daptomycin arm.

[Slide]

This graph is a graph called display of a 2 X 2 table. What we see here is that above the X axis we have patients who are 60 years and older and below we have patients who are under 60 years of age. To the right of the Y axis we have patients who were treated for above the median duration of therapy and below we have patients who were treated less than the median duration of therapy.

[Slide]

In particular, I wanted to point out that in the patient population where we found there to be the greatest rate of renal toxicity, which is

the patients who were 60 and older who had the longer duration of therapy, there is an imbalance between the two treatment arms. We thought that might be driving some of the difference between the two drugs.

[Slide]

If we look at where the cases of renal toxicity fall within this graph, we see that, indeed, the patients who were 60 and older and who had longer durations of therapy had the highest rate of renal toxicity. If you take these 116 patients and redistribute them so that their distribution is equivalent to the distribution that we see here and then apply these rates to that new distribution, we can correct for this imbalance.

[Slide]

When we do that, we see that there are still more patients in the comparator arm but it is more similar.

[Slide]

This is a CPK analysis using a delta graph and looking only at the central lab data. In this

graph what we see that in the daptomycin and comparator arms each one of these lines or points represents an individual patient. So, this graph contains all the patients in the study. What we have is, for the blue points, patients whose baseline CPK measurement was their maximum measurement. They didn't increase any further. For the red line we have patients whose baseline is on the left and their peak maximum measurement is on the right. So, when looking at this graph we can see that there are a total of 9 patients who started out with CPKs that were under 500 and then increased over 500; 2 additional patients who had CPKs that were already significantly abnormal that then increased. For the comparator arm there is 1 patient.

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Of interest, we notice that of those 9 patients who increased to above 500 we found that 4 of them had prior or concomitant treatment with a statin, which led us to wonder whether or not that could possibly have influenced the increase in CPK.

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So, in conclusion, there was a greater number of infection-related serious adverse events that were reported in the daptomycin arm. The increase seemed to be related to an underlying disease process or propensity for gram-negative infections.

There were greater numbers of patients in the daptomycin arm who developed CPK increases to over 500 units per liter from baseline, and there is a possible association with prior or concomitant treatment with a statin drug.

There was a similar although slightly higher rate of renal toxicity cases, using the definition that we used, in the comparator arm than the daptomycin arm. Thanks.

Committee Questions to the FDA

DR. LEGGETT: First of all, are there any questions for any of the speakers? Steve?

DR. EBERT: I noted that the median time to eradication for MRSA was I believe somewhere around 89 days for all strains. Obviously, we have

this emergence of strains with elevated MICs. Do we have any information on when, in the course of therapy, those strains emerged? Was it early in the course? Later in the course?

DR. SORBELLO: Could we put up backup slide number 7 from my slides?

[Slide]

This slide shows subjects who had a shift in daptomycin MIC where the MIC was 2 or above and basically the study day when that was reported. There actually was 1 patient in the comparator arm and there were 7 in the daptomycin arm. The study day when daptomycin MIC of 2 or more was reported ranged from day 4 following initiation of study all the way out to 20 days after the end of treatment.

DR. LEGGETT: John?

DR. BRADLEY: On slide 5 where you looked at the portals of entry and in one percent you found that the portal of entry was the lung. Having heard this morning that daptomycin was inferior to comparator for treatment of staphylococcal pneumonia, and knowing that in

complicated staph. bacteremias, disseminated staph., you can certainly get involvement of the lung, were there any patients who were bacteremic who ended up with a complication in the lung for whom you might have some concern that daptomycin, although it might clear the bacteremia, would not effectively treat the lung? Maybe that would be appropriate for you or Dr. Boucher, or both.

DR. SORBELLO: I can only say, based on my review of the data--well, first, pneumonia was to be an exclusion criterion but a couple of patients turned out to be enrolled who had pneumonia. But there was not much data from sites other than the blood so I don't remember specifically. That is actually two patients so I can't tell you specifically on a case-by-case basis but, in general, the data from other sites than the blood was very limited. So, you weren't always able to make a one-to-one correlation between what was out of blood and what was out of lung even though the patient would have a chest x-ray or a CAT scan, or whatever, that would report an infiltrate. Again,

that kind of made it difficult to know what the pathophysiology was.

DR. BOUCHER: We did pre-specify looking for septic pulmonary emboli and infarcts so they were collected prospectively, and we looked at outcome in patients who had septic pulmonary emboli and infarcts and I can share that with you. Slide up, please.

[Slide]

It turned out that there were 10 patients in the daptomycin group and 13 in the comparator group who were identified prospectively as having septic pulmonary emboli present at baseline. It included mostly folks with right-sided endocarditis but a couple of patients with left and one complicated bacteremia patient. Overall, success was seen in 60 percent of the daptomycin and 46.2 percent of the comparator agent treated patients with septic pulmonary emboli. So, this is consistent with Dr. Alder's model data of efficacy in hematogenous models of S. aureus.

DR. LEGGETT: Jan?

DR. PATTERSON: This is for Dr. Sorbello. On slide number 8 you mentioned that you had added a couple of failures to the persistent/resistant S. aureus infection and you mentioned that one was an intravenous drug user that relapsed on day 85.

DR. SORBELLO: Yes.

DR. PATTERSON: Just as a clinician, I guess my experience would suggest that would probably be a re-infection due to recurrent drug use rather than a relapse which tends to occur earlier than three months with S. aureus. I am just wondering if there is any clinical or molecular evidence to suggest that that really was a relapse, and where that got put in this table on slide 8.

DR. CODERRE: The data provided by the sponsor--they presented some pulse-field gel electrophoresis indicating that the clones were the same.

DR. PATTERSON: Okay. I have another question. Presumably the reason that there is an increase in gram-negative infections in the

daptomycin group is because the comparator group had gentamicin, and that could be one reason. I guess it was difficult to avoid antibiotics that were potentially effective, non-study antibiotics, in this study. But were patients allowed to have astrinam [?] for empiric therapy of gram-negative infections? Because I guess almost any other choice could have some activity against staph.

DR. BOUCHER: That is right, Dr. Patterson. Astrinam [?] was allowed and it was considered by the adjudication committee in their assessment of potentially effective antibiotics. But other things like beta-lactam and beta-lactamase, inhibitor combination or something may well have, and were indeed considered potentially effective.

I think on the subject of these infections it is important to note that there were a number of comparator patients with fungemia and fungal infections and clostridial infections, and the way the serious adverse events and adverse events in general are reported is by whatever the

investigator writes down. So, one investigator's sepsis is another investigator's Klebsiella pneuomoniae bacteremia or another investigator's S. aureus bacteremia. So, in looking retrospectively at these it is hard sometimes to sort out exactly what the investigator is referring to.

DR. LEGGETT: Joan?

DR. HILTON: Dr. Sorbello, I also have a question on slide 8. Comparing that with table 14 in the FDA briefing, it looks like there are a lot of missing data. It seems like the denominators should be 28 and 23 when they are 21 and 11 in slide 8. I am kind of confused about that. Microbiologic failures according to table 14 are 28 and 23.

DR. LEGGETT: Actually, Joan, you mean 15 I think.

DR. HILTON: In table 15 there are 21 and 11. I am just trying to explain the discrepancy between those two.

DR. SORBELLO: Well, I believe in table 14 what is also included is the microbiologic failure

beside persistent and relapsing bacteremias or patients who had no blood cultures drawn at the test of cure. So, if they have a missing test of cure blood culture, it looks like they were included as a microbiologic failure, as well as if they had a positive culture from another non-blood source. There is one in each arm.

DR. LEGGETT: Much of the analysis had to do with persistent or relapsing S. aureus infection. Could someone please remind me of just exactly how that was defined before the study? Perhaps Dr. Boucher might help us.

DR. BOUCHER: I would be happy to, Dr. Leggett. The definition used in the protocol for persistent and relapsing S. aureus bacteremia was positive cultures on or after therapy. So, in the protocol that is how it was defined and that was the criteria the adjudication committee used in assessing the reason for failure in all patients who failed.

DR. LEGGETT: I am just asking for the definition of persistent infection because if it

takes 8 or 9 days to clear the bacteremia, that is persistence. Was there some other twist to it, like you were negative for a day and then you were positive again, or something like that?

DR. BOUCHER: It was not delineated between a particular day or days. It was persisting or relapsing. That was the definition used. So, it could have been clear for a few days and re-progressed or never cleared.

DR. LEGGETT: So, basically you are saying it is up to each individual investigator, who was not blinded to the study, to say three days is too much; that is persistent, we will change it?

DR. BOUCHER: Actually, I am very glad you raise that. The investigator assessed cured, improved, failed or not seen. This is part of the reason we actually decided to convene the adjudication committee, because of the difficulty in interpreting a checked yes/no. The difficulty in assessing both the diagnosis and the outcome led to having the adjudication committee perform a blinded review of all the patient data, and when

they assessed failure asking them to declare if it was for persisting or relapsing S. aureus infection, death, etc.

DR. LEGGETT: And how did they, without seeing the patient and post hoc, decide it was persistent versus it was okay? I mean, so it is persistent at three sometimes but at eight it is okay?

DR. BOUCHER: I think I will ask Dr. Corey to comment on that as they made these assessments.

DR. COREY: The definition of persistent really was up to the investigators. If the investigators decided at day eight that patients still had persistent bacteremia and discontinued the patient, then they were discontinued because of persisting infection. If the investigator decided on day three that it was too long and the patient was too sick and they had persisting blood cultures on day three and they took them off the trial, then it was still persisting bacteremia.

In setting up a trial of this sort, it is very difficult if you don't allow the investigator

freedom to assess a patient at the bedside and having us arbitrarily say, for instance, that you have to keep them on the drug for six days before you can stop it. Most investigators won't enroll their patients.

DR. LEGGETT: And do we have any data or do you have any data about the kind of numbers that we are talking about? Because the reason I brought it up is that that has a big impact on trying to assess whether this higher MIC of daptomycin really has to do with failure due to persistence or not.

DR. BOUCHER: There are a couple of ways I think I can address that. In terms of looking at the groups who failed due to persisting or relapsing S. aureus bacteremia, the median duration of therapy in both groups was about 12 days. Specifically, in the group of patients who failed with rising MICs, we looked at their duration of therapy. There, we can go back to that slide from the main presentation that showed duration of therapy.

[Slide]

What we found is that the duration of therapy was shorter for the two patients with left-sided endocarditis, 7 and 8 days, and longer for the other individuals with right-sided endocarditis and complicated bacteremia. So, as Dr. Sorbello mentioned, there was a range but clearly for the left-sided endocarditis patients it was shorter.

DR. LEGGETT: So, we could sort of assume that most people tried to hang in there?

DR. BOUCHER: I think that is a fair statement. When we looked in both groups there were individuals in each group, three or four in each group, who had three or four days for instance and the rest did receive longer durations. DR. LEGGETT: Dr. Borer?

DR. BORER: Thank you. Dr. Sorbello, I would like to come back to your primary analysis of efficacy and the subanalyses. You know, that was nicely detailed in our briefing document and it was a very thought-provoking analysis. Once you get past the primary pre-specified analysis and get to

the subanalyses and use the end of therapy diagnosis I find that the data are confusing, and Dr. Follmann said it before but I am going to say it a different way.

In practice, there are only two ways you could have gone from possible endocarditis to definite endocarditis, from possible endocarditis at the beginning of the study to definite endocarditis at the end. One would be a total and complete catastrophe and going to surgery and getting a pathological diagnosis. The other was developing a vegetation by echocardiography. The latter would indicate a treatment failure also. In fact, one of the problems here I think--and, you know, I am not an echocardiographer per se and perhaps Dr. Cabell would be the appropriate person to comment on this, but I think it is important to understand the limits of resolution of an echocardiogram to pick up some minor anatomic evidence of infection short of a vegetation of a certain size. So, I don't know how much weight it is reasonable to give a determination of efficacy

based on the end of treatment adjudicated diagnoses. I would like perhaps for you to comment on that a little bit. How did you justify using the end of treatment as such an important determinant in your analysis?

DR. SORBELLO: Well, that was a source of confusion for us as well because going through the case report forms and looking at the other data, there were cases where we had questions about what the final diagnosis was and it was clear that by using modified Duke criteria you overestimated the number of cases who potentially had endocarditis compared to those who were actually considered as having endocarditis by the IEAC. As far as an objective marker, we thought that using the echocardiogram would be something where you have a visualized abnormality that maybe would be a correlate to at least specificity to a diagnosis. Because, without that, just going with modified Duke criteria, you are overestimating the number of patients who may potentially have endocarditis in the entire population.

DR. BORER: I would have to question that. I think the echo is not a sufficiently sensitive tool--

DR. SORBELLO: That is why we were concerned about the heterogeneity in this population from baseline and how it was characterized because we couldn't get a great handle on exactly what the details were of this whole commerce experience. In trying to piece together portals of entry with data that wasn't collected prospectively, we were very hampered in doing that. We had to piece it together to try to come up with the post hoc analysis that we did and you can see we were very limited even in those attempts to do that.

DR. CHAMBERS: If I could comment on the sensitivity and specificity of the echocardiogram and endocarditis--I am not a cardiologist but as I take care of a lot of patients with endocarditis maybe what I have to say is helpful. The specificity of even a transthoracic or transesophageal echo is quite good. It is about 95

percent. The problem with these tests is the sensitivity, which ranges between 70-90 percent. If you look at a population that ends up going to surgery, to the autopsy table, one can do considerably better but we are not really interested in that patient population today.

So, I think the sensitivity is probably around 90 percent. Now, what we know about this patient group, and you alluded to this earlier, is that they are enriched for patients who have a severe and extreme form of staphylococcal disease and they are complicated and there is a large group of definite endocarditis, and almost certainly there are patients in the group that have endocarditis plus but it is not able to be detected given the sensitivity of the echocardiograms. So I think, if anything, there are probably more patients with endocarditis than were identified in this patient population.

DR. BORER: Yes, and that was my point really, that looking at the end of treatment diagnosis may actually confound the analysis a

little bit, but I understand the great difficulty you had because of the lack of prospective data of other sorts.

Committee Discussion

DR. LEGGETT: Any other questions by the group? Why don't we move on to some discussion about the assessment? So, it will just be sort of free for all for a few minutes and then we will try to rein it in. Go ahead, Dean.

DR. FOLLMANN: I am a little confused about the concern about resistance actually. If we look overall the rates of success are very similar and you properly related that in the daptomycin group there is an increased rate of failure due to resistance. This has to be balanced because you know if the rates are equal this is a zero sum game. We see an excess of failure due to treatment-limiting toxicity in the comparator arm. So, overall there is not an issue but you focus on imbalance for the daptomycin group and you don't talk much about the associated imbalance which must exist for the comparator arm. So, why the concern

about resistance? Drugs, I know, develop resistance but if they are useful for a while that is a good thing. You know, anti-malarial drugs--there is resistance developed in those now but they have been very successful for a long period of time. Also AZT in individual patients, that develops resistance over a while but while it is working it is good. So, is there something I am missing why we should be especially concerned about this form of failure and not just look at the overall rates?

DR. CODERRE: Well, what we noticed here was an increase in MICs during therapy. Now, we don't have an intermediate or resistant breakpoint for this drug. What we have to go on is what we have for complicated skin and skin structure infections. But because we saw this increase in MICs which we did not see to the same extent with, say, vancomycin this sort of raised some concerns. When you put all of these things together you see this tendency of these increasing MICs. Those reports from the literature that I showed you have

all been reported in the literature since late spring of last year. So, I think we just sort of put all these things together.

Also, I think the concern is that we may have these sub-inhibitory concentrations in the vegetations. Sixty percent of the daptomycin penetrates into the vegetations. Now, we heard talk about a three-log reduction in the number of bacteria. However, we all know that a three-log decrease in bacteria--I mean, is it a big difference? Are you going from, say, 108 to 105? Even if we are going down to, say, 105 or 102 we still have organisms that are there and we don't need many of them in order to re-initiate some kind of infection.

We also don't know the effect of daptomycin on the biofilm if you have differences in the composition of the biofilm that will affect the penetration of antibiotics into vegetations. We just don't know exactly how daptomycin affects the biofilm. It may be that, you know, we have cases where it positively affects the biofilm.

DR. LEGGETT: Jan?

DR. PATTERSON: I would just add that in terms of the clinical significance of that, having seen a couple of patients with this increasing MIC to staph. on therapy and also one with the increasing MIC in a very serious infection, even though we have vancomycin failure similar to the one that Dr. Chambers described this morning where the patient either initially responds and then relapses or may take a while to respond, doesn't respond as quickly to, say, methicillin-susceptible staph. to semisynthetic penicillins, at least my, albeit anecdotal, experience is that these patients really don't respond. I mean, you know, they may initially respond but then they relapse early as opposed to responding or slowly responding. So, I think there is clinical significance that we don't see in comparison to vancomycin and, to me, that is at least the clinical significance of this.

DR. FOLLMANN: So, you think these failures are sort of worse in some sense than the failures in the other group where we have the

imbalance of treatment-limiting toxicities? That these are more lost souls or lost cases than that other type of failure?

DR. PATTERSON: I think in the setting of these kinds of serious infections they are clinically significant, yes. To me, that is the difference. I don't know, John, have you had any experience with these?

DR. LEGGETT: I would also like to throw in that we are talking about individual resistance not population resistance. So, when you bring up the other aspects it is a different question. John?

DR. BRADLEY: I just had a few global comments on resistance. Any naturally occurring antibiotic always has a naturally occurring resistance mechanism and all of them are millions of years old. So, the fact that you will get resistance is absolutely no surprise.

I think the fact is that in the serious infections the consequences of development of resistance are huge, and we follow vancomycin MICs

in patients with serious infections and look for rises so I think this will be no different. But this kind of information probably isn't a deal-breaker on our recommendations to the FDA for approval or not, but these kinds of data can go into the package label to caution physicians that resistance may occur and to watch for it, and also may allow the agency to request more information on development of resistance post approval.

DR. LEGGETT: Alan?

DR. CROSS: I would like to agree with what John said. There is a slightly analogous experience that we have when we deal with serious gram-negative infections. That is, we often will start therapy with a beta-lactam antibiotic in the course of therapy of a serious infection. I think the moral of the story is that once you start therapy you still have to monitor your patient, and when you have a delay in clearance of your organism you have to go back and re-look at the susceptibility of your isolate and change therapy accordingly if warranted.

DR. LEGGETT: So, that is saying that on one side we are dealing with resistance; on the other side we are dealing with more toxicity. From the clinician standpoint, the toxicity for the most part you can handle. You can change things around. The resistance--if you can't use the drug, this is down to the last drug. We have to remember that too.

DR. FOLLMANN: You couldn't put them on vancomycin?

DR. LEGGETT: Well, they are probably on daptomycin because they couldn't tolerate the vancomycin.

DR. FOLLMANN: But not in this trial. Right?

DR. LEGGETT: Not in this trial but we are talking about what it means as a clinician. Dr. Boucher?

DR. BOUCHER: Thanks, Dr. Leggett. I just wanted to clarify something about the persisting and relapsing infections. I think it is important to remember that the comparator group had two

agents. So, in the daptomycin group we had the 19 patients out of 115 who had persisting or relapsing infection. In the comparator group we had 9 vancomycin and 2 semisynthetic penicillin patients. So, 9 of the 53 vancomycin patients had persisting or relapsing S. aureus infection, 6 of whom had vancomycin MICs potentially of 2 at the local and/or central lab. Clinically, these patients looked remarkably similar, a couple of left-sided endocarditis, a couple of right-sided endocarditis and the remainder complicated bacteremia with various foreign bodies. So, in terms of perspective I think it helps to make sure we have the denominators of these as we are discussing them. Thanks.

DR. LEGGETT: Peter?

DR. CODERRE: Yes, one thing I wanted to add regarding biofilms is that there was a study done by Jolie et al. in 1987. They did some in vivo studies which indicated that bacterial killing within vegetations required antibiotic levels that were 224-greater than the concentrations required

to kill ketonic [?] bacteria. There have also been some studies done--one by Hooke and another one by Gotschek--where they treated animals to alter the composition of the biofilm. One study, by Hooke, involved valve-injured rabbits that were treated with warfarin which inhibits fibrin platelet matrix formation. They found that the resulting illness was characterized by a very high fever, constant bacteremia and increased mortality. However, the actual antibiotic treatment was more effective in the warfarin-treated rabbits. So, this is just, you know, an example. It is not just the concentration of the antibiotic in the vegetation but also how you affect the biofilm, the structure of that biofilm.

DR. ALDER: I have a comment on biofilm stationary phase that would be appropriate.

DR. LEGGETT: Go ahead.

DR. ADLER: Daptomycin has been studied in biofilms and really an associated phenomenon of biofilms is that the bacteria tend to be in stationary phase or in a lower metabolic profile

than bacteria in a vegetative state. It was indicated from the 1987 study. We have done studies showing daptomycin bactericidal activity against bacteria in biofilm and bacteria that are non-growing. Slide up, please.

[Slide]

This is from am in vitro pharmacodynamic model. What you can see amongst the growth control at the top is that this is an MRSA starting at about 109.5 with no growth across 72 hours. Daptomycin, shown here in the gold, achieved cidality within 24 hours against a very dense non-growing bacterial population in a biofilm simulated endocardial vegetation. Another important factor, vancomycin still maintained activity but it took progressively longer in order to achieve cidal activity.

[Slide]

In a similar model with MSSA, nafcillin lost much of its bactericidal punch. It is a similar system except it is MSSA, cidal activity of daptomycin in a non-growing biofilm. Nafcillin

typically has great cidal activity in this model against vegetative growing bacteria. However, against the stationary phase non-growing culture nafcillin loses much of its cidal punch. Slide up.

[Slide]

Also addressing the penetration issues and protein binding, daptomycin has consistently shown penetration and bactericidal activity. This is from Bob Carbone's lab. Lead author Caron was showing homogeneous penetration of daptomycin into vegetations in vivo in a rabbit endocarditis model--homogeneous distribution, bactericidal activity, including activity in the rabbit model.

The one model that was quoted during the presentation as far as induction of resistance was from 1987. It was a rabbit model in which the drug was dosed three times a day at very low levels. In 1987 the once a day dosing concentration-dependent activity of daptomycin was not known. Three times a day, low levels in the rabbits, a grand total of two rabbits out of 16 produced colonies with elevated MICs. Of those two rabbits, one of them

produced one--and I mean literally one colony that had an elevated MIC. The other produced several more. So, in total, the bulk of the evidence shows that daptomycin is no more prone than vancomycin or many other bactericidal drugs to induction of MIC increases, stationary phase biofilm or MRSA. Thank you.

DR. LEGGETT: Can we segue from that discussion about resistance and penetration to have comments of our two biostatisticians about Ns of 9?

DR. FOLLMANN: Nine is small.

[Laughter]

DR. HILTON: I agree.

DR. LEGGETT: Go ahead.

DR. FOLLMANN: You know, that is my short answer. I guess the FDA was concerned about heterogeneity of the treatment effect and they looked at small subgroups and they said in small subgroups you can't really say much statistically because they are small. That happens in any study when you look at small subgroups. They are small; there is not a lot of statistical power.

I didn't really get the point of the final diagnosis analysis actually. In clinical trials that is really very rare to do. Usually you define subgroups on the basis of characteristics that you see prior to randomization for two reasons, one, if you are treating someone you want to make a decision on information that is available there so it is important for that reason. The other reason is that if you define groups on the basis of stuff that happens after randomization they are not sure to be comparable any longer. So, I didn't really pay much attention to that actually, so I just focused on subgroup analyses using baseline variables. When I look at that I see pretty consistent rates across various subgroups.

DR. LEGGETT: Anything to add, Joan?

DR. PATTERSON: I agree with what Dr. Follmann said. As far as an important baseline covariate, it doesn't seem to bother other people on the committee but I certainly would have stratified the analysis by comparator type, the SSP group and the vancomycin group. But, again, I saw

fairly consistent results in the data that we did see that were stratified by that variable.

DR. FOLLMANN: I should mention I guess that the only thing I saw, and it sort of caught my eye, is that the success rate in terms of renal function. So, the sponsor did an analysis, on page 23, where they looked at renal function, I guess creatinine clearance greater than 80 and less than 80, and there the success rates are different between the two groups, about 57 versus 28 percent. So, if you do a statistical test of whether there is a difference in the effectiveness, it is sort of marginally significant. So, I just bring it up. I don't know whether it is biologically plausible or anything, but just looking at the numbers and looking at what rates seem similar or not, this is the only thing that caught my eye.

DR. LEGGETT: The complicating effect when I read that, of course, was people with worse renal function are sicker. Speaking about the failures or successes and the heterogeneity in this group, I think part of the problem that I was wrestling with

is because S. aureus bacteremia is heterogeneous so I don't know how we are going to get away from heterogeneity.

The other thing is that if you look at the success rates in complicated bacteremia whether or not you defined it pre or post test it looked about the same. It is only in that left-sided endocarditis that was the worrisome thing to me, not only the small N but the lousy outcome.

I think in our sort of clinical viewpoint there is not really any difference clinically, or very little difference clinically between complicated S. aureus bacteremia that you can't find the source of and something that you just know is right-sided endocarditis, which is why the drug addicts always do better than the folks with the bicuspid aortic valves who get spontaneous S. aureus. I don't know if others would concur or would debate that. Jan?

DR. PATTERSON: I would agree.

DR. LEGGETT: Anything else anyone wants to bring up? Shall we skip a break and go right to

the questions? John?

DR. BRADLEY: In 2004 the advisory committee, after a lecture by Dr. Soreth, looked at the complexity of staphylococcal bloodstream infections and the fact that it was many different diseases, all folded into one, and there was a real call to try and move forward with better diagnostic techniques, molecular diagnostic techniques and better imaging. And, I can see that the study that we are discussing now has all of these aspects which haven't been well defined, and it is one of the reasons that we are having trouble figuring out if there is one disease entity where the drugs work and one where the drugs don't work. Being able to define the disease is important.

In this particular trial, set up as a non-inferiority trial, vancomycin is admittedly not the best drug. Everyone is looking for something better. Yet, in the experimental trial design and the statistics daptomycin is not inferior to vancomycin. So, the drugs look fairly similar and, clearly, the outcomes in many of the patients are

not good and clearly we need to keep looking for better drugs. So, my observation that I am trying to share is that it is complicated. This drug looks like it is not necessarily better than vancomycin but not inferior, and there is really a need, as you had mentioned in 2004, for new even more effective therapies. So, I think that the door is still wide open for better investigations and new drugs in addition to daptomycin.

DR. LEGGETT: We also talked about hard versus soft endpoints and the thing that I struggle with and why I kept harping on persistent and relapsing, as well as the renal failure, is that they are compared to sort of try to decide which drug is non-inferior or the same but they are soft endpoints because we don't have that little magic bullet, and we don't know why a creatinine of 1.5 is not called renal failure or is called renal failure, and it is that arbitrariness and fuzziness of the diagnoses about which we are trying to make a hard decision. Steve?

DR. EBERT: A question for Dr. Boucher.

Dr. Chambers talked about his patient having a vancomycin regimen normalized the troughs of 15. In the study, did patients have their doses of vancomycin adjusted?

DR. BOUCHER: Thanks, Dr. Ebert. The vancomycin was to be administered according to the local hospital practice, and we did collect vancomycin troughs. I can share those data with you. Slide up, please.

[Slide]

So, 53 of our 115 comparator patients received vancomycin and for 44, 83 percent, of these patients we have trough levels reported and the mean trough level was 14.1. So, this is pretty good, analogous to Dr. Chambers' sort of goal of 15. Many of us would agree that that is a reasonable trough for vancomycin.

DR. EBERT: The reason I bring it up is that I was struck by the pharmacokinetic data in the sponsor's package. Although every patient received 6 mg/kg per day, the clearance in the individual patients varied by as much as 10-fold,

which obviously would translate into a very wide range of exposures which, certainly, the discussion previously notwithstanding, may have some contribution to some of the failures that we see.

DR. DRUSANO: Dr. Leggett?

DR. LEGGETT: All right, George.

DR. DRUSANO: I would just like to comment about that. Drs. Bob Nonny[?], Ambrose and I actually looked at all the daptomycin concentration time data and, while Dr. Ebert is dead on, there was a wide range somewhat related to the GFR at entry into the study, as you would expect for a renally cleared drug, I think it is important to recognize that when we went to the Bayesian step and got the Bayesian estimates and then normalized to the MIC the lowest AUC to MIC ratio that we observed in all the 99 patients that we could examine that had an outcome and AUC to MIC ratio was 711. So, I think that the vast, vast, vast majority of folks had a quite robust AUC to MIC ratio.

Questions to the Committee

DR. LEGGETT: Are you guys ready to move on to the questions or did people want to take a break? Let's go ahead. I think it will help some of the members who have to leave and it will help some of the sponsors to relax a little.

[Laughter]

Do you want to give us your rationale for why you asked us these questions?

DR. SORETH: I think they are the typical questions that we ask advisory committee members to advise us on.

Before I go through the questions, I have been told by my children that laughter or levity sometimes increases blood flow. So, since we are just at that point after lunch where there is maybe a post prandial dip in the energy curve, without asking us to stand and do a seventh inning stretch, I wanted to share a joke with the committee.

Apparently a new store opens in town. It is called "The New Husband" store. Anyone can go in and choose a mate. There are six floors with escalators going to each floor. The only rule is

once you go up you can't come down until you exit. So, a woman sees the store and she decides to go in. On the first floor is men with jobs. She thinks that is pretty interesting. She decides to go to the second floor, takes the escalator and there she finds men with jobs who love kids. This is getting interesting she thinks. So, she decides to take the escalator to the third floor. There, there are men with jobs who love kids who are good looking. My, she thinks, this is really getting good. She decides to keep going and on the fourth floor she sees men with jobs who love kids, who are really good looking and help with housework. Fantastic, she thinks. So she goes on. She presses on to the fifth floor where she sees a sign "men with jobs who love kids, who are really good looking, who help with the housework and have a deep romantic streak" My, she thinks. She takes the elevator to the sixth floor and so she goes up. She gets to the sixth floor and it is empty. And she sees a sign, "you are the 31,517,322 visitor to this floor."

[Laughter]

Now, the moral of the story may be one of many things, including beware of buildings with six floors. That is kind of an inside joke because we, at White Oak, work on the sixth floor. Or maybe another moral to the story is be careful what you ask for and, depending on your perspective, you may or may not get it.

So, now that we have increased blood flow to the brain--

DR. LEGGETT: Janice, I thought the answer was going to be there are no men like that.

[Laughter]

DR. SORETH: I leave it to the committee to decide! Which floor am I on? I have to be silent on that.

Do the data from the pivotal study provide substantial evidence of safety and efficacy of daptomycin in the treatment of S. aureus bacteremia? We would like it if in the deliberations you would include a discussion of the significance of patients with persistent or

relapsing bacteremias, and whose staphylococcal isolates had increasing MICs to daptomycin. I guess in some measure you have done that but you may have more to say.

If your response is yes, are there specific comments that you have regarding product labeling? If your response is no, what additional work would you recommend?

Then to the second question, do the data from this study provide substantial evidence of safety and efficacy of daptomycin in the treatment of patients with infective endocarditis? Please include in your deliberations a discussion of whether the efficacy results in the all-comers population with S. aureus bacteremia can be extrapolated to the subgroup with infective endocarditis. Similarly, if yes, if we could have any comments with regard to labeling. If no, then what additional work would you recommend?

Then to the third question, do you recommend additional study or studies of daptomycin in the treatment of patients with S. aureus

bacteremia, including infective endocarditis?

Lastly, what recommendations do you have for future study or studies--this is in general. Should they ever be done? Should other sponsors rise to the challenge of S. aureus bacteremia and endocarditis? Please include in your discussion of study design such issues as case definitions, specificity of diagnosis at baseline, inclusion and exclusion criteria, endpoints, etc. Thank you.

DR. LEGGETT: Regarding the first question, which is do the data provide substantial evidence of safety and efficacy for the treatment of S. aureus bacteremia, why don't I allow anybody who wants to speak up before I invoke the chair's prerogative? In talking about the discussion, I think it is important, as we have done in the past, to include not every minor little detail but at least some of the major thrusts of why you are saying yes or no. Would anyone like to start off? John, you are not usually that quiet.

DR. BRADLEY: I am a pediatrician. I don't generally take care of that many adults with

infective endocarditis. We do have kids with congenital heart disease though who get endocarditis so it is a disease that I am not too foreign to.

If I may ask you a question because you made a comment earlier that has an impact on the use of this drug should it be approved, and that is, you would reserve it for patients who fail vancomycin. In the global perspective now of where does this fit in and how is the approval going to match with clinical practice, I think those observations are important.

DR. LEGGETT: Yes, I think part of that is that you have early adopters and then you have Luddites and I am one of the Luddites. I would rather see somebody else do the learning curve for six months or a year before I adopt any new thing. I am like one of our partners, whom many of you know, who is bald!

[Laughter]

Jan, you take care of adults.

DR. PATTERSON: For question number one, I

would say yes, there is substantial evidence of safety and efficacy in the treatment of S. aureus bacteremia. Regarding the persistent or relapsing bacteremias with the isolates that have increasing MICs to daptomycin, I would say that I think these are clinically significant particularly in patients who have complicated bacteremias and certainly endocarditis.

While I question whether there is evidence to use it certainly in left-sided endocarditis and perhaps reservedly in right-sided endocarditis but even in complicated bacteremia, I think that the MICs should be monitored probably at least weekly and perhaps, you know, more frequently than that if there is evidence of persistence of bacteremia or non-clinical response. So, I would suggest that that be included in the product label. For safety, of course, there is already monitoring of the CPK and avoidance of statins if possible.

DR. LEGGETT: Alan?

DR. CROSS: Addressing just the first question on the bacteremia, not the endocarditis,

first of all, I think that the sponsors ought to be commended on really a very good study. We all have issues, but those of us who have done clinical studies have really wrestled with even how to set up a study of staphylococcal bacteremia. It is very difficult.

I think there is substantial evidence certainly of safety. In terms of the efficacy, although my first impulse in reading this was that I was shocked at how low the overall cure rate or success rate was, that was, in fact, reflected in the initial assumption based on previous studies of a 65 percent cure rate. The fact that we were even below 50 percent was a real surprise to me. Nonetheless, it was as good as current therapy and, therefore, I think that the data does support it. Furthermore, after taking care of S. aureus bacteremia for over 30 years, I am shocked to see how the situation has changed and more and more, as an ID consultant, I am asked to okay discharge of patients on vancomycin once a day without having any data at all. So, the fact that with daptomycin

we do have at least some very good data on once a day therapy is very reassuring to me.

I share Jan's concern about the rise of the MICs. I think it is clinically significant but, as I said, we have to monitor it at the bedside as we do with all patients who have serious bacteremias.

What additional studies would I recommend? I would agree with Jim that we really have to do another study and prospectively define what PRSA is and not just leave it to each individual investigator to say what he thinks is persistent bacteremia. Secondly, I think that, as Dr. Sorbello pointed out, it would be useful to have some data on what type of metastatic infections we do have with bacteremia because that often will help in deciding about the duration of bacteremia. I would remind the audience that the original recommendation for six weeks of antibiotics was not to clear the blood of the bacteremia, but it was to treat the metastatic infections. Until we have a better handle on what that is we still won't know

how long to treat these infections.

DR. LEGGETT: Go ahead.

DR. OMEL: I also feel that the drug does show efficacy. The increase in MICs and the higher rates of microbiologic failures in daptomycin are a concern. The implication, of course, is that eventually some potential resistance is going to show up but, unfortunately, that is the nature of S. aureus. Once upon a time plain penicillin G killed it. The label should state that daptomycin should be used very judiciously coupled, obviously, with good culture and sensitivity techniques just like vancomycin. I think patients should probably be switched to semisynthetic penicillins if CNS reports show sensitivity, just like we do with vancomycin also.

DR. LEGGETT: Steve?

DR. EBERT: For now I will stick with question number one and say I agree, yes, that there is substantial evidence of safety and efficacy. A lot of the comments have already been mentioned though. I will just try to point out

that I believe that if we look at our comparators, and in particular vancomycin, certainly there appears to be at least similar efficacy, if not potentially greater efficacy in some subsets here.

I am not convinced that the two drugs were on a level playing field with regards to emergence of resistance or increasing MICs. I think that that was probably scrutinized more highly for the daptomycin arm than it may have been for the vancomycin arm.

I think it also gets into these issues of when you start to see increasing MICs or failures, have we pushed the drug to its limit? Is it time, as has been mentioned earlier, for surgical intervention and something that needs to be done beyond simple medical management? Certainly, the nature of the beast here with these complex bacteremias requires more in many cases than just simple antibiotic therapy.

DR. BRADLEY: Just to summarize a few of the things that I have mentioned before and bring up one or two other things, the question is, is

there substantial evidence of safety and efficacy, and each entity that we treat, each clinical indication would have a different target that we would like to achieve. Certainly, if this was meningitis even, you know, a 70 percent efficacy would not be sufficient but, indeed, since there is nothing better and it is shown to be non-inferior, then I would answer this question only in that I wish there were something better but it certainly demonstrated equivalence--well, non-inferiority to be exact.

I think that the community-acquired MRSA is actually a different creature than the old hospital-acquired MRSA or the old garden variety community MSSA. And, I think it may well be that the natural history of clearance of that organism and complications is going to be different and that it will be tougher to treat actually. So, to have drugs to treat that will be a greater challenge.

In terms of further studies, I would encourage more investigation into the toxicity. It is very encouraging to know that the toxicity is

reversible, and the sponsor is aware of how that reversal occurs, but something to allow us, hopefully, to predict who it is that is at risk of toxicity would be very, very helpful for the clinician.

Finally, in terms of emergence of resistance, we have seen that happen with many other drugs. I think the clinical world will be cautious and that clinical recommendations from experts like Dr. Corey and Dr. Borer will help guide actual clinical use in infective endocarditis based on those sorts of issues.

DR. LEGGETT: So, I take that as a yes. Jeff, did I see your hand up? You can make comments.

DR. BORER: Well, the comments I was going to make are really more relevant to questions two and three because (b) is only appropriate here if you vote no.

DR. LEGGETT: Okay. Jan, go ahead.

DR. PATTERSON: I just wanted to add about the label that I think it should emphasize using

the appropriate dose and not under-dosing for bacteremia.

DR. LEGGETT: Dean, did you want to say something? DR. FOLLMANN: Yes, I would vote yes. I don't have much to add to what has been said already. In hearing the discussion, it seemed like it might be of interest to see how the failures who had increasing MICs were treated and, you know, what happened to them. You know, there are ideas you can get on treating those failures which, if this is out there, will inevitably occur.

DR. LEGGETT: Joan?

DR. HILTON: I also think that there is substantial evidence of safety and efficacy, and with regard to the MICs, it is my impression that they may be increasing with respect to all anti-infectives so considering daptomycin relative to others might be worthwhile, rather than just looking at it itself.

DR. LEGGETT: It appears that there is a general consensus so, rather than repeat stuff, I will just throw in some things that came up here.

Alan and John talked about the success rate seeming so low and I had exactly the same impression. I say, "oh, my God" but I think part of this is that it is the first study that we have looked at to see what these kind of numbers look like in a study like this. What I did was I took the "clinical failures" and took away the people who left and assumed that they would seek care elsewhere. If you take all those folks and take them away from failures and make them successes the numbers jive with what we feel like when we treat a patient with endocarditis, which is certainly better than 40 percent.

DR. CROSS: It is still low.

DR. LEGGETT: Still low. So, I think the consensus on question one is yes. Sorry, I didn't think you were a voter.

DR. TOWNSEND: Well, I don't have much to add. I think I would echo the sentiments of the other committee members. I think that obviously there are concerns about the persistent and relapsing bacteremia and increase in MICs, but I

don't think that it is a deal-breaker. I think that there is enough evidence to suggest that this drug is at least as good as whatever else is out there for treating these infections. So, I would say yes.

Again, as other committee members have said, I would make sure that the label states that the appropriate dose is used for this drug and that the patient be monitored very closely for evidence of persistence or relapse.

DR. LEGGETT: Any other parting shots before we move on to question two?

[No response]

Number two, do data from the study provide substantial evidence of safety and efficacy of daptomycin in the treatment of patients with infective endocarditis? Please include in your deliberations a discussion of whether the efficacy results in the all-comers population with S. aureus bacteremia can be extrapolated to the subgroup with infective endocarditis. Yes, Jeff?

DR. BORER: I would think, although

obviously I cannot vote, that the data can be extrapolated to infective endocarditis but I have to qualify that a little bit. Let me come at it a different way. For this population, the population that was studied the primary question was does this drug work in the all-comers population as it was defined and collected. The question of the efficacy for endocarditis is a secondary question and I think is confounded by the fact that the diagnosis is very difficult to make.

I would say that for infective endocarditis, as we can best make the diagnosis prospectively, yes, these data are consistent with the drug being effective in patients with endocarditis. And, I think that is the only way that it is reasonable to define the population. I think the best one can do is use the modified Duke criteria, make the diagnosis, give the drug and see what happens. This is a population at very high risk for disaster at the front end and you have to treat with something without knowing the precise diagnosis, and we have said that.

I would have to point out that the standard for comparison against which we use the Duke criteria is not the best. The best standard would be opening the patient up, looking directly at the valve, taking a piece out and sending it to the histology and bacteriology laboratories which, of course, we can't do. So, the next best thing we have is sort of clinical outcome in a sense and the echocardiogram.

Once again, just to make the point, I agree that the echo would be very specific. Dr. Sorbello, you said this and I think it would be very specific. Specificity is two negatives over two negatives plus both positives. The echo in general does not show pictures of structures that don't exist so false positives would be relatively uncommon. A test that isn't terribly sensitive, however, would not be likely to fail on the two negatives over two negatives part. So, the specificity would be relatively high. I would expect it would be quite high. It is the sensitivity that is the problem because we don't

know what the target is. We actually don't have the anatomic information about the target we should be looking for with echo, but the spatial resolution of the technique necessitates that it must have limited sensitivity.

So, I think that to use the echo as the standard of comparison and say, well, the Duke criteria were wrong because the echo didn't show something after we treated the patients is not the appropriate approach. The appropriate approach is to use the best criteria we have to make the diagnosis and see what happens. And, I think if you look at these data, they show that the drug works when the data are looked at that way.

Now, the issue of left-sided infective endocarditis is a problem but even there--and the numbers are very small obviously and this drug didn't really do any worse than the comparator so far as we can tell, but I would make another point here. There was a difference--small numbers but a difference nominally between the outcome at the end of therapy and the outcome at time of cure testing.

I think that is important to consider before suggesting that this drug or the comparator, which didn't do any better, shouldn't be used in people with left-sided endocarditis where, in fact, one of the hopes is sterilizing or semi-sterilizing or doing the best you can do with the infected valve before you take the patient to surgery.

In fact, as I recall, the majority of patients with left-sided endocarditis by the front end diagnosis actually did have a success at end of therapy, which is the time by which patients might well be sent to surgery. That is a good thing. So, I don't think that it would be necessary to be so terribly pessimistic about the use of the drug in left-sided endocarditis. Moreover, I would suggest that the label can be written such that it is made clear to prescribers what is known and what is not known; what data exist and what don't exist about left-sided endocarditis. I don't think that is an approvability issue. I think that is an instructions for use issue.

So, my analysis to the second question

would be that there is substantial evidence of efficacy and acceptable safety for the intended use of daptomycin in treatment of people with infective endocarditis, and that the data can be extrapolated to the subgroup of infective endocarditis using the best tools for diagnosis that we now have.

DR. LEGGETT: Greg?

DR. TOWNSEND: I think the short answer to the question is that, for me, the data don't provide substantial evidence that this is a drug that is effective and efficacious in the treatment of infective endocarditis. I think the problem is not with the drug really. I think the problem is with the study. I think the study was probably as best as can be done in the circumstances but, you know, there aren't enough total numbers in the study. Then if you try and break it down to the subgroups and analyze them--and I think it is important to try and do that because right-sided and left-sided endocarditis are different beasts--then, you know, you are talking about vanishingly small numbers.

So, to me, there aren't enough data; there aren't enough data points in the study to say that this drug is, indeed, at least efficacious. It is safe probably. And, I would not use extrapolated data from the all-comers population because, again, I think that S. aureus endocarditis and S. aureus bacteremia are not equivalent and I wouldn't try to extrapolate data from the bacteremia population, especially when you are talking about bacteremias that may be coming from primary sources, and use that to determine whether or not this drug is effective in treating endocarditis. So, my answer to the question would be no but, again, I think it is not a problem with the drug; it is with the study.

DR. LEGGETT: Joan?

DR. HILTON: I am concerned in the infective endocarditis patients about how low the control response rates are, coupled with the 20 percent non-inferiority margin. So, I can't justify a 20 percent non-inferiority margin when, for example, in the left group the control response

rate is 22 percent. So, I didn't find that margin well justified. So, I think that the answer would be no in this subgroup, and one of the particular problems is that the control response rate varies dramatically by these diagnostic subgroups.

You know, for future studies more should be done to investigate who the candidates are for success, rather than assuming a 65 percent response rate in the controls and then actually getting something a lot closer to 45 percent. That should be nailed down. If the margin is going to be based on the end of therapy endpoint, then that is a different margin than should be used for the test of cure endpoint. So, those two should match up.

DR. LEGGETT: Jim, do you have something?

DR. OMEL: I think the real concern comes down to the initial presentation of the patient. At presentation you just find it very difficult to come up with a diagnosis to put patients in these subcategories into a study. The fact that the echoes showed such variance also makes it obvious that diagnosis itself is difficult. Despite these

obvious diagnostic difficulties though, the study really does show efficacy compared to comparator.

I would remind us to look at the sponsor's page 40 in which they indicated that for infective endocarditis the adjudication committee itself indicated 45 percent effectiveness with daptomycin versus 40 percent with the comparator. The success rate is certainly as good as vancomycin, if not a bit better, on this particular graph. I would think that vancomycin itself would have a harder time passing some of the hurdles that we are asking this drug to pass. I would vote, yes, I think that the efficacy in infective endocarditis is just as good as the comparator from what we have seen, even though the numbers, granted, aren't as good as we would like them to be.

DR. LEGGETT: So, that is a yes. Alan?

DR. CROSS: I don't think that there is enough evidence to say that it is effective in endocarditis, and that is because primarily the numbers are too small. On the other hand, this really isn't a problem for me because I think there

is evidence that it is efficacious in complicated bacteremia which I treat like endocarditis. So, I think if one has on the label that it is useful for complicated and uncomplicated bacteremia I don't think we have to argue beyond the numbers. The problem with arguing beyond the numbers is just what we saw at the outset. I mean, the first comment was that imipenem was approved on the basis of 11 patients and I would hate to have the data later impugned or to have me defend the efficacy for endocarditis based on the numbers that we have here. As I say, I think it is not necessary.

The other thing, which we haven't talked about, is how echoes are actually used. In our hospital, and I assume it is true in lots of hospitals, folks have transthoracic echoes rather than TEEs. In a published study, done at our institution by Mary Claire Robin, she found out that the initial therapy was rarely changed based on the results of echoes, and the choice and duration of therapy was based primarily on what the bias was at the outset even before the echo study

was done.

Finally, just given the difficulties in this very well controlled and very well done study on differences between local echoes and what was found centrally, even allowing for wider interpretation of abnormalities done centrally, I think that it would be very difficult to make a diagnosis of endocarditis and then show that the daptomycin is efficacious. So as I said, finally, having said that it works for complicated bacteremia for me is sufficient.

DR. LEGGETT: So, that is yes.

DR. LEGGETT: It is a no.

DR. LEGGETT: Oh, it is a no? Okay.

DR. CROSS: It is a no for endocarditis but it is a yes if we have complicated bacteremia.

DR. LEGGETT: Got you!

DR. GOLDBERGER: Dr. Leggett, it would be helpful, as committee members talk about this issue, if they would try to be a little more specific in giving us some advice, and some already have, about what should be said in the labeling

about endocarditis. There are a variety of choices. We could say nothing. You know, just say for complicated bacteremia. That, of course, doesn't provide much information, such as there is, to treating physicians. We could, for instance, say that it has not been studied or there has not been demonstrated safety and efficacy, although people sometimes don't understand whether that means it was never studied or the studies didn't show safety and efficacy. We could say it was contraindicated in bacterial endocarditis. Or, we could say something along the lines of there is limited experience in patients with bacterial endocarditis. Response rates for daptomycin--this is just off the top of my had--and comparator were low, and if the drug is used it should be used with frequent monitoring, etc. So, there is a range of things we could say. It would be helpful to get an idea what committee members think.

Now, I realize it is a little difficult for you because, for instance, the latter choice almost, in fact, does provide an indication for

endocarditis at the same time that it provides significant caveats. But, you know, we want to know what you think about what we should say or not say in the label because, as Dr. Borer said, it is, one way or the other, some way of providing information for clinicians who will be out there using this product and who will not have had the benefit of sitting here all day hearing a lot of information in great detail.

DR. LEGGETT: Thanks, Mark. Why don't we catch up before we go forward? Greg?

DR. TOWNSEND: I think I would say what is true, which is sort of along the lines of what your last statement was, that this drug has been studied; it has been demonstrated to be at least as safe and efficacious as the standard of care, but with limited experience definitive recommendations cannot be made. And, if it is to be used in the treatment of infective endocarditis the patient should be monitored very carefully for treatment failures.

DR. LEGGETT: Jim, I thought I did hear

you say something about labeling.

DR. OMEL: Yes, I indicated that the label should state that daptomycin should be used very judiciously, just like we use vancomycin, and that patients should be switched over to a semisynthetic penicillin if a CNS reports sensitivity.

DR. LEGGETT: Alan, any further statements that should be made? I haven't heard anybody say contraindicated yet, but I am not saying that you should.

DR. CROSS: No, I am comfortable with the statement that there is limited experience in the treatment of infective endocarditis, and just leave it at that if that satisfies the thrust of this.

DR. LEGGETT: Joan, anything?

DR. HILTON: No.

DR. LEGGETT: Steve?

DR. EBERT: Again, I think a lot of this hinges on the diagnosis and whether you are making it at the time of selection of therapy as opposed to at the end of therapy or later on. I feel comfortable saying yes if you are going to use the

Duke criteria to initiate therapy being either definite or possible endocarditis based on modified Duke criteria.

I think the caveat may be, as Dr. Borer mentioned, that if you have very clear evidence that you are dealing with left-sided endocarditis and presence of a vegetation, then I think that the clinician needs to be cautioned that, first of all, there is very limited data available regarding efficacy and, secondly, that the data is not that great with regards to its efficacy. So, that is probably something that needs to be included in the labeling as well.

DR. LEGGETT: Dean?

DR. FOLLMANN: I am going to answer yes to this question. The only way I can define infective endocarditis is based on what you have at baseline, and that was given in table 14 and was suggested by Dr. Omel. We see very similar rates of success across IE and not IE compared to comparator. So, you know, what happens on down the road; what might happen if we could do a biopsy--you know, that is

not going to be available when we have to make a decision so I don't really get the question. You are saying, you know, what would happen in something that would be very difficult to know--say, biopsy confirmed endocarditis. So, I would say yes. You know, the caveat would be you prescribe according to the criteria, I guess the Duke criteria that made that table.

DR. LEGGETT: Jan?

DR. PATTERSON: Well, as has already been discussed, it hinges on whether you define your population for infective endocarditis as the entry diagnosis or the final diagnosis. In terms of this study, I think it is fair to say, you know, the entry diagnosis in daptomycin was not inferior.

My problem with that is that if you say it is not inferior for the treatment of infective endocarditis and then you put in the label that it has an indication for endocarditis the average clinician, in reading that, is not going to, I think, read the fine print about the difficulties in interpreting that, and that of the 75 percent of

patients that entered the study with a definition of endocarditis in the final diagnosis only 25 percent actually were defined as having that, and there was really just one patient with left-sided endocarditis treated successfully with daptomycin and that was in combination with gentamicin. That would really bother me in terms of having that as an indication for endocarditis.

So, my suggestion--well, I would vote no and my suggestion would be, however, in the label to say that it has been studied and that it is not inferior to the comparator in a study for S. aureus endocarditis where the entry diagnosis was the Duke criteria for endocarditis. But I agree with Alan that complicated S. aureus bacteremia is similar I think to right-sided endocarditis, and I think that many of those possible infective endocarditis cases fit in that category. That I think would suffice for me in terms of where this drug should fit, complicated or uncomplicated S. aureus bacteremia.

I would also include in the label not only the things that we said before about monitoring the

MIC for complicated bacteremia and appropriate dosing, but also that adjunctive therapy for complicated bacteremia in terms of drainage and so forth, should be used in combination with the medical therapy.

DR. LEGGETT: John?

DR. BRADLEY: I have a question of Drs. Goldberger and Soreth before I give an answer, and it goes back to the subtle differences between approving a drug as safe and effective for an indication and having a sponsor do a clinical trial, a non-inferiority trial. On table 15 of the sponsor's background package, the success rate in left-sided infective endocarditis with daptomycin was 11 percent. I don't think anyone would say that is effective therapy. However, there is not much that we have that is better. If you lump it in with all the other cases of infective endocarditis, it was not inferior.

So, I have two answers. It is not effective but it is not non-inferior. Can you tell me which answer you want me to give you?

[Laughter]

DR. LEGGETT: Luckily, you just gave them both.

DR. BRADLEY: Seriously. I am putting them on the spot.

DR. GOLDBERGER: You know, I could respond by saying that is why we pay you the big bucks to come here--

[Laughter]

--but anybody who knows how much you get paid would realize what a joke that is! I think that in a way I tried to transfer some of our problem to you a few moments ago by asking what we should say in the label. I think, you know, the indication and what we say in the label is going to have to be some sort of merging here. You know, when we start talking a lot about how it was studied; it was similar to comparator; the overall response rates were not very good, that is truthfully almost a de facto indication. I want to make that clear to everybody. The alternatives are to contraindicate it or say nothing. Certainly

saying nothing is very unattractive. I am not sure that people believe strongly enough to say it should be contraindicated because that puts treating physicians in a difficult position as to whether they can use it.

We are almost asking you, I suppose, at one level to synthesize--and part of one of the questions goes to this--all the available information to come up with a final conclusion of what your overall gestalt is. Although we are having a vote on the question, I think realistically at the same time we are also asking you more generally for what will go in the labeling. It is going to be on the edge about whether this is a true indication or simply described as part of complicated bacteremia. How we are going to handle it really depends on sort of the strength of people's feelings here on the committee.

So, we are trying to put you on the spot a little. I was actually going to wait till all the committee members had finished voting. Since we do

have Dr. Corey here who has spent much of his life studying this, once all of you were done so you couldn't be biased by what he said, I was going to ask Dr. Leggett if we could have Dr. Corey come up and say how he would recommend that such a product be labeled and the advice he would give to clinicians who would, you know, actually have to make decisions. So, I would like to have the company's consultants sometimes earn the money they get, which is a touch more than the advisory committee members.

[Laughter]

But I don't know if that helps you, you know, right now in terms of what we are asking you to do.

DR. BRADLEY: It helps.

DR. GOLDBERGER: I mean, you know, the answer that was given a little while ago when we asked about what kind of number nine is and the answer was it is a small number--I mean, you know, that is part of the issue here. But we also recognize that as controlled clinical trials go in

this area, this is the first that I guess has been done in over two decades. It is three times the size of the last one to be done. So, you know, it does have small numbers but it isn't as though there wasn't a major effort. So, to get the kind of numbers everybody would like with the heterogeneity, it would probably have to be three-fold more than what this is which would be really an enormous undertaking.

DR. BRADLEY: Right, and to say that it is not effective in endocarditis, knowing that there is nothing that is more effective, would also penalize this particular drug and the whole investigation program. So, I would vote yes.

DR. LEGGETT: Any comments about any caveats or anything?

DR. BRADLEY: No, the whole idea is that the label needs to say that overall the effectiveness is 44 percent and let people know that it is not greater, and that that is based on small numbers and a mixture of different clinical entities--if that is all available, then that is

what I would request.

DR. LEGGETT: My comments go along the lines of everybody else, in other words, in all sorts of directions. The way I understand things, if the trial is set up as an all-comers that is how it goes down from our committee's point of view, however much we are worried about subgroup analyses. So, of course, people with uncomplicated bacteremia can't be extrapolated to left-sided endocarditis but I think that people with right-sided endocarditis are pretty much the same as are complicated bacteremias because we don't usually get those so I don't even know. But I know that they all get treated for four to six weeks. Since the treatment is the same I don't really care.

The other thing I would like to point out is that the sponsor noted that 25 percent of off-label use right now is for bacteremia at the 4 mg/kg. I would like to at least have it out there that we should be using 6 mg/kg if you have bugs in your bloodstream. So, I think that would be

another reason that I would sort of say yes to this.

I guess in terms of further studies--I will jump ahead here so I don't forget, one thing that might be done is a smaller trial with those folks who just happen to turn up with a positive echo. I don't think it would have to be a huge trial because you have a real hard endpoint there. You know that you have a positive bloodstream and a positive echo and you might be able to get a much smaller trial, even though it might take some while to do. The company could come to our place and we could give them a lot and I am sure they could go to San Francisco and get a lot pretty easily.

Finally, the one caveat I would probably say as strongly as you could is that there is very limited data and frequent monitoring would be necessary for anyone who was thought to possibly have left-sided endocarditis. But, to me, there is almost as much danger from discitis and epidural abscess in paraplegia as there is from somebody failing their heart valve and needing a new

artificial valve. At least in my experience that happens just as often. Go ahead.

DR. BORER: I would certainly agree with Jim's suggestion about a small trial, but if we are moving on to this next question here I think there is something else that should be done. Setting up a randomized trial in this area obviously is very, very difficult and I don't think that that by itself will answer some of the questions that need to be answered here. I think what is necessary, in addition to whatever trial is done, small trial or whatever, is a registry but a specific kind of registry where consecutive patients are entered. That would be something the sponsor would need to set up. The FDA would have to ask the sponsor to do it and the sponsor would have to agree, and all those legalistic things that we all know about. But I think the key point is that we need to know more about the relation of outcome, of clinical outcome, bacteriologic outcome to the MICs with this drug and to the isolate genotype, and that a registry of sufficient size to provide absolute

point estimates that could be used to improve the label and inform clinicians would be very, very useful.

I think it would be easier to do that, a lot easier, than to mandate another randomized trial with all the problems that are involved, and it would provide a more real-world estimate of what is going on than we have from the randomized trial data with all the inclusion and exclusion criteria that are necessarily involved with that. So, I wouldn't in any way disagree with Jim's suggestion but, over and above that and separate from it, I think that this is something that is necessary.

DR. LEGGETT: Thanks. This is jumping back to question two because I had too many scribbled notes. One of the things that the FDA might sort of look at, there was this table of all the possible infective endocarditis with all the different possibilities in different boxes--you know, three of this and none of that. It might be worthwhile in your sort of deliberating about what you want to do to go back and look at the

distribution of the possible infectiove endocarditis that went back to complicated bacteremia from each of those boxes. That might be a way to improve on the modified Duke criteria by figuring out from this trial which of those things work well. I understand there are other trials much bigger than this but it might be an opportunity to at least get some numbers about where all those folks are coming back that were thought to be possibly endocarditis that were adjudicated as not having that at the end. Sorry about that interruption.

Anybody have any comments about question three? Do you recommend additional studies of daptomycin in the treatment of patients with S. aureus bacteremia, including infective endocarditis? Good, Steve, because I was just going to comment that we didn't have any ideas.

DR. EBERT: I apologize if this is out of order, but I guess my other question, whether this is for the company or for the panel, would be whether there is a need to pursue treatment of

other causes for endocarditis, for example enterococcal endocarditis. I could see many clinicians extrapolating these recommendations to other pathogens and maybe that is appropriate and maybe it is not. But I would think somewhere along the line that might also be an appropriate study to perform.

DR. LEGGETT: Jan?

DR. PATTERSON: I think it would be of interest to look at gentamicin in combination for some of the serious S. aureus infections.

DR. LEGGETT: You mean longer than four days?

DR. PATTERSON: Well, at least four days but perhaps longer than four days.

DR. LEGGETT: Alan?

DR. CROSS: Actually, I was just shocked that even what seems to be a very short exposure to gentamicin at a low dose may have had a huge impact on the renal toxicity. So, I think at some point that has to be studied. I don't know whether it ought to be required with daptomycin.

DR. LEGGETT: Certainly with vancomycin we did that for a while. Dean, any comments from a statistical point of view about things we should worry about for further studies?

DR. FOLLMANN: I didn't think there would be additional studies needed. My answer to three would be no. I thought the evidence was pretty strong here. I have comments on four if we get to that.

DR. LEGGETT: Does anyone else have any comments? If we vote yes or no on three, is that helpful? I mean, the ideas are the things that count unless you need it for some sort of FDA reason.

DR. SORETH: As I sat and took notes, I think you have pretty much accounted for it individually as you made your comments, unless the team has any comments that they want to make.

DR. LEGGETT: Okay, question four, what recommendations do you have for future studies of S. aureus bacteremia and endocarditis? Please include in your discussion study design issues such

as case definition, specificity of diagnosis at baseline, inclusion and exclusion criteria and endpoints. John?

DR. BRADLEY: I briefly mentioned it before but I think community-acquired MRSA should be analyzed as a separate group compared to MSSA.

DR. LEGGETT: Of course, as it is mutating and picking up more and more MICs that is going to be harder and harder to figure out.

DR. BRADLEY: Well, then maybe we will say PVL positive.

DR. LEGGETT: Dean?

DR. FOLLMANN: Yes, I have some comments about trial design. I guess the theme that I have had earlier is, you know, that diagnostic groups should be made using baseline data so in future that is what I would focus my efforts on. I wouldn't worry about the final diagnosis groups. To get better diagnostic groups at baseline maybe you could wait a day or two to get the echo on everyone before you randomize. I don't know the particulars of how you would do it necessarily but

it is just important to make these groups using baseline data.

Another thing I noticed in this study--I am more familiar with studies where you have a time of randomization and then two months later or 12 weeks later you measure people and say are they successes or not, so there is a fixed time of evaluation which is the same for everybody. That is not the case in these studies apparently where you wait until therapy is over and then you start the clock ticking so you have different evaluation times effectively for different people. So, I fear that that can cause a bias. In particular, in this study there was, I believe, for right infective endocarditis a described or suggested treatment time of 14-28 days which was different in the comparator arm, I believe, of 14-42 days. So, one group is being followed longer for risk of death, etc., and it is just an unfair way to compare the groups. I don't think it caused a real problem here but from first principles you want to have a fair endpoint for the two groups. So, I would

suggest you are look at, like, 12 weeks past randomization or something like that, and not have it be defined at therapy or patient response. I think intention to treat should be the primary analysis and I would have included those 10 or 11 failures that were not included for different reasons in the sponsor's analysis.

So, this was an unblinded study. I don't know if consideration was given to blinding. I know it would be more difficult. So, it is a trade-off I guess between the difficulty of blinding and this concern we have, or would have sitting around this table with how could an unblinded study here mess things up. I can think of two particular ways that an unblinded study caused me some worry. One was that basically an investigator can define anyone to be a failure, let's say. You know, I am going to put him on a pen. or, you know, a non-authorized antibiotic and that patient is a failure. He knows whether he is going to get the comparator or daptomycin and so you just want to rule out that possibility.

Another concern had to do with the treatment-limiting toxicity, which was another form of failure. Once again, in an unblinded study you worry that knowledge of the antibiotic or the treatment that people are getting might cause you to have your threshold for toxicity be different or bigger. You know, that is why we do blinded studies, not because investigators are going to cheat or be dishonest but they might have an unconscious predilection towards doing something that would be unfair between the two groups. I think that is it. Those were the main comments that I had.

DR. LEGGETT: Alan?

DR. CROSS: Well, as I said earlier, one issue would be perhaps to get a better handle on the PRSAs by actually having an up-front definition of what that is so we know how important a problem it is.

The second is one other piece of data which we haven't mentioned. If you look at table 18 in the sponsor's background package, it is the

importance really of the length of therapy, even in relatively uncomplicated bacteremia, having therapy for 14-27 days has a better outcome than 1-13 days. Now, in some of the presentations we had earlier the standard of care, at least as present in Victor Hugh's study, was up to 14 days but, yet, what we have in this is treatment for 1-13 days and then we have a large group of 14-27 days. I think it would be helpful to know whether or not there is any difference between two weeks and three weeks, especially when you look at the really huge differences even, as I mentioned, in uncomplicated bacteremia between short therapy and much longer therapy. That always is an issue that comes up as far as how long do we have to treat, and even more so as outpatient therapy progresses.

DR. LEGGETT: Steve, did I see your hand up?

DR. EBERT: Probably not, but just to maybe add a couple of issues, I noted that in this study there were some contraindications of prosthetic valve, intravascular, arterials. Again,

I see those as clinical questions that are going to come up and at some point to include a population of patients that would have those risk factors as well I think would be useful for clinicians.

DR. LEGGETT: We also talked about that in 2004 and I can see that coming up not only for intravascular things but hips and knees. Jim, did you have anything?

DR. OMEL: Of all the questions, this is the hardest and it is difficult to come up with a good study design. Remember that the sponsor actually worked with the FDA to try to design this study. One of the major dividers of any study should really be MRSA and methicillin-sensitive S. aureus. As clinicians, we really have extra concern when we have that methicillin-resistance to contend with. So, I think in any study design there should be a differentiation between those two as one of the main headings.

DR. LEGGETT: Thank you. Jan?

DR. PATTERSON: I agree with a couple of the points that have been made already, especially

about excluding the community onset MRSAs as a separate group because that is really a different disease, different kind of clinical presentation, virulence and so forth. And, also define the groups better at baseline. I think the problems with the congruence with the echoes, and so forth, was really a difficulty in this study. Then, finally, looking at the MICs prospectively. I know that it is an issue. It would be helpful in future studies to have that data prospectively rather than retrospectively.

DR. LEGGETT: Any other comments? Would anyone from the sponsor like to say anything to the committee or to the FDA about any of these issues, especially these latter ones about further trials?

DR. BOUCHER: Maybe I will ask Dr. Corey if he wants to discuss this because he was very involved in a lot of aspects of the execution of the trial and does a lot of clinical trials in S. aureus.

DR. COREY: Thanks. I really appreciate this opportunity. I have been struck by how

thoughtful the advisory committee has been. You have taught me a lot. Before we get to future trials, I think the key question for me is do I feel comfortable in taking a patient who comes in that I think is pretty sick and probably has complicated bacteremia and putting him on daptomycin, knowing that I have a significant chance of him having endocarditis. And, the answer is yes.

When I find that he has left-sided endocarditis, do I want to continue him on that drug? If it is MRSA I would say yes. If it is MSSA I would say no, I would switch drugs. That is my feeling about this right now and I think, you know, right-sided endocarditis, to me, is sort of endocarditis for beginners.

[Laughter]

It is like going to Brazil instead of Africa when you go overseas and work. It is easy. They don't die and the left-sided die. Dr. Karchmer and I were talking and the failure rate for vancomycin left-sided endocarditis is abysmal

for MRSA and we don't have much to lose with that group but I think we do with the MSSA. So, that is how I feel about how I would use it. I feel comfortable using it just the way you all thought about it.

Future trials are tough, tough to design. My wife is an echocardiographer so I hear about how stupid ID guys are all the time in diagnosing endocarditis. She actually wrote the modified criteria so I quote her a lot. But I think as we are setting up at home echo reads, it is going to be great at midnight when they call up and say we want an instant echo read now. You can do that in a trial. Now that we have the electronics to allow us to do this, you can do that in a trial and transmit that so you don't have this disparity between the core lab reading that comes out after the trial is done and the local lab reading that you have to deal with now. Truthfully, having looked at a bunch of these echoes, they are frankly wrong. They missed major things that you would have taken a patient to surgery for. I think that

is the use of the echo. To me, it is less to find the disease but it is to define what other treatment I am going to do.

Finally, I think the idea that we are looking for metastatic foci is tough. The guys in Marseilles did this in a whole bunch of patients. They did total body scans, total body CTs or MRIs. Can we get that through an IRB? Is that logical to do? Is that incredibly expensive? That would be ideal but I am not sure we could functionally do that. So, I appreciate the great thoughts of the committee. DR. LEGGETT: Could Cubist could afford it?

DR. COREY: I don't think I could.

DR. VIGLIANI: I would like to ask Dr. Frank Talley, our chief scientific officer, if he wants to make a comment for the company about future trials.

DR. TALLEY: Cubist has a long, I think productive relationship with FDA in trying to approach the use of this drug for unmet medical needs and trying to design studies to try and

answer those. I think the study that we have talked about all day today points to that collaboration in moving forward. It was a tremendously difficult study to do. We were able to enroll the biggest study and we plan to move forward to try and answer the questions. I don't think we have completely finished our analyses, as was evident today with the presentations. We will continue to do that with the FDA, looking toward the label as was talked about.

Cubist continues to try and look at other areas of unmet medical need and is in constant contact with both the FDA and regulatory bodies in Europe to try and design studies for these unmet medical needs. As you have heard, these are difficult, complex studies which take a long period of time and huge resources so we have to do that very carefully. We will be thinking about how to explain the label for this drug in the future and look forward to continue working with these regulatory bodies. Thank you.

DR. LEGGETT: Any final requests from the

FDA, Mark or Janice?

DR. SORETH: No, I don't have anything.

DR. LEGGETT: Great! For the first time in my experience we finished ahead of time. Thank you.

[Whereupon, at 3:55 p.m., the proceedings were adjourned.]

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