But I say this with the understanding, that I think that risk can be managed for this. I mean, I'm not giving this an emphatic no. But at the same time I would have liked to see some better superiority over other things, because there are a lot of other things that can address this issue as well. So, looking at risk benefit ratio that's what conclusion I came to.

DR. RELLER: Dr. Alston.

DR. ALSTON: I voted yes because I think Vancomycin is sort of a dying drug. And in clinical practice I see Vancomycin failures all the time. And if this is son of Vancomycin and an improved Vancomycin within the same class with manageable toxicities, at least the nephrotoxicity is something we can easily detect and should be reversible, and hopefully we can keep it away from pregnant women, then I thought it justified voting yes.

DR. RELLER: Dr. Goetz.

DR. GOETZ: I essentially agree with Dr. Alston's comments. While there are clearly concerns about the drug in persons with impaired renal function, I think that's a manageable risk that we can provide

 

providers with warnings in regards, similarly in regards to pregnancy and prolongation of QTc.

DR. RELLER: Dr. Fleming.

DR. FLEMING: Well, I've long thought that it's -- I have concerns that Advisory Committee members vote. I don't think it's our role. I think our role should be providing advice to the agency about what the issues are that they need to carefully consider as they decide. We are advisory. You decide. And these are situations where I find it really difficult. A yes, no vote isn't going to capture the essence.

I voted yes. But there are major issues here. The strength of what I see is that we have two trials where, when we focused on patients with wound and ulcer infections, and cellulitis, and erysipelas leaving out the sub two abscess patients, we are in those trials hitting the margin of 10 percent. I think it's a suboptimal endpoint and suboptimal timing. I prefer the type of endpoint that was advocated and discussed in the IDSA document. And I'm concerned about the timing of this as a time point where we don't have as much evidence to justify the noninferiority margin. But all things

 

considered, I accepted that this was establishing efficacy.

The nonMRSA patients fortunately are not distinctly different from the MRSA patients in terms of their affect. When the -- you have a relatively neutral result, if the MRSA was a lot better, then the nonMRSA would be a lot worse, then I would have trouble having the indication be brought in an MRSA. But in this setting it doesn't seem to be that much of an effect modifier. So, I can see it being inclusive to those patients.

But the 10 percent margin, as we were discussing, is very substantially influenced by managing the safety profile. And, so, my question to you, Ed, was specifically setting up my justification for voting yes, which was that I'm making an assumption -- and it's -- I'm always a little uneasy about this assumption -- but I'm making an assumption that we're going to be able to identify the patients that -- in which the risks would outweigh the potential benefit when you consider the other options that patients would have with other agents that are available here.

 

So, with renal toxicity there's a substantial increase in SAEs. There's a substantial increase in discontinuations for renal events due to SAEs. There are eight versus one patients that had death as the outcome where there had been renal insufficiency or renal failure in advance. Three of them called related. It's always hard to know what's related and what isn't, but there were three such cases in the Telavancin group and none in the Vancomycin. This is a substantial issue. And there needs to be management of patient selection based on this issue.

The sponsor had talked about focusing on identifying patients with comorbidities as being problematic. Both the FDA and sponsor's analyses also point out that patients with baseline clearance less than 50 ML, and particularly less than 30 ML, seem to have a much less favorable benefit to risk profile.

Regarding QTc prolongation, it's been -- the sponsor identified that the target areas to exclude would be known prolonged QT interval, uncompensated heart failure, and severe left ventricular hypertrophy. And then we will come in the second question to dealing with

 

this issue of pregnancy.

So, under the assumptions that we're right about being able to characterize where these risks are, and that we can manage the use of this agent to avoid its use where it's unfavorable benefit to risk based on that insight, it seemed to me that under that condition, benefit to risk could be judged to be favorable to justify a yes.

DR. RELLER: Dr. Leggett.

DR. LEGGETT: I voted yes, because I think that -- to keep things brief -- the efficacy definitely was established and across a wide enough range that I was satisfied that it existed. And I think that the toxicity such as it -- such as it is manageable.

Addressing the renal thing just -- in this -- sort of -- I would like to keep this in the context of our current drugs, that would be alternatives on neither of the other -- for Gram-positive drugs or without their problems.

And in terms of the nephrotoxicity, you know, aminoglycosides have lots more known toxicity and has lots of alternatives, and yet we keep them around. And

 

there's a reason. And I can foresee the same thing occurring with Telavancin. And I won't -- I'll address the pregnancy issue later.

DR. RELLER: Dr. Bennett.

DR. BENNETT: I voted yes. I thought the toxicity is manageable. We're used to seeing bone loss oppression with Linezolid, rhabdomyolysis with Daptomycin, striking clinical failures with Vancomycin. So, we're dealing with the problems. And I think the drug that we're looking at, Telavancin here, has enough to offer with manageable toxicities that we should approve it.

Now, what about the patients in the subgroup analysis who had decreased renal function less than 50, particularly less than 30? It's been pointed out. I have some concern about multiple subgroup analyses. As soon as you start breaking down things into multiple subgroups, you go -- you find phenomena that don't make sense. Maybe someday this will make sense, but at the moment I can't make sense out of it. And I think it's just a signal we have to look for, but I don't believe that we should then reject the drug just based upon that

subgroup.

DR. RELLER: Dr. Lesar.

DR. LESAR: I voted yes. Again, I echo the other previous comments.

One additional thing is the statement made to the QTc and the warnings, and that the operationalization of warnings related to use with other drugs that prolong QTc is extremely difficult in a clinical study. And I'll just throw that out as a comment.

DR. RELLER: Dr. Nelson.

DR. NELSON: I voted yes. And I think what I feel has been captured already.

DR. RELLER: Dr. Septimus.

DR. SEPTIMUS: I voted no. And actually I agree with a lot of the statements that Dr. Katona made. I think there are other agents that are out there, and some agents in development, which is very different from Gram-negative organism, which is a different topic. But I was disturbed a little bit about the decreased efficacy with some of the sicker patients. Those people had decreased renal function, and those people had certain underlying diseases, the exact place where I might want a

 

drug that was more efficacious than Vancomycin.

And then weighing the toxicity. I really could have gone either way, but I think those are the issues that made me slant towards no rather than yes. But I do think the toxicities, though, can be managed.

DR. RELLER: Dr. Mirkes. And as we go around the room, if anyone has recommendations about postmarketing studies to further evaluate toxicity, which was part of this question, please, comment on those.

DR. MIRKES: Yes. I also voted yes having listened for the past day and a half to a lot of information, which convinces me that the drug certainly is efficacious. And in terms of the toxicity, I didn't hear anything that would have forced me to vote no. And I will comment more specifically on developmental tox issues, with regard to question two.

DR. RELLER: Dr. Paganini.

DR. PAGANINI: I actually voted yes as well. I believe that there should be a labeling that warns about potential AKI. One of the things that I really keyed in on was the AT group with a lower 95 percent value that was way away from the 10 percent that we were

 

considering. It was more along the lines of 5 percent. So, I thought that was reasonable.

In other words, you altered -- they fortuitously altered their 95 percent low, 95 percent, which was far away from the line of 10 percent that everybody was concerned about. So, I think that fulfilled my need to have a little bit tighter. But I do believe that there needs to be warning on the label for folks with CKD, and the fact that there is a higher instance of problems with that group.

And as far as postmarketing studies, I think close attention to renal function is extremely important as you are giving the drug. And that would be the only thing I would ask and add.

DR. RELLER: Dr. Smith.

DR. SMITH: I voted yes. And I think the growing problem with resistance to these drugs is really important and played a big part in my decision. I also think, as a toxicologist, there are no completely safe drugs, and I think the risk can be managed.

DR. RELLER: Dr. Shelby.

DR. SHELBY: I voted yes, perhaps a little

 

reluctantly. I mean, it looks like it's got efficacy similar to Vancomycin. It's got some separate problems that didn't exist there.

The developmental tox studies raise some concern in my mind. At the same time I'm not convinced by them. At the same time I can't dismiss the results there. But I think the risk there and elsewhere can be managed if properly dosed.

DR. RELLER: Dr. Kopp.

DR. KOPP: I voted yes. In terms of the benefits, I'll echo some of the comments that were made before, that the overall efficacy seemed, if anything, slightly greater than Vancomycin. And as Dr. Paganini commented, the 95 percent confidence interval stayed well away from the minus 10 percent margin.

I did have some thoughts about managing the nephrotoxicity. One is that all of our data was MLs -- GFR expresses MLs per minute from a creatinine clearance. But I think more and more of our laboratories are reporting using the so-called MDRD or Levey equation, MLs per minute, per once .73 meters square. And it makes a difference. Some of our patients are at the BSA of

 

1.5, some have a BSA of 2.5. And bigger people need bigger renal function to clear a larger plasma volume and to excrete toxic waste coming from muscle. So, I think it would be much more appropriate for the FDA to consider dosing intervals, or dosing guidelines, adjusted to 1.73 meters squared. So, that was one point.

Another is, I would agree with a warning. I don't know if it rises to the status of black box warning or another warning, listing not just CKD, but also some of the other risk factors that held up in the multivariable analysis. We didn't hear exactly what those are from the sponsor, but I'm sure they can supply them and presumably include hypovolemia, sepsis, diabetes, pre-existing hypertension and so forth.

Another would be some thought to giving -- stopping rules for rising creatinine. Although I'll have to say that has to be individualized. But I think in general in the nephrology service we get nervous when we see a rising creatinine by 50 percent and somebody receiving a nephrotoxic drug, realizing that typically nephrotoxins work in a multifactorial context, and other things, such as hypotension, and other drugs contrast

 

might be driving that.

So, I'm not sure if you can write a specific rule that says, you know, you need to stop when the creatinine has doubled or gone up by 50 percent. But it's something that I, anyway, wrestled with.

And, lastly, in terms of Phase 4 studies, I guess I didn't specifically ask the sponsor if any urine was saved from these individuals early in the course, but there's a lot of incidence -- a lot of interest on the part of the FDA's critical path to identify better biomarkers in the year, and other than our traditional tubular epithelial cells and muddy brown casts.

So, I know there's a list of five to ten molecules that have been suggested by gnomic studies, by early clinical studies. And the FDA in particular is looking for patient cohorts to gather urine samples on, say, at two -- day two or day three to try to predict later nephrotoxicity.

I think this has broad, general utility to the medical and patient community, and then potentially to this particular medication, in terms of deciding early on who is having a significant renal hit.

 

DR. RELLER: Dr. Cragan.

DR. CRAGAN: I voted yes as well for most of the same reasons. I think it's clearly high effectiveness with increasing resistance to other drugs. It appears to, perhaps, fill a clinical niche that could be critical to a patient's survival in certain situations. And I agree that the risks are manageable. And I'll save comments about the management of pregnancy for question three.

DR. RELLER: Dr. Black.

DR. BLACK: I also voted yes, a little bit reluctantly as well. I think there is an unmet need coming, if it's not already here, and that this may well fill it.

DR. RELLER: Miss Thomas.

DR. THOMAS: I voted no. I think the risk is greater than the benefits. Having experienced Vancomycin long-term myself, I know how toxic that is. I certainly would not want to have a drug that is more toxic.

I think additional trials are needed for renal impairment and risks to women that could be pregnant or are pregnant. Many MRSA patients have recurring

 

infections, and a study on the long-term effects of the drug should be conducted.

DR. RELLER: Dr. Steckelberg.

DR. STECKELBERG: Yes, for the reasons exactly as articulated by Dr. Bennett in nonpregnant patients. And I would hope that there would be some postmarketing attention due to patients who have baseline renal insufficiency and efficacy, because that's such an important intersection to patients with these infections.

DR. RELLER: Dr. Cross.

DR. CROSS: I also voted yes. I think that, in addition to what's already been said, I think it's important that in the future physicians do have some options. And although this was not shown in a clinical study, they did show a slide where there were a number of Staphylococcal agents that were resistant to Daptomycin and a lot of the other drugs which we consider alternatives. And I -- and, you know, as mentioned, even though this was certainly not shown in the clinical study, I think it's good to have an agent available that may in that situation be useful. And I do think that the risks are manageable.

 

DR. RELLER: Dr. Hilton.

DR. HILTON: I voted yes. It seems that the patients who are most at risk can be well identified at baseline. And I also found it encouraging that the MRSA results were relatively positive, in terms of efficacy.

And I echo Miss Thomas' remarks about the need for studies in recurrent infections in the future.

DR. RELLER: Mr. Levin.

MR. LEVIN: I voted no, because I'm not ensanguine about the ability to manage risk without aggressive risk management programs in place. And because there's no assurance that's the way we're going to go today, I don't feel comfortable -- I wouldn't have been comfortable voting yes.

I certainly recognize the need for new drugs in the face of galloping resistance, but I am concerned about a number of the safety signals that we're getting. It makes me reflect that this sort of up or down process that we have really has to be rethought, because there should be some intermediate ground where we can say yes, but we've got some real concerns. We'd like to learn more along the way.

 

We have treatment INDs. We don't seem to want to use them because sponsors don't want to use them. But we would have the opportunity for getting the drug out to people and learning a lot more about it in a controlled way.

The -- so, I'll stop there. I'm sorry.

DR. RELLER: Dr. Weinstein.

DR. WEINSTEIN: I voted yes with some concerns about the toxicity, but I think ultimately they can probably be managed.

DR. RELLER: Dr. Gutierrez. Follmann. Dr. Follmann.

DR. FOLLMANN: Thanks. Yeah. I voted yes. I thought, you know, the drug showed that it was efficacious. It beat the noninferiority margins. I thought that the risks could be managed. I had some concern about the difference in cure rates for poor creatinine levels, and also obviously renal adverse events, which I thought showed a consistency of signal as you went up the grading of severity.

DR. RELLER: Dr. Gutierrez. Could you repeat your comments closer with the microphone on, please?

 

DR. GUTIERREZ: Okay. I did vote yes, you know, for reasons that have previously been articulated. I think, you know, it did meet the noninferiority standards. I do have some concerns, particularly about the developmental toxicology, but we'll discuss that in the next question.

DR. RELLER: Dr. Kauffman.

DR. KAUFFMAN: I also voted yes. And I think that there definitely should be some postmarketing studies done in evaluating the nephrotoxicity issue. I think we've learned a lot over the years of Vancomycin, and I think we can start out right on the ground floor with postmarketing studies with Telavancin and maybe figure things out a little bit better that it took us so long to do with Vancomycin.

DR. RELLER: I was one of the minority five. And the basis for that was the safety concerns in multiple systems, not just one, that I think complicates risk management, the details of which have been amply expressed. And in weighing the balance, the paucity of those organisms with a elevated MIC to Vancomycin for which we currently have experience, not that it isn't

 

important to have alternative agents.

And, thirdly, that I was -- I'm much more enamored of an alternative or supplemental drug that has a fundamentally different mechanism of reaction for addressing emerging resistance. And I was not sufficiently convinced that the mechanism of action. So, without more experience with the elevated MICs, I don't know how much of a difference this will make in adding to the armamentarium for resistant organisms based on what we've heard today, that coupled with the multiple systems is why, without further information studies, that I fell on the seesaw to the no side.

Question number two --

DR. FLEMING: A quick clarification.

DR. RELLER: Yeah.

DR. FLEMING: You had asked for the postmarketing recommendations after you --

DR. RELLER: Yes.

DR. FLEMING: -- passed me. I just wanted to --

DR. RELLER: Please.

DR. FLEMING: -- quickly add to that.

 

I endorsed what a number have said, that we definitely do need to have postmarketing studies to evaluate nephrotoxicity. So, pharmacovigilant studies that would allow us to more clearly understand the rate of serious adverse events and any potential linkage to mortality would be very useful. That's an art. That's very difficult. It's often best to be able to discern causality when you have a proper control.

Pharmacovigilance works when you're trying to detect something that's ten-fold or 100-fold and you're looking at whether the rates are higher than what was historically the case as, Dr. Chen was talking about earlier on, when he was talking about interpreting the safety data IN pregnancy.

If, however, one has a two-fold, three-fold increase, for example, in events that would be causally influencing mortality mediated through nephrotoxicity, you're not going to discern that unless you have randomized control. So, if there's any way in the future to build in an evaluation of this in randomized studies that would be looking at Telavancin, that would be an important part of the approach postmarketing to evaluate

 

the frequency and influence of nephrotoxicity.

And just one, I think it's clear, but to make it very explicit rather than implicit, as I've voted for efficacy, it's efficacy in wound, and ulcer infections, and cellulitis, and erysipelas, of course, not in subcutaneous or a major abscess.

DR. NELSON: Can I just make that one comment as well, because you had asked that question after you passed me. But I would just -- I would just like to --

DR. RELLER: This is Dr. Nelson speaking.

DR. NELSON: Thank you. I would like to just put in a plug that QT issues really have to be looked at as well. I think this drug, given a little bit of in vitro and other data that we have, is potentially a setup for producing torsade and other QT-related complications, once it's available to a larger population of patients who are relatively unselected, unlike those who are in clinical trials. And this historically has been something that has been overlooked, for sometimes years, before it's picked up as a real signal.

DR. RELLER: Given the realities of time and the discussion that's taken place, I think that we must

 

vote on question number two.

Yes, Mr. Levin.

MR. LEVIN: The question of FDA, the language -- I mean, the way the question is asked, and the language distinctions between C and X, one could read that as saying, you could never use this drug in a pregnant woman under any circumstance. And, one, labeling isn't law. And we know that people deviate from labeling all the time in both positive and negative ways. So, it strikes me that we need to think about a break-the-glass situation, which to me says, this shouldn't be interpreted. This is me, myself, my own view, as saying, that if you exhausted all alternatives and there was a pregnant woman, that you couldn't use this drug. I mean, that would be a clinical judgment to make and that this is -- this is the label -- the label is the label. And the evidence from study is that physicians don't follow labeling a lot of the time.

So, I'm just -- you know, the way it's worded it sounds like that could never happen. So, you would sort of be dooming a pregnant woman who is -- in whom all other treatments had failed and had a serious infection

 

to death. And I don't think that's the way I want to think about it, frankly.

DR. RELLER: Dr. Cox, for clarification, in sharpness in this question, how I would interpret it -- this question is a yes would mean that it should not be used in pregnant women. That does not mean that there would not be overwhelming clinical situations where it couldn't be with justification and acceptance on the risk by both parties, the patient and the physician, in order to preserve life. Is that a fair rendition, or does that help or confuse things?

DR. COX: So, yeah, I see the fine point of distinction you're making here. And probably the important thing will be to provide a rationale as we -- if we can go around the table after we have the vote.

You know, we really are asking you, you know, are there situations when, you know, you would, you know, see utility in using the drug in a pregnant woman, or would it be appropriate to do so? So, if there are situations that you would expect that would arise, then, you know, that would be, you know, a yes answer. And then if you can describe those situations, that would

 

also be helpful to us.

Does that help, Dr. Reller?

DR. RELLER: So, that is, that if you would ever use it -- in other words, it has nothing to do with how frequently this might be encountered? I mean, it hinges on if you would ever use it. I mean, the common clinical situations, or does it come up frequently, or can one conceive of a situation where you would want to use it?

DR. COX: On the -- I'm sorry. Let me gather my thoughts here. The issue of -- you know, I mean, the comment Dr. Feibus made is another piece of advice to put out there is to look -- to think about the overall risk and benefit, you know, that you're evaluating when looking at the situation where you would -- you know, might or might not consider using this agent in pregnant women.

The other thing to think about, too, it would be helpful to have some feel for what the frequency would be of situations, you know, that might arise where folks would think it would be reasonable to take on, you know, or consider administering the drug to a pregnant woman.

 

DR. RELLER: Dr. Mirkes, Fleming and Steckelberg, and then we will vote.

DR. MIRKES: Well, I've refrained from making a comment about the developmental tox studies, as I wasn't quite sure where the appropriate time was, and I think this may be it.

A lot of the decision as to whether you think this ought to or ought not to be given to pregnant women is based upon these development toxicology studies in animals. And, so, I think we really need to address the adequacy of those studies. And we've got two very conflicting opinions, one from industry, one from FDA, as to the adequacy.

As I read them, and I wasn't privy to the entire studies, but only the redacted studies. And my take on them is that the rabbit study in which there was one fetus with a limb defect, you know, I don't know what to make of that. There's no dose response. So, that one fetus, even though it may not have been in historical controls, to me, is relatively meaningless. And I don't know what that study tells me.

The rat study, where there were two that had

 

malformations, it turns out the one that was thought to have shortened limb when the skeleton was looked at didn't. The other one wasn't -- the skeletal wasn't done. So, again, in the rat study, I would say I don't know what that says. I'd throw that one out.

The mini pig study to me is totally uninterpretable, because there's something going on in this study based on the fact that the pregnancy rates were so low, and the fact that several -- a fairly high percentage of the pregnancies were terminated earlier for reasons that I don't understand. So, I don't know what to make of those other -- so, I don't think there's strong developmental toxicology evidence that -- as FDA indicated, that this is a highly suspected human teratogen. I would disagree with that characterization.

DR. RELLER: Thank you. Dr. Cox, and then Dr. Fleming and Steckelberg.

DR. COX: Yeah, just one other point on the question. I mean, you know, the reason we are asking question two is to get to the issue of how we would label this product. So, you know, we are trying to understand what the frequency might be where a situation would arise

-- if such a situation would arise. And, you know, the question as Dr. Mirkes -- the points he's bringing up with regards to, you know, assessment, with regards to degree of concern about teratogenicity. Okay.

DR. RELLER: Dr. Fleming.

DR. FLEMING: Well, I'm just -- this following up on what Ed said was my comment. The question doesn't seem to be really precisely what I understood you were getting at. It says, are there clinical situations when benefits of Telavancin use in pregnant women would outweigh the risks?

It's really more rich than that, it's whether -- are there clinical situations where it has been established that the benefits of Telavancin use exceed alternative options in a pregnant woman who -- would exceed alternative options in a pregnant woman and where those would out -- or such that it would outweigh the risk. Because essentially Category X's wording is, for example, safer drugs or other forms of treatment are available. And, so, if one says, there are safety issues here that are of concern, there is efficacy here, but if that efficacy could be provided by alternative therapies

 

that are safer, then that is the exact wording for Category X. So, isn't that really the spirit of what you're asking us to comment on?

DR. COX: Yeah, I think that's a fair way to characterize it, and that does reflect the wording, with regards to Category X. It asks the issue of safe alternative. You know, we're trying to understand, are there or are there not situations, you know, that would arise where people would turn to this drug in a pregnant --

DR. RELLER: Dr. Steckelberg.

DR. STECKELBERG: I apologize, but even after all the discussion I'm still unclear as to what the question is. It strikes me as ambiguous. This sponsor -- sponsor's expert has said, that in his estimation there's practice that 99 percent of the time there's safe alternative therapy. So, it's not sort of a question -- is the question -- is it conceivable that there ever could arise a situation, or is it a Saddam and Gamora question of what percent -- or how frequent does this happen? Or perhaps you just want to ask us, should it be Category C, or X, or B, or something like that.

 

But in any case, I need to know what the question is, if you want me to vote.

DR. COX: So, on this question, I'm just trying to think, you know, perhaps the way to handle this is, you know, to think about this in terms of, you know, are there situations today, you know, a patient that you might encounter today where you would, you know, consider it appropriate or inappropriate to give this drug, based upon what we know about the drug?

And then also to give us a feel for -- and we can do this perhaps as we go around the table and the comments -- the frequency with regards to what -- you know, when such a situation might arise. And then if -- I guess as a sort of an add on, and I realize we'll have to be very efficient here in trying to address this, would be if folks want to make a recommendation with regards to the pregnancy category, we can also include that in the comments.

Does that sound okay, Dr. Reller? I know that's a lot to try and chew.

DR. RELLER: You're fusing question two and question three?

 

DR. COX: Am I?

DR. RELLER: Because the Category X delineates that there must be a risk management program, as I interpret Category X. Not so?

DR. COX: Well, the two things are related. And I think there we're asking more for, you know, should a risk management program be there, so, if one were to feel that X were the appropriate way to go, then it would follow that in three you would vote yes. And then -- you know, then you would actually describe the additional elements that you would, you know, actually include in such a risk management program.

DR. RELLER: I had been educated that the risk management program is a separate decision from a Category C or Category X. I think there's no way around this, other than through explanation of the comments. But taking everything into consideration, come down on the side of a yes or no, and amplify on that vote in the discussion. And we'll go swiftly around the table.

I realize that we're over time. I think it's important not to short change these questions, but it's also important to be fair for this afternoon's sponsor.

 

Dr. Cox.

DR. COX: Yeah, and I think your point, Dr. Reller, is critical. And that is, understanding the rationale to thinking and how you arrive at your answer. If we can understand the rationale, that will be very helpful to us.

DR. RELLER: So, we must vote the question as it is, amplify and the comments thereafter. It's time to vote.

Everyone certain of the right button?

The voting is closed.

The votes are 18 yes, 5 no, and 3 abstentions.

Dr. Kauffman.

DR. KAUFFMAN: I voted yes. I have clinically seen patients in whom I had none of the alternatives for treating a serious MRSA infection. Obviously pregnancy wasn't a part of that issue at the VA. However, I think overall this is going to be an uncommon event, but I think physicians will need to have that option in extreme circumstances.

DR. RELLER: Dr. Gutierrez.

DR. GUTIERREZ: Well, I voted no. And the

 

reason I voted no, is that I still don't have a very good sense of either what the benefits or the risks would be in this particular patient population. And I guess being a pediatrician I'm more cognizant of needing to understand exactly what the risks would be potentially to the fetus. So, I think, sort of given a lack of information about the risks, and the discussion about the integrity of the studies in the animal models, I felt that I would vote no for this. It -- I agree that there could be a conceivable situation where, if you had no other alternative, then you can argue benefit would outweigh risk. But that's the reason for my no vote.

DR. RELLER: Dr. Follmann.

DR. FOLLMANN: I voted yes. I thought the FDA's analysis of the data was more compelling to me. I was struck by the consistency across the three species, and also by the independent consultants FDA hired.

The sponsor's analysis just didn't seem so compelling to me. It seemed like they were more explaining the way these abnormalities. So, I don't really have a good clinical explanation of why I would have voted yes, other than I can imagine a situation,

 

perhaps, where this would be the only alternative between, you know, saving the mother's life if there was no other viable option. So, I'm assuming that such a situation could exist and that's why I voted yes.

DR. RELLER: Dr. Weinstein.

DR. WEINSTEIN: Yeah. I voted yes. I think that there could be clinical situations where the benefits would outweigh the risks. I'm trying to think about it. I've thought about VISA isolates, hVISAS. Certainly there have been reports that VISA isolates are also resistant to Daptomycin. And I think that might be a situation where you might need to use this drug.

DR. RELLER: Mr. Levin.

MR. LEVIN: I voted no, not because I can't conceive of a situation where it would be appropriate, as I said, in a sort of break-the-glass sense. But I think, frankly, this question is joined at the hip to the issue of categorization, and the very specific and confining language that FDA uses in categorization. I don't think I could vote yes on this and then vote for the category I might be interested in.

DR. RELLER: Dr. Hilton.

 

DR. HILTON: I abstained, because I feel that the teratogenicity data are incomplete, inadequate for us to make this assessment.

And also I think that no amount of limb malformations are going to be acceptable. One of my first positions as a researcher was on diethylstilbestrol adenosis study where eight men born of women who had taken that during pregnancy went on to have malformations as young adults. I just don't think our society accepts that. So --

DR. RELLER: Dr. Cross.

DR. CROSS: I voted yes, because I can conceive of a situation, albeit rare, when there aren't any other alternative in which it may be useful. I think we do need more data on risk, but I was also impressed that the observations made, in terms of risks were, at close to the human dose. And while I -- I'm impressed with Dr. Mirke's analysis that we really don't have enough data. I think that was of interest to me.

Having said that, I think, you know, that its use would be rare, because there are presently alternatives.

 

DR. RELLER: Dr. Steckelberg.

DR. STECKELBERG: I voted yes, because I can conceive -- I can construct in my mind a situation where this might be true, although I haven't seen such a situation. If you had asked the question about C versus X, I would have said X for the following reasons. There are really two components to it, one is whether or not the animal studies have shown defects. And I'm not sure what the answer to that is, but I do know the sponsor's expert has said he clearly thinks it's Category C. And Category C says, animal reproduction studies have shown an adverse effect on the fetus, otherwise it would be Category B.

So, then it kind of comes down to Category C versus X, and that question then comes down to the second part, which is whether the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefits. And the specific examples are given as to whether other forms are -- of therapy are available. And the sponsor said 99 percent of the time there are. And, so, it kind of comes down to that 1 percent.

My main concern would be that -- would be the

 

protection of the safety of the patient in this situation. And without further data, I would come down on the side of avoiding inadvertent use on the basis of the labeling. And just the -- I think my experience with physicians, is that if it's in Category C, there's probably more likely to be use without really having that hard discussion about it, or hard thought about it. So, it's just a judgment call, but that's the basis for it.

DR. RELLER: Miss Thomas.

DR. THOMAS: I voted yes, because I think it should be used when there is resistance to all other antibiotics. It's the last resort. But I think it's very important that the patient be told of the side effects and -- with her doctor, so, yet it -- she really knows what the risks are involved.

DR. RELLER: Dr. Black.

DR. BLACK: I voted yes as well, because it's impossible for me to not think of a situation where you could -- you might not use this. And, so, I think the way the question was worded, it was impossible to answer any way but yes.

DR. RELLER: Dr. Cragan.

 

DR. CRAGAN: I voted yes as well for the same reasons that I think it should be used, if there are no alternatives and it's a life-saving situation. I intend to agree with Dr. Mirke on the interpretation of the animal studies. But clearly there are questions that remain, and just the dichotomy of the two interpretations that we've heard needs -- is going to be out there and needs to be addressed. So, I would not recommend it as first line use or frequent use, et cetera. But in a patient who is pregnant who -- or who may be pregnant and it's a life-saving situation, yeah, I think it should be used.

DR. RELLER: Dr. Kopp.

DR. KOPP: I voted to abstain, just because I don't have enough personal knowledge on the infectious disease side of the seesaw, or the teratogenic side.

DR. RELLER: Dr. Shelby.

DR. SHELBY: Since all my clinical experience is as a patient, I didn't feel like I had enough knowledge to actually reach a conclusion as to the clinical situations. All right.

DR. RELLER: Thank you. Dr. Smith.

 

DR. SMITH: I voted yes. I think that, if a woman is pregnant and all other therapies have failed, she, you know, needs the option to do this. And I think the -- again, the teratology is weak, the studies are weak, and it's hard to make a judgment based on those.

DR. RELLER: Dr. Paganini.

DR. PAGANINI: I voted yes and I'll let Dr. Steckelberg -- all his discussion is exactly the discussion I would have. I'd probably place it in an X with all of the caveats listed there.

DR. RELLER: Dr. Mirkes.

DR. MIRKES: Yeah, and I believe I was confused by the question, and I probably should have voted yes. But what I tried to convey, was that I don't think we know what the risks are in terms of the teratogenicity. And, so, I don't distinguish this drug from Vancomycin, in terms of how we deal with it. And, therefore, I would be in favor of a Category C. And that's what I was trying to convey.

DR. RELLER: Dr. Septimus.

DR. SEPTIMUS: Well, this time I voted yes, because we voted yes on the first question. But I can

 

conceive of a situation which this might be indicated. I think one of the obligations we have, both as physicians and here today, is that we have to think of patient safety first. And, so, although I think there is a reason that we might give this drug in someone who is pregnant, I think it has to be done very carefully with the risk management program in place, both for this category and for the next question, and obviously to establish a registry so we monitor for any potential low level toxicity.

DR. RELLER: Dr. Nelson.

DR. NELSON: Yeah. I voted yes as well. I think -- I deal frequently with patients who take or get exposed to substances that are potentially teratogenic while they're pregnant. Sometimes it's intentional. And, you know, these discussions come up very frequently. And I think patients have a very strong sense about whether it's cultural, political, philosophical, religious, about what you're going to do in a situation like that. And this is not an all-or-none teratogen, this is a drug that has a potential to be teratogenic. And it seems unrealistic to sentence a

 

pregnant woman essentially to death, if you believe that's going to be the outcome, because of some potential to have a teratogenic event, which many people, you know, feel is resolvable. So, that's why I voted yes.

DR. RELLER: Dr. Lesar.

DR. LESAR: I voted yes as well. Again, my comments, many have to do with what question three, will be in terms of what that risk management is. Because I think that my response has a lot to do with how we manage this issue.

DR. RELLER: Dr. Bennett.

DR. BENNETT: We use the Vancomycin in my hospital. It just sky rocketed. We see so much MRSA, suspected or proven, that we're using Vancomycin. It's one of the most commonly used antibiotics. And what this means is, we're seeing more patients who are getting skin rashes, particularly the ones with -- this is something Carol Kauffman brought up, that is diffuse erythroderma. And I'm afraid, if we continue the drug, they'll exfoliate or go on to Stephens Johnson.

So, Ed Cox was asking, is there a situation where you don't have very many alternatives? And one of

 

the things is, would you reach for Vancomycin in a person who had a skin rash like that? And the answer is, no. Particularly the pregnant female you wouldn't want to reach for something -- a drug that would have some serious delayed hypersensitivity.

Another point to bring up is, although I voted yes to use this drug, I don't like the teratogenicity data we've got. I do not know why they didn't use higher multiples of the dose we use in humans. It may be because there's a factor here of volume. Perhaps the stuff is so diluted, the Cyclodextrin, that you physically can't get in that much in the experimental animal.

But when Dr. Scialli said there's nothing else to be done, I wondered why we weren't using higher doses to study teratogenicity. So, I'm concerned about it enough to think about it, other than having it in the X category. But I do think we need it. I think there will be times when we would reach for Telavancin.

DR. RELLER: Dr. Leggett.

DR. LEGGETT: I voted yes for many of the same reasons as before. I can think of several plausible --

 

very infrequent, but plausible scenarios where this would be -- the benefit would outweigh the risks.

One thing I would mention that hasn't been brought up, I think we have to consider ourselves not only with the known pregnant woman, but with the unknown pregnant woman. And I would make a plea for as much consistency and constancy as possible on the part of the FDA regulators going forward. One of the things I'd point out is that we have several Class D drugs, aminoglycosides, Tigecycline still is labeled D as far as I'm concerned, even though the person said it was the equivalent to C. And then we have favorance. We use those all the time. So, whatever the FDA decides about this drug, should keep in mind what is currently around and in use right now.

And in terms of the teratogenicity, I sort of concur with Dr. Mirkes that, you know, this could be a Class C drug, and I would like the FDA to reconsider after they've read Dr. Scialli's Vancomycin reference. This may be a moot point.

Regarding Class X drugs that I'm aware of that would sort of fit in the anti-infective category, we've

 

got Quinine and Ribavirin, which I think are very different than what we are considering this drug to be as a Class X or -- yeah.

And, so -- or class -- and then I think I'll just -- that will do it.

DR. RELLER: Dr. Fleming.

DR. FLEMING: For this question I would have voted yes if I believed that there were clinical situations where it's been established that the benefits of Telavancin use do exceed alternative options in a pregnant woman, and where those unique benefits would outweigh the risk, then I would have voted yes.

We haven't established that. The teratogenicity issues are very significant. As Dr. Hilton was pointing out, they're not established. But the evidence to suggest this risk is sufficient, in my view, that it takes more than a hypothetical, I can conceive of a situation, or if there were no other alternatives where the patient would die and this will save the life, there's been no evidence to indicate that that, in fact, exists.

And my sense is, the wording in Category X,

 

for example, safer drugs or other forms of treatment are available applies. And with the concern that's legitimately been raised about the safety issues, I voted yes to question number one, recognizing that we've only established noninferiority relative to Vancomycin, with the idea that we would be protective against these issues of safety that could tip the scale in the unfavorable benefit to risk. So, I voted no.

DR. RELLER: Dr. Goetz.

DR. GOETZ: I voted yes, not surprisingly. Many of my reasons echo that of the previous people who voted yes. I would limit -- but having said that, at the present time I see that the number of circumstances for the use of Telavancin would be justified in pregnant women can be quite unusual. I would limit the use to people who clearly have Vancomycin resistance, or clear evidence of Vancomycin intolerance. Then at the same time have a life, limb, or function compromising infection.

But this may change in the near future. We are seeing changes in the MICs of Staph aureus isolates, and we are seeing consideration given to where the

 

appropriate break point is for Vancomycin susceptibility. But the break points haven't changed in the last two years. They may change yet again.

So, I think we need to have the flexibility to have this drug available in pregnant women when there is a serious infection, and when there's evidence of lack of Vancomycin susceptibility, or clear absence of Vancomycin tolerance.

DR. RELLER: Dr. Alston.

DR. ALSTON: I voted yes. And I have nothing further to add.

DR. RELLER: Dr. Katona.

DR. KATONA: I voted yes. I'm curious amongst those that voted yes, if we had substituted the toxicity of Thalidomide, which was rare but very dramatic, whether that would have made a difference in that voting.

But what it comes down to to me, is you can't have a category for drug of last resort. You know, you can give it a Category C and eventually it will be looked upon by the practicing physician as every other drug that it's a comparator to that is also a Category C. So, I think you have to look at it in that way, and not look at

 

it as the drug of last resort when all other options are being taken off -- the way we're actually asked to look at it currently.

DR. RELLER: I voted no for much of the same reason that Dr. Fleming has already outlined. I recognize that to save a life no one would hesitate to use this drug based on the efficacy.

On the other hand, we're anticipating a greater need, at the same time we have such a sparse experience on the development of resistance of this drug going to the number of exposures. So, I'm not certain. I just don't think that it should be given to pregnant women unless there is -- unless one has exhausted other alternatives based on the uncertainties that have been presented today.

Question number three. This should be relatively more straight forward. Since labeling of the drug is not automatically linked to risk management, let's vote.

Question three: Is a risk management strategy needed to prevent an unintended use in pregnant women or women of childbearing potentials? Please note -- vote

 

yes or no.

All set?

Time for the vote. We have a moment for technical corrections.

We wish to vote as soon as we have blinking lights in the bottom panel.

We're ready for the vote. Please vote.

Voting is closed.

Results. Question number three, 22 members voted yes, 1 no, 0 abstentions. Excuse me. What did I say? Even without the glasses. The vote is 25 yes, 1 no, and 0 abstentions.

Dr. Cox, need we go to each individual, or can we simply ask if there's anyone who wishes to comment?

DR. COX: I think you can ask for folks who would like to specifically make comments on this issue about things that they'd like see included.

DR. RELLER: Please raise your hand and we will -- you will be acknowledged.

Dr. Cragan.

DR. CRAGAN: I voted yes on this because -- not because I'm concerned that this is a major teratogen

 

along the lines of Accutane, and Thalidomide, and some of those drugs. But I think it's realistic to be -- you need to be realistic about what can be done in the postmarketing arena.

One of my activities at CVC is I'm on the Scientific Advisory Committee of four of the pregnancy registries by -- as a consultant to -- on several drugs to the pharmaceutical industry. And I think you have to be realistic about what that can accomplish. Because if there is not a risk management strategy then, you know, it's Category C and, well, we'll do a pregnancy registry. And these are -- the way they're typically done are voluntary registries, a physician or a woman enrolls themselves or enrolls their patient. And the registry calls them up after the pregnancy is over and find out what happen, and what was the outcome, and did the child have any problems.

Their prospective that -- they're voluntary. They're not random. They're not population based. There are, you know, characteristics presumably associated with participation that very well may be associated with the risk of having a birth defect.

 

They're underpowered, in terms of they do okay with looking at all birth defects across the board, so, if you combine everything that could go wrong and look at risk levels, it may tell you something there.

But in this instance where there's -- concerns have been raised about a particular type of malformation, or a particular organ system, a prospective registry of that nature typically is not going to get there. You're talking about very rare events. And you're talking about the ability to only identify huge increases in those rare events.

Most pregnancy registries have a very tiny proportion of the total drug use that happens in pregnancy.

So, my feeling about it is that, you know, even this is a Category C and such, there needs to be a more active kind of hands-on approach to identifying the pregnancies that happen that do get exposed, and finding out what those outcomes were, to be at all informative. Because if it's left as the typical -- the more usual approach that a pregnancy registry has, I don't think it's really going to be informative.

 

So, I don't know if that means, you know, working directly with hospitals or directly with infectious disease specialists who are going to be prescribing these -- this drug or recommending its use.

I do think there is always potential for an inadvertent use when you don't know -- a woman doesn't know that she's pregnant, and you don't realize that she is before you use it. So, that always has to be a factor in this kind of use. But I think you need to be realistic about what the alternatives are.

DR. RELLER: Miss Thomas.

DR. THOMAS: You know, I voted yes, but with a caveat. Fifty percent of inpatients are not told they have MRSA. They don't know that this is what they have. And they're not given instructions on home care or information about the disease on discharge.

So, due to hospital staff shortages and lack of communication, and I see an educational program for pregnant women or women of childbearing potential just would not occur.

DR. RELLER: Mr. Levin.

MR. LEVIN: So, Dr. Cox, we're not talking

 

about category, right? We're not being asked that question. And, so, my question is: That short of the Category X, how much can be required?

So, we have the model from Accutane and other drugs with proven teratogenesis of how we try to manage risk. And even Accutane is not 100 percent in terms of avoiding exposure. So, we know all the tools. And the complication here is, if it's not Category X, or, you know, if it's one or the other, does that effect what tools can be used?

And, number two, I think the really important point that was brought out in the FDA presentation on risk management, this is sort of a different animal than the risk management experience we've had, because it has a huge inpatient component. And a lot of what we've done in risk management is around outpatient. So, it's quite different how you operationalize this in a hospital setting, from how you operationalize this in a physician's office.

So, do we need to -- I mean, do we need to be throwing suggestions out? You guys have worked with, we've developed in other settings the tools for risk

 

management as regards to pregnancy. Why don't we just say to you guys, figure it out? Work with the hospitals, work with doctors, and figure out, what are those tools? I mean, I don't think -- we're going to take a lot of time to talk about all the possibilities. I don't know where that's going to get us. We know the tools. We've sort of had that experiment already. We know how well each of them work and don't work because they've been evaluated. And I think the difficulty here is the different logistical issues of inpatient versus outpatient. And I don't think we can solve that for you in 15 minutes today.

So, what do you need from us in addition to what you have?

DR. COX: Yeah. And to your first question, I think it is fine to disassociate the issue of category with regards to tools that you think are appropriate for managing the risks. So, if there are suggestions with regards to tools that we should be considering, we'd certainly welcome those.

I also understand your second point, which is that this is a complex issue because we're dealing with

 

the situation of, you know, inpatient versus outpatient. So, maybe a way to phrase this is, if there are additional suggestions that folks would like to volunteer to us that -- you know, to advise us on tools that we should be considering with regards to management risks, we'd certainly welcome those comments.

DR. RELLER: Thank you. Dr. Rex.

DR. REX: Very briefly. I want to introduce an observation from the industry standpoint that goes back to question one. During these comments Dr. Fleming introduced a view on the analysis of efficacy that differ somewhat from the spirit of yesterday's discussions. In particular his statements have implied that there is no role for any microbial therapy as part of the management of abscess.

I'm concerned that we not lose sight of the problem we had yesterday with defining serious or major abscess, abscesses associated with constitutional symptoms, abscesses in threatening locations, abscesses in abnormal hosts are complicated skin infections that appear to benefit from any microbial therapy, as we've shown by the IDSA review. And it's a view that I heard

 

supported by the comments of the clinicians at the table.

Our supported data may be imperfect, but yesterday's consensus found them to be clinically meaningful.

A comprehensive program does need to include disease forms, other than abscess. I absolutely agree. I have no difficulty with doing a sensitivity analysis by subcategory. And I thought it was useful to see that presented today. But I do wish that we avoid introducing a new idea here accidentally or by implication. Thanks.

DR. RELLER: Any other comments on question three?

We will have the opportunity to emphasize some of these points in today -- this afternoon and tomorrow. We'll now break for lunch.

As yesterday, across the hall in The Prince George's Room, anything that -- we'll be setting up for the next meeting -- take with you. The room will be closed. We'll reconvene at 2:15 p.m. 2:15 p.m. The hours have been extended in the restaurant to accommodate us. 2:15 back here. Thanks.

 

(Pause in proceedings.)

DR. RELLER: Power having been restored to the microphones, we'll begin the afternoon session of the FDA Anti-Infective Advisory Committee -- Anti-Infective Drugs Advisory Committee Meeting.

I'll now call the meeting to order and make our opening remarks. For the topics, such as those being discussed at this afternoon's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is this afternoon's meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption.

Thus, as a reminder, individuals will be allowed to speak into the record, only if recognized by the Chair.

We look forward to a productive meeting. Going to the time constraints of this afternoon, if we are so fortunate as to have time for a break, we'll have one, but probably not. And, consequently, if there be a physiologic need to briefly exit from the meeting, please do so.

 

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

The press -- FDA press contact for the meeting is Miss Karen Riley. Karen is standing in the back.

UNIDENTIFIED SPEAKER: It's Sandy Walsh.

DR. RELLER: Sandy Walsh will be pitch hitting for Karen Riley as the FDA press contact.

Also I would now like to turn the meetings attention to introduction of the committee members who are voting -- participating this afternoon.

We will start this afternoon for a separate recording with Dr. Katona to my left.

DR. KATONA: Peter Katona, I'm an Infectious Disease Physician at UCLA.

DR. ALSTON: Kemper Alston, I'm an Infectious

 

Disease Physician at the University of Vermont and Fletcher Allen Healthcare in Burlington, Vermont.

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

DR. FLEMING: Thomas Fleming, Department of Biostatistics, University of Washington.

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

DR. BENNETT: Jack Bennett, Infectious Disease Division, NIH.

DR. LESAR: Timothy Lesar, Director of Pharmacy, Albany Medical Center, Albany, New York.

DR. NELSON: Lewis Nelson, Emergency Physician and Medical Toxicologist at New York University.

DR. SEPTIMUS: Ed Septimus, Infectious Diseases, University of Texas in Houston.

DR. MOLEDINA: Nasim Moledina, Medical Officer, Division of Anti-Infectives and Ophthamology Products.

DR. VALAPPIL: Thamban Valappil, Statistician,

 

CDER FDA.

DR. ALEXANDER: John Alexander, Medical Team Leader, Division of Anti-Infective and Ophthalmology Products.

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

DR. COX: Ed Cox, Director of Antimicrobial Products, CDER FDA.

DR. THOMAS: I'm Jean Thomas, patient representative (inaudible).

DR. RELLER: We've just heard introduced Jean Thomas who is the patient representative on the committee.

DR. CROSS: Alan Cross, Infectious Disease Physician, University of Maryland, Baltimore.

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

MR. LEVIN: Arthur Levin, Center for Medical Consumers in New York and the Consumer Representative.

DR. WEINSTEIN: Mel Weinstein, Infectious Disease Physician, Robert Wood Johnson Medical School in

 

Brunswick, New Jersey.

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

DR. GUTIERREZ: Kathleen Gutierrez, Pediatric Infectious Disease, Stanford, Lucille Packard Children's Hospital.

DR. KAUFFMAN: Carol Kauffman -- excuse me -- Carol Kauffman, University of Michigan Medical Center, and Chief of Infectious Diseases at the Ann Arbor VA.

DR. KIM: Janie Kim, Designated Federal Officer for Anti-Infective Drugs Advisory Committee.

DR. RELLER: Barth Reller, Infectious Diseases Physician and Medical Microbiologist at Duke University Medical Center.

We will now have the conflict of interest statement read by Dr. Kim.

DR. KIM: Thank you, Dr. Reller. The Food and Drug Administration is convening today's meeting of the Anti-Infective Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all

 

members and temporary voting members of the committee are special government employees or regular Federal employees from other agencies and are subject to the Federal conflict of interest laws and regulations.

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

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

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular Federal employees with potential

 

financial conflicts, when necessary, to afford the committee essential expertise.

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

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

Today's agenda include -- involves a new drug application, NDA 022-153, Oritavancin, Targanta Therapeutics Corporation proposed treatment of complicated skin and skin structure infection. This is a particular matter involving -- meeting during which specific matters related to Oritavancin will be discussed.

Due to their past involvement with Oritavancin, the product at issue for today's meeting, Dr. James Steckelberg, and Dr. John Rex, FDA's invited

 

industry representative, will not be participating during this portion of the meeting.

We would like to remind members and temporary voting members, that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with any firms at issue. Thank you.

DR. RELLER: We will have two sequential 45-minute presentations, first by the sponsor, Targanta, followed by the FDA presentation.

Dr. Parr.

DR. PARR: Thank you. Good afternoon. My name is Tom Parr. I'm the chief scientific officer of Targanta Therapeutics. And I'm going to present to you the introduction and handle the questions and answers, as well as a short resume of the microbiology of Oritavancin.

 

My presentation will be followed by Dr. Pierre Etienne, our chief development officer, who will present the efficacy and pharmacology of Oritavancin. And Dr. Susan Moriarty, our senior director of medical affairs, who will present the safety and the benefit risk.

This -- on this slide are additional experts with the company and also consulting experts who will introduce themselves, if they are called upon to answer any specific questions.

The NDA for Oritavancin has been submitted for the indication of complicated skin and skin structure infections, for the treatment of susceptible organisms, using a daily administration of 200 milligrams unit dosing, or 300 milligrams for patients with a body mass over 110 kilograms, for a three to seven day dose in course. The application is supported by two Phase 3 trials, each of which met its primary endpoint.

Oritavancin has been administered to almost 2,000 subjects, including more than 1,600 patients. It is also the case that there are 13 Phase 1 studies, and four Phase 2 studies that have been conducted that also

 

support the dossier.

Oritavancin is a semisynthetic molecule with a chlorobiphenyl methylene group circled on this slide, added to the natural product chloroeremomycin. This semisynthetic modification is the exciting new addition and changes the attributes to the molecule in several ways.

The substitution to the natural product enhances the potency of the molecule very dramatically. It makes the molecule active against many antibiotic resistance strains, including glycopeptide-resistant strains. This substitution also changes the pharmacokinetics of Oritavancin and how the body handles the molecule.

With the substitution, the molecule has a long residence time in the body, and this allows a short dosing course. Once a day for three to seven days is our proposal. From the trials supporting this we will show.

This short course has been successful, and increased relapse rates have not been seen. The molecule has eliminated unchanged slowly, both in urine and in feces. As will be explained by Dr. Moriarty, the long

 

residence time is not associated with adverse events in our clinical studies. And, in fact, Oritavancin has demonstrated statistically fewer treatment emergent adverse events in our trials versus the comparator.

The semisynthetic substitution also adds additional mechanisms of action to Oritavancin, changing the way the molecule interferes with bacterial proliferation. It now attacks -- attacking the bacteria in several ways.

The molecule inhibits several -- I'm sorry, multiple steps of bacterial cell wall synthesis, independent steps, and Oritavancin is also a bacterial membrane perturbing agent that's attribute is associated with the very rapid bactericidal seen -- bactericidal activity seen. And I will show you the -- a bit of that data from the briefing document in a moment.

These multiple mechanisms of action may help forestall the emergence of resistance through mutation. And, in fact, none of the clinical failures seen to date have been associated with the emergence of pathogens with increased MICs to Oritavancin.

The important attributes of Oritavancin are:

 

The greater utility that we believe we will see, in part due to the spectrum and potency, including antibiotic resistance, Gram-positive organisms, such as MRSA. Preclinically you will recall from your briefing document that we have seen substantial activity against Vancomycin-resistant Enterococci, Vancomycin-resistant Staph aureus strains, Daptomycin, and Linezolid nonsusceptible isolates.

A short course of therapy, as Dr. Etienne will review, our trials have been successful with the application of 3 to 7 days of once a day dosing, compared with 10 to 14 days in the control arm of the studies.

This is consistent with the expectation from in vitro studies, from our preclinical animal model studies, and the multiple mechanisms of action of Oritavancin.

This short course will allow convenience in the hospital and for successful application to otherwise resistant strains. Oritavancin has shown fewer side effects and fewer treatment related issues than as compared to Vancomycin in our clinical studies.

Dr. Moriarty, in the safety portion of the

 

presentation, will run through these data with you. She will show that there is no need for monitoring levels of Oritavancin in hepatic nor renally impaired patients using the unit dosing schedule which we are proposing.

Finally, Oritavancin has significant future potential. We have completed a Phase 2 study using Oritavancin single dose or infrequent dose. We have two Phase 2 bacteremia studies exploring the drug in that application. We have strong published data on clostridium difficile colitis as an oral formulation of Oritavancin. And we have unusually strong also published preclinical data on bacillus anthracis inhalation Anthrax.

As we have but a short time to present to you today the microbiology dossier, I will share but two pieces of information from the preclinical data taken from our briefing document. This is an in vitro study using the MRSA strain clone, the community-associated USA-300 strain.

On the vertical axis is the bacterial density in log scale, while time is on the horizontal axis. In this experiment all drugs were tested at their free peak

concentrations, taking into account serum protein binding, that resulted from the standard clinical doses for complicated skin and skin structure, taken from the package insert of the registered drugs, and the unit dosing of 200 milligrams that we are proposing for Oritavancin.

You can note the steep slope of the decline of the bacterias well being for Oritavancin, with more than log kill within 30 minutes in this experiment.

In data in the briefing document you will also recall that Oritavancin's activity is concentration dependent, with more rapid bactericidal effects seen as concentrations are increased.

Oritavancin has been shown to be very active in many animal models, including models that are pertinent to skin and skin structure infections, and against multiple bacterial pathogens, including antibiotic resistance strains.

In these animal model systems, measures under the -- measures of area under the concentration curve, or peak to MIC, or peak to MIC levels, best protect efficacy in mice. This is true for both the neutropenic thigh

model using Staphylococcus aureus and Streptococcus pyogenes, including MRSA, and pneumococcal pneumonia using Streptococcus pneumonia. These data are -- concur with the concentration dependent bactericidal activity of Oritavancin in vitro.

Finally Oritavancin's activity in animals is very prolonged and long lived. I will finish this compact summary of Oritavancin's preclinical profile with an animal study that displays such long lived in vivo activity.

This is a representation of data from a rat granuloma pouch model using methicillin-susceptible Staph aureus. The bacterial burden is again indicated in log scale on the vertical Y axis with time now extending to 144 hours on the X axis. In these experiments, single applications of drug were applied, 100 milligrams per kilogram to the rat of Vancomycin, and 30 milligrams per kilogram in the case of Oritavancin.

During the first 24-hours of the infection, both drugs show a positive antimicrobial activity. But Oritavancin's activity is prolonged with the return of growth not occurring until, perhaps, 72 hours or you

pick, but certainly much longer than Vancomycin.

These data are supportive of the once daily dosing strategy that the NDA for complicated skin and skin structure infection is proposing.

In summary, we are approaching you today to propose Oritavancin for the treatment of complicated skin and skin structure infections, using a once daily dosing of a unit dose of 200 or 300 milligrams for a duration of three to seven days. We will demonstrate the effectiveness of this profile and its strong safety characteristics.

Oritavancin will be recommended for dosing once daily, three to seven days. We anticipate no special laboratory monitoring for either efficacy or safety. It -- Oritavancin has an enhanced potency in spectrum in comparison to other glycopeptides on the market. Strong activity against VRE and VRSA, in both in vitro and in animal models, multiple mechanisms of action, which we believe will forestall the emergence of resistance. It is very rapidly bactericidal and has a sustained activity.

With that introduction I'd like Dr. Etienne to

 

teach us about the efficacy and pharmacology of Oritavancin.

DR. ETIENNE: Thank you, Dr. Parr.

Good afternoon. I'm Dr. Etienne, chief development officer at Targanta.

Today I present efficacy data for the two Phase 3 studies that demonstrate Oritavancin's effectiveness and low relapse rate, with short course therapy for cSSSI. And there are three areas I'd like to focus on.

I'll briefly summarize the pharmacology and population pharmacokinetics of Oritavancin that are relevant to the dosing we propose. Then I'll describe the Phase 2 -- the Phase 3 studies in chronological order, starting with ARRD, a weight-base study, and following with ARRI, a fixed dose study.

Finally I'll summarize the results in the pooled Phase 3 studies, including outcomes and subgroups.

As you will see, Oritavancin was found to be consistently effective across all populations, disease categories, pathogens and subgroups, even with the inclusion of patients at risk for worse outcomes.

 

Now, a few words about clinical pharmacology. The clinical pharmacology of the drug has been characterized in 11 Phase 1 studies. It's pharmacokinetic parameters are predictable and linear in all doses studied up to 1,200 milligram. The drug is well described by a three-compartment model. The plasma concentrations display a multiexponential decline. The terminal half life is about two weeks.

Our population pharmacokinetic model also indicates that no dose adjustments are needed for renal or hepatic insufficiency, or for elderly subject.

This figure shows the plasma concentration time profile of Oritavancin following 200 milligram IV infusions every 24-hours for seven days. As you can see, the drug is rapidly distributed out of the central compartment. Twenty-four hours after the first dose, Cmin is about 10 percent of the first Cmax. By day three Cmin increases approximately three-fold with only a slight increase beyond that. Over seven days of dosing Cmax does not increase significantly.

And importantly three concentrations of Oritavancin remain above the MIC 90 for the pathogens of

 

interest for several days after the last dose.

With regard to the drugs ADME profile, it is extensive redistributed into tissues. It's protein bound, primary to albumin, which results in a very modest impact on its in vitro activity. It is not metabolized. And there is no evidence that it effects the metabolism of other drugs. And it's slowly eliminated from the body via the urine and feces.

Now, I'll move to the two Phase 3 studies. And the two studies are similar. And I'll present these similarities first before going to the individual results of each study.

The primary objective of both Phase 3 studies was to show that three to seven days of Oritavancin was not inferior to 10 to 14 days of Vancomycin Cephalexin for cSSSI. Patients who did not have an MRSA or an Enterococcal infection could be switched down to oral Cephalexin after at least three days of IV treatment with Vancomycin. And Cephalexin was dosed at 500 milligram twice a day -- or 1,000 milligram twice a day in the first of the Phase 3 studies, and 1,000 milligram twice a day in the second study, ARRI.

 

Next I'll share with you redefinition of cSSSI that we used in those studies. Nothing surprising here. These are complicated infections that require surgical intervention, involve deeper tissue, or occur in patients with significant underlying diseases or conditions.

It's a fairly standard definition, but it does not do justice to the seriousness of the cases enrolled in the two Phase 3 program.

In both Phase 3 studies, patients were enrolled with underlying diseases, including diabetes, HIV/AIDS or immunosuppression. And there was no limit on prior hospitalization or expected hospitalization, and any level of renal or hepatic insufficiency was allowed.

Next I'd like to share with you the intent and logic behind the design of both Phase 3 studies. The intent was to impose an early termination of Oritavancin treatment and let the comparative treatment run its normal course. Logic wise, that Oritavancin would still be active in the relevant tissues for several days after therapy was discontinued.

To protect blinding, just by different lengths of active therapy, all patients received 10 to 14 days of

 

study drug, either as active study drug or placebo.

Now, let me walk you through the details of drug administration. So, the bright yellow bags represent the active drug, and the white bags represent placebo. Administration of study drug was to last a minimum of 10 days and could be prolonged to 14 days. So, that's the optional part.

Let me start with a situation for patients who were to stay on IV therapy, because it's easier to explain. So, these were the patients who had MRSA, or Enterococcal infections, or patients who did not meet the IV-to-oral switch-down criteria. Because of the intended design of this study, an early termination was imposed on the Oritavancin treatment arm. So, these patients were to receive seven days of Oritavancin.

In contrast, in the Vancomycin arm, these patients were to receive a minimum of 10 days of Vancomycin, and the Vancomycin could be prolonged up to 14 days.

So, to protect the blind, patients of Oritavancin received placebo on days 8, 9, and 10. So, all patients who completed therapy had an apparent active

 

treatment of 10 days. Ten days minimum.

Now, for the majority of patients, that's about 80 percent of them, an IV-to-oral switch down was permitted beginning at day four, in patients who were clinically improving, who could tolerate oral therapy, and had no need for continued hospitalization. The same color code is used here. So, in the Oritavancin arm, the IV-to-oral switch was to placebo, and in the Vancomycin arm, the IV-to-oral switch was to Cephalexin. And to protect the blind, either oral or IV placebo was given in the Oritavancin group to complete the ten-day minimum treatment duration.

So, as you can see in the Oritavancin group, the minimum duration of active treatment was three days, and the maximum duration of active treatment was seven days. Whereas in the Vancomycin Cephalexin group, the minimum duration was 10 days, and the maximum was 14 days.

Now, I'll move to the individual studies. And I'll first describe ARRD. So, this Phase 3 study was a weight-based dose study. It had three treatment arms, 1.5 milligram per kilogram, 3 milligram per kilogram per

 

day and comparator. In a noninferiority margin of 15 percent -- minus 15 percent was selected using the principles that were in effect at the time this study was conducted.

Over 500 patients were enrolled in ARRD. And approximately 70 percent of the patients completed therapy, and roughly three-quarter of the ITT population was clinically-evaluable.

Enrollment was stratified by the disease categories of wound infection, major abscess, and cellulitis, with slightly more patients enrolled with a diagnosis of cellulitis. And the mean duration of disease prior to study entry was approximately five days.

Here you can see the depth of tissue involvement in the patients enrolled in ARRD. You can see that greater than -- more than 25 percent of patients had infections with fascial plain or muscle involvement.

Now, I'd like to move into the efficacy results. Though by first saying, the treatment groups were well-balanced for demographics, including age, gender, and weight. And let me orient you to this slide that has the same structure as a few slides that will

follow. So, each treatment group is color coded with the 1.5 milligram per kilogram in darker blue, the 3 milligram per kilogram in light blue, and the comparator in gray. And at the bottom of each bar you can read the ratio of cure to total. And the percentage skewer is at the top. So, the vertical axis actually represents the percentage of clinical cure.

So, in Study ARRD, the primary endpoint was the clinical response at test of cure in the clinically-evaluable population as determined by the investigator. And both Oritavancin arms were noninferior to comparator, although the lower bound of the 95 percent confidence interval came close to the margin.

Here you can see the cure rates in the different analysis populations. And they are maintained across analysis populations.

Now that we've seen the outcomes, that the outcomes were comparable and consistent for the primary outcome variable, I'd like to share with you the outcomes with the sponsor-defined clinical outcome. So, the sponsor-defined clinical outcome was DCO was derived from the IDCO after review and revision by the sponsor. And

it was derived by strictly applying protocol criteria while never improving the IDCO. So, failures remain failures and indeterminates remained indeterminates or failures. Only downgrades were allowed. And as expected, the cure rate for SDCO is always lower than for the IDCO.

Using the sponsor-defined clinical outcome, Oritavancin cure rates were also comparable to Vancomycin cure rates. On this slide you can see the comparable numbers of patients were enrolled in each of the three disease categories of wound infection, major abscess, and that -- and cellulitis, and that cure rates in patients treated with Oritavancin were similar to comparator across all three disease categories.

Now, on Page 23 of the FDA's briefing document, it is stated that multiplicity could be an issue, if the intent of this study was to determine which or both, the two Oritavancin regimens, were noninferior to the Vancomycin treatment.

The intent of this study was to determine that both Oritavancin regimens were not inferior to the Vancomycin treatment. And the issue of multiplicity was

 

raised in a request for recalculation of the 97.5 confidence intervals after ARRD and ARRI were completed.

But if one were to conclude that multiplicity was an issue in Study ARRD -- I mean, you can see on Page 24 of the FDA briefing document that the FDA proposed analyses were conducted with larger confidence intervals and using the primary endpoint of the study, that is the investigator defined clinical outcome, you can see that the 3 milligram dose would still meet the prespecified noninferiority margin for the prespecified clinically-evaluable population. And the 3 milligram per kilogram dose is the dose that is most relevant and most similar to the dose that we propose.

Now, I'll talk about Study ARRI, the second of the Phase 3 studies. Similar design to ARRD with the main difference being the dosing regimen. The population pharmacokinetic model show that subjects weighing more than 110 kilos required a dose of 300 milligram to match the exposure achieved with 200 milligram in patients weighing less than 110 kilos. So, ARRI used a fixed-dose regimen of 200 milligram once daily for patients weighing less than 110 kilos, and 300 milligram for patients

 

weighing more than 110 kilos. Randomization was two to one.

The second important difference is that a 10 percent noninferiority margin was selected for this trial based on the '98 ICH guidelines.

Over 1,200 patients were enrolled in this study. It was just under 90 percent of the patients completing therapy, and roughly 80 percent of the population being clinically-evaluable.

In contrast to Study ARRD, a cap of 25 percent was imposed on the enrollment of patients with cellulitis. And this resulted in a higher proportion of patients with cultured pathogens at baseline. And the mean duration of illness prior to study entry was the same as in ARRD at approximately five days.

And the percentage of patients with the involvement of deep tissues was higher than in ARRD, with over 40 percent of patients with fascial plain and muscle -- or -- and muscle involvement.

The primary endpoint for this study was the sponsor-defined clinical outcome in the clinically-evaluable population. Oritavancin was noninferior to

 

comparator with a clinical cure rate of approximately 79 percent for Oritavancin and 76 percent for comparator. As you can see, the primary endpoint was achieved well within the 10 percent noninferiority margin, with the lower amount of the 95 percent confidence interval around the point of stimulate treatment difference at minus three percent. In this study, by the way, resists the removal of abscess cases.

And as in Study ARRD, cure rates were comparable in all treatment groups and efficacy is maintained in all four patient populations.

Now, for the investigator defined clinical outcome, the Oritavancin cure rates were also comparable to the Vancomycin cure rates, and so were the patient level microbiological outcomes.

You can also see that cure rates in patients treated with Oritavancin remain similar for all disease categories.

Now, I'll present some data from the combined Phase 3 studies. We combine them regardless of the Oritavancin dose to examine safety overall, and efficacy overall, and to increase the denominators for

 

microbiological outcomes and outcomes in special populations. These are the high level efficacy outcome variables in the combined data that show that comparability is maintained, which is no surprise.

The subgroups represented here, represent patients for whom treatment may be more challenging. So, outcomes in these subgroups were analyzed, and Oritavancin was shown to be effective in all age groups, diabetics, renal patients with low creatinine clearance, or hepatic insufficient patients, and immunocompromised patients.

The other group for whom treatment may be challenging is patients with associated bacteremia, which I'll speak to now.

In the briefing document, you will see the outcomes of patients with baseline bacteremia. But I would like to note, however, that the outcomes are in the briefing document reflect the outcomes for the primary study condition of cSSSI, and are not reflective of the clearing of the underlying bacteremia.

So, to better understand this population, we performed a thorough review of all the patients with

 

associated bacteremia at baseline. And what we found was that, based on cultures, and those events reported during the trial period, 90 percent of Oritavancin-treated patients, and 89 percent of Vancomycin-treated patients with bacteremia at baseline, had no evidence of ongoing bacteremia.

I'd like to share with you some efficacy data by pathogen. These are presented here on Staph aureus, including MSSA and MRSA. There is Streptococci species common to cSSSIs and Enterococci faecalis. Eradication rates were comparable between treatment groups across the three types of pathogens.

Now, the lower microbiological outcomes in MRSA, regardless of treatment, are associated with higher disease severity and more difficult surgical treatment. Now, since those -- these pathogens were collected a few years ago, due to the history of the Oritavancin development program, it was important to compare the sensitivities of the Phase 3 pathogens with more recent surveillance isolates.

And what was found was that the susceptibility to Oritavancin for recent surveillance isolates of Gram-

 

positive pathogens is similar to the Phase 3 studies, thus indicating a broader predictability of the study results to recent clinical pathogens.

Another important point that the Oritavancin MICs of pathogens isolated terminally from patients in the Phase 3 cSSSI Studies remained within two-fold of those determined at baseline. Actually of the 17 patients who showed a doubling of their MIC from baseline at any time post baseline, only four had a critical response of failure.

And the relapse rates that were determined approximately one month after the test-of-cure visit also show no difference in either the ITT or the clinically-evaluable groups, and were around 2 percent.

So, let me conclude and leave you with five points. Both Phase 3 studies achieved their primary efficacy endpoint within their predefined noninferiority margins. And efficacy was consistent in all patient populations in disease categories. Notably, in patients with underlying diseases, including diabetes, HIV/AIDS, and renal, and hepatic insufficiency, Oritavancin was as effective as comparator. Microbiological efficacy was

established for several common pathogens for cSSSI, including Staph aureus, MRSAs, Strep pyogenes, and Enterococcus faecalis.

And last but not least, you know, a short course of Oritavancin was as effective as 10 to 14 days of comparator with a low relapse rate.

I thank you for your attention. And I would like to now to turn the podium back to Dr. Parr -- or Dr. Moriarty who will share with you the safety data on Oritavancin.

DR. MORIARTY: Thank you, Dr. Etienne.

Good afternoon. I'm Susan Moriarty, senior director of medical affairs for Targanta Therapeutics. Today I'll present a brief overview of the safety data and analyses for Oritavancin. I'll concentrate primarily on Phase 3 safety data, but I'll also touch on some relevant, nonclinical and earlier clinical findings.

I hope to demonstrate to you through this brief review, and through the information provided in the brief document the following points: Oritavancin is well-tolerated in patients with complicated skin and skin structure infections. Safety data do not indicate a need

 

for dose adjustments in special populations. This finding supports the same conclusion based on PK data. And no special laboratory monitoring is indicated for safety.

There were 1,173 patients who received any amount of Oritavancin in these Phase 3 studies, and these patients comprise the safety-intended treat or ITT population.

To summarize the exposure to Oritavancin in this population, 96 percent of the patients received IV therapy for three to seven days, 85 percent received the recommended cumulative dose range for cSSSI of 600 to 2,100 milligrams. And the mean duration of treatment with Oritavancin was 5.1 days. Patients were then followed for 39 to 90 days from the first day of dosing.

Now beginning our review of the standard safety analyses, we'll start with adverse events. I'd like first to clarify, that throughout this presentation, significant refers to statistical significant with a P value of less than .05. On some of the slides you will note specific P values.

To summarize the overall adverse events in

 

these Phase 3 studies, I'd like to start by orienting you to this graphic. Illustrated here is the percentage of patients with at least one treatment emergent adverse event on a vertical axis, with the Oritavancin-treatment group again in blue, and the Vancomycin-treatment group again in gray.

As we look at the percentage of patients in each treatment group with at least one adverse event, we see that significantly lower percentages of Oritavancin than Vancomycin-treated patients had an adverse event. This is true when we look at the entire study period where comparator was IV Vancomycin, with or without follow on Cephalexin, and it's also true in the -- during IV therapy, during which comparator was Vancomycin alone.

In addition, a significantly lower percentage of Oritavancin than Vancomycin-treated patients had an adverse event that the investigator considered to be possibly related to study drug.

Next, as we look at the most common adverse events in these studies, noted on the vertical axis are the adverse events occurring in at least 2 percent of Oritavancin-treated patients.

 

On the vertical axis, the adverse events shown in yellow text were seen in a significantly lower percentage of Oritavancin than Vancomycin-treated patients. Those events are insomnia, pruritus, and rash.

You'll note the adverse event of dizziness shown here in red text is the only adverse event that occurred in the significantly higher percentage of Oritavancin patients. This finding prompted us to look very closely at the study data for each of these patients with dizziness, where we found no specific evidence to indicate vertigo, vestibular or inner ear toxicity, or concurrent clinically relevant decreases in blood pressure, ventricular arrhythmias, or central nervous system events.

In addition, we found in our study that comparable percentages of Oritavancin and Vancomycin-treated patients had an adverse event of dizziness considered to be possibly related to study drug by their investigator. And we found that the incidents of dizziness did not increase in patients receiving higher doses of Oritavancin.

In an effort, then, to sort through these

 

adverse events and focus on those that we felt were most likely to be related to study drug, we defined treatment emergent adverse events of interest. These events were potential glycopeptide class related events, or those events that occurred in at least 1 percent of Oritavancin-treated patients in the during IV therapy phase where we saw most adverse events occur, and in a significantly different percentage of Oritavancin, compared to Vancomycin-treated patients.

Illustrated here on the vertical axis are the 12 adverse events that fit our criteria for adverse events of special interest. Of these 12 events, there are seven noted here in yellow text, which occurred in a significantly lower percentage of Oritavancin than Vancomycin-treated patients.

In looking at these events, it's interesting to note that these are symptoms and signs which can represent histamine-like infusion reactions, or red man syndrome.

The remaining five events seen were seen in comparable percentages of Oritavancin and Vancomycin-treated patients. Four of them are symptoms and signs

potentially related to injection site vein inflammation or phlebitis. As noted in the briefing document, Targanta's focused and comprehensive review of injection site phlebitis also demonstrated a comparable incidence in Oritavancin and Vancomycin-treated patients.

Next we'll look at the categories of adverse events frequently referred to as notable events, where we see that Oritavancin and Vancomycin-treatment groups had comparable percentages of patients who had serious adverse events, including a comparable percentage who died.

In contrast, though, we see a lower percentage of Oritavancin than Vancomycin-treated patients who discontinued study drug due to an adverse event.

To address any potential safety concerns related to Oritavancin's long residence time in the body, Targanta analyzed the timing of onset of adverse events, and the time to resolution of adverse events.

First, illustrated here, we see the rate of adverse events per patient on the vertical axis, and the study date displayed on the horizontal axis. Please note that the final bars on this figure represent days 28

 

through 90, with a gray bar reflecting a higher rate of events over this time frame in the Vancomycin-treatment group.

We see no indication of later adverse event onset, nor of any increased rate of events beginning later in the study in the Oritavancin-treatment group.

We then used the Kaplan-Meier method to construct this illustration of timing of resolution of adverse events. By looking at the fraction of these events resolving per day after onset displayed on the vertical axis, we see that the time to adverse event resolution was similar in the Oritavancin-treatment group shown in blue, and the Vancomycin-treatment group shown in white.

As discussed in the briefing document, safety review of clinical laboratory and vital signs measurements demonstrated no clinically relevant safety differences between the Oritavancin and Vancomycin-treatment groups, including no indication of renal or hepatic toxicity with Oritavancin, and no safety signal in the Oritavancin-treatment group.

Subgroup analyses of adverse events and

 

laboratory studies were done in patients with varying demographics or underlying diseases or conditions at baseline. Despite the allowance of medically-complex patients in these studies, including those with any degree of hepatic or renal insufficiency, any degree of underlying immunocompromise, the data demonstrated no clinically relevant safety findings in any of these treatment groups.

This lack of safety signal supports PK data concluding that no dose adjustment is required in any of these patient groups.

Next I'd like to briefly summarize our analyses of potential glycopeptide-related effects, which are discussed in more detail in your briefing document.

Although Oritavancin is a lipoglycopeptide, we knew from nonclinical and earlier clinical studies that it does share certain adverse effects with some of the other glycopeptides, specifically injection site phlebitis and histamine-like infusion reactions.

When we look at Oritavancin compared to the well-known, widely-used glycopeptide Vancomycin, we see no evidence of drug associated endorgan toxicities with

Oritavancin, including no evidence of renal or hepatic toxicity. And we see no evidence of Oritavancin associated cytopenias. And Targanta's comprehensive review of adverse events demonstrated a comparable incidence of injection site phlebitis, and a significantly lower percentage of Oritavancin-treated patients with histamine-like infusion reactions or red man syndrome.

In understanding the evaluation of Oritavancin, with regards to cardiac safety, some background information is helpful. Nonclinical data revealed a potential signal in a hERG channel in vitro, primarily at higher concentrations of Oritavancin.

Subsequent dog studies did not reveal any evidence of QT prolongation or of arrhythmias with treatment with Oritavancin.

Then in 2007 Targanta completed a thorough QTc trial in accordance with the current E-14 Guidelines, which included an active control of Moxifloxacin, a concurrent placebo control, and both a clinical 200 milligram and a super therapeutic 800 milligram dose of Oritavancin.

 

The study demonstrated adequate sensitivity, with a significant QT effect with Moxifloxacin and no QT effect with either the clinical or the super therapeutic dose of Oritavancin.

In addition, we have in Phases 1, 2 and 3 ECG data, which was collected on patients and healthy subjects specifically for evaluation of QT interval, read in a blinded fashion at a central lab, demonstrating no evidence of QT prolongation with Oritavancin.

As noted in the briefing document, review of laboratory testing that might indicate adverse effects of Oritavancin on the liver, demonstrated comparable percentages of Oritavancin and Vancomycin-treated patients, starting at normal baseline, with subsequent elevations of hepatic transaminases, alkaline phosphatase, and/or bilirubin.

In addition to these standard laboratory analyses, we also screened the Phase 3 safety database for potential drug-induced liver injury cases, using the relatively inclusive laboratory screening criteria of greater than three times ALT or AST, along with a significant elevation of bilirubin, but without regards

 

to alkaline phosphatase levels.

In conducting this screening, we found identical percentages of Oritavancin and Vancomycin treated patients who met these inclusive screening criteria. Both of the Oritavancin-treated patients had ongoing pre-existing liver disease at study entry. In fact, one of them met screening criteria at study entry. And then neither of these had significantly -- significant worsening of liver laboratory test following the administration of Oritavancin.

The one Vancomycin patient did not have documented prior liver disease, though they did have a complicated clinical course.

In conclusion, no Oritavancin-treated patient met Hy's Law criteria.

In summarizing the safety of Oritavancin for the treatment of cSSSI, I'd like to leave you with the following observations. Oritavancin has a comparable or better safety profile than Vancomycin in patients with complicated skin and skin structure infections. Overall, compared with Vancomycin, Oritavancin showed a significantly lower percentage of patients with treatment

 

emergent adverse events, with a possibly related treatment emergent adverse event, and with discontinuation of study drug due to an adverse event.

In addition, there were lower or comparable percentages of patients in the Oritavancin-treatment group with potential glycopeptide related events.

Further, both the safety and PK data support the conclusion that Oritavancin does not need to be dose adjusted in special populations, including those with renal or hepatic insufficiency. And there is no indication for special laboratory monitoring for safety when administering Oritavancin for complicated skin and skin structure infections.

Now I would like to summarize the benefits versus the risks for using Oritavancin in treatment of cSSSI.

As you know, all of the currently available therapies have some limitations of their usefulness related to the antibacterial spectrum, or the development of resistance, to poor tolerability, or to efficacy and safety in certain patient populations. Because of these factors, there's an ongoing medical need for new

 

therapies to treat Gram-positive cSSSI, particularly in medically complex patients.

As you've read in your briefing documents and heard summarized briefly today, Oritavancin has demonstrated efficacy in the treatment of medically complex patients with cSSSI, and a favorable safety profile compared to Vancomycin, with or without follow-on therapy with Cephalexin.

Of note, a lower percentage of Oritavancin-treated patients had an adverse event, a related adverse event, discontinued treatment due to an adverse event, or had a possible histamine-like infusion reaction.

A wide range of laboratory studies have demonstrated that Oritavancin has potent activity against common Gram-positive pathogens, it's rapidly bactericidal, and it has multiple distinct mechanisms of action. These properties should result in a reduced potential for the development of resistance to Oritavancin. In fact, there have been no increases in Oritavancin MICs in clinical studies to date.

Oritavancin has demonstrated clinical efficacy and safety in treating cSSSI with simple, once daily IV

 

dosing, requiring only a single dose adjustment based on body mass.

This simple dosing should result in fewer medication errors and a lower risk for under or overdosing, for example, in patients with changing renal function.

Patients with renal or hepatic insufficiency require no changes in dosing, and blood levels do not need to be monitored for efficacy or for safety.

Further, there's no indication for special laboratory monitoring for safety. As with all medications, the risk of clinical adverse effects not seen in clinical studies, there is a risk of them being reported after more wide spread use. Targanta will monitor for such occurrences through post approval safety monitoring and in future clinical studies. And as with all antibiotics, there is the ongoing risk of development of resistance. We will be monitoring resistance trends and planned surveillance studies, and in future clinical studies.

In summarizing the benefits and risks of treatment of cSSSI with Oritavancin, I would like to

leave you with the following points. Oritavancin offers the benefits of demonstrated efficacy and a favorable safety profile in a broad range of patient populations, no laboratory monitoring indicated for efficacy or for safety, a simple once daily three to seven day treatment course for complicated skin and skin structure infections, with a single dose adjustment based on weight. These features should result in a decreased risk of medication errors, and of under or overdosing, especially in patients with changing renal or liver function.

Oritavancin also offers multiple distinct mechanisms of action, rapid bactericidal activity, and activity against quiescent nondividing bacteria, features that are anticipated to forestall the emergence of resistance, and potent in vitro activity against pathogens resistant to other available therapies.

On the other hand, risks include the infusion-related events of injection site phlebitis and histamine-like infusion reactions. The risk of these events with Oritavancin administration is similar to or lower than the risk of these events with the administration of

 

Vancomycin. Targanta has studied these events in clinical trials and will include clear instructions for healthcare professionals in the package insert to help minimize their occurrence and their severity.

Other potential risks not yet seen with Oritavancin include rare adverse events not seen in clinical trials to date. Targanta has initiated discussions with FDA and other partners, planning pharmacovigilance and microbiological surveillance studies to monitor and manage the risks of seeing rare adverse events, or of seeing development of resistance in the future.

We believe we've demonstrated to you that Oritavancin is a new, valuable therapy for complicated skin and skin structure infections, with a robust and promising benefit risk profile. Thank you for your attention.

DR. RELLER: We shall now hear the presentation of the FDA from Dr. Nasim Moledina.

DR. MOLEDINA: Good afternoon. And I don't know how exciting my presentation will be after the sponsor's presentation, but I'll try my best and point

 