out a few things that are different.

As an overview of my presentation, I will give you a background, and present some PK characteristics of this drug, and describe the two studies that have already been described in great detail, present efficacy results, and the safety, and then -- and some issues for discussion.

As a background, the proposed indication for this Oritavancin is treatment of adults with complicated skin and skin structure infections caused by susceptible isolates of the Gram-positive organisms. And this includes the methicillin-resistant Staph aureus.

The dosage proposed for Oritavancin is 200 milligrams daily for three to seven days, and 300 milligrams for those patients who weigh more than 110 KGs.

Some of the PK characteristics of Oritavancin are as follows: The pharmacokinetics show that its linear doses ranging from 0.05 milligrams per KG to 10 milligrams per KG, and at fixed doses ranging from 100 milligrams to 800 milligrams.

But when you look at the plasma

 

concentrations, it declines within the first 24-hours to less than 11 percent. That is not substantial accumulation of Cmax after 10 days. But when you look at the Cmin after 10 days, it's -- there is a three-fold accumulation.

And the volume of distribution shows that it distributes in a wide -- about 1,000 liters, and it distributes into the phagocytic cells.

As you already heard, Oritavancin is not metabolized, but when you look at the excretion pharmacokinetics of Oritavancin, less than 5 percent of the dose is excreted in urine, and less than 1 percent in feces after 14 days.

Most of the PK studies were done for 14 days in the Phase 1 study, and when you look at it the terminal half-life was approximately 320 hours.

I will now discuss each of the studies separately. I will not attempt to combine the two studies. And you will -- I will discuss that as I go on in my presentation why I'm not doing that.

The bigger study was the second study, actually, which was Study ARRI. And this was set up as a

 

Phase 3, randomized, double-blind, multicentered study where patients were randomized to receive either 200 milligrams of Oritavancin, and those patients who weighed more than 110 KGs received 300 milligrams. And the comparative group was Vancomycin, and they received 15 milligrams per KG. And if they did not have resistant organisms, that can be sort of switch on to get oral therapy.

The randomization was also stratified by disease categories where it was separated by wound infection, major abscesses, or cellulitis.

In the second study, which is Study ARRD, this was also a Phase 3 randomized, double-blind multicenter study, but this study was set up as a three-arm study where Oritavancin was given as two different doses, one was 1.5 milligrams per KG, and the other one was 3 milligrams per KG, but the comparative drug was the same as the previous study. And in this study, also, the treatment duration was three to seven days in both of the Oritavancin arms, and 10 to 14 days for the Vancomycin arm.

Now I will just like to give you an overview

 

of how the 3 milligram dose of Oritavancin in the ARRD Study compares to the 200 milligram dose in the ARRI Study.

The few slides that follow after this slide were given to me by our clinical pharmacologic reviewer, Dr. Ryan Ovin (ph). So, if you have any questions about that, I'm sure he's in the audience today and he can help you out with that.

So, the mean comparisons were done between the dose of ARRD that was 3 milligrams, because virtually the entire 1.5 milligram per KG arm would have received a lower dose than 200 milligrams. And this is the dose that sponsor wants to use in the label. In the ARRI Study, of course, the patients were dosed on a fixed 100 milligram dose.

So, when you look at the comparison of doses in these two studies, the number of patients -- excuse me -- in the ARRI Study who received a dose of 200 milligrams, or who were more than 110 KGs, received a dose of 300 milligrams. But when you compare those patients in the ARRD who received a dose of 3 milligrams per KG, and you look at the range of patients who were

 

between 49 KGs and 110 KGs, they were -- this is not inclusive of all patients, because there were some patients who received less than 49 KGs who received -- who weighed less than 49 KGs, but they were just identified as less than 49. So, those patients we have not included in this table.

And here you can see that, in the ARRD Study patients who received 3 milligram per KG dose, the maximum dose that they received are -- sorry, the mean dose that they received was 224 milligrams. So, it was more than the 200 milligram dose.

The purpose of this slide is to illustrate how close the 3 milligram per KG dose in the ARRD was to the fixed dosing in the ARRI. In the second column -- I don't know if I can -- in this column, in the second column, we have doses that would correspond to 10 percent, 15 percent, and 20 percent difference from the ARRI fixed doses of 200 milligrams, and 300 milligrams; separated by the weight range in the third column, the percentage of patients that were dosed within this range. When you look at this, then, about 10 -- 21.3 percent of patients in this dose range received more than

 

10 percent of the ARRI dose. When you look at the third column, this is the percentage of patients in the ARRD that were dosed at less than or equal to higher dose bound, which is like 220. And there were 42 percent of patients in -- who received either 220, or less than 220 milligram.

So, overall the point of this slide is to illustrate that the dosing regimens between ARRD and ARRI were not at all similar. And that many of the patients in ARRD, 300 -- 3 milligram per KG dose received a much higher dose than if they would have been in that ARRI Study.

This is the graphic presentation of the same information that I provided at -- the patients in the ARRD, 3 milligram per KG dose were -- received a higher dose, because they were heavier patients.

So, in conclusions, on average, patients in ARRD 3 milligram per KG received a higher dose and had higher exposures, as compared to patients in ARRI.

So, any differences that we find in efficacy between ARRD 3 milligram per KG group and ARRI fixed dose, are definitely not due to patients in ARRD 3

 

milligram per KG dose receiving a lower dose.

Now, moving on I will present each study outcome -- efficacy outcome separately. I'll start with the larger study, which is Study ARRI, where the primary efficacy endpoint was sponsor-defined clinical outcome at the first follow-up visit, which was a test-of-cure visit. The noninferiority margin set up for this study was 10 percent.

When you look at the baseline demographics in this study, in two -- core primary population, which was the ITT population and the clinically-evaluable population, in regards to sex, and ethnic origin, or the age, they were comparable in both the groups.

When you look at the success rate in this slide, the only difference that I have that is different from the sponsor's projection of the efficacy data, is all the missing and undetermined values were counted as failures. So, when you look at the ITT population, you might find that the cure rates are slightly different than what the sponsor presented.

And basically what I want to show you, that when you look at the 95 percent confidence intervals, the

 

difference between the two groups, whether it is the ITT group or the clinical-evaluable group, it meets the 10 percent noninferiority margin.

We just looked at the ITT population and calculated the 99.875 confidence intervals, which would be like you are, you know, using this one study as two studies. And the confidence interval was minus 5.9 and upper bound was 12.

When you look at the baseline pathogens in this study -- I have not included all the pathogens -- but these are, you know, the majority of the pathogens. And I just want to bring your attention that -- when you look at the Staph aureus, including MSSA and MS -- MRSA, you see that the outcome was comparable to Vancomycin. But when you look at MRSA, the outcome of -- for Oritavancin group was about 12 percent less. But, just to be fair, when you look at the Strep pyogenes, Oritavancin did almost 20 percent better than the Vancomycin group.

In the second study, ARRD, the primary efficacy endpoint was investigator defined clinical outcome at test-of-cure visit. The efficacy analyses

 

methods using this study were the same as in the ARRI, except for the noninferiority margin, which was set at 15 percent.

This multiplicity issue has already been mentioned by the sponsor, but I still would like to point out that this study was set up to compare two different dosing of Oritavancin with a comparator group. And the sponsor had calculated the 95 percent confidence interval for the success rate. And we requested that 97.5 percent confidence interval should be calculated to sort of adjust for this multiplicity issue.

And the demographics for this study also, in both the core primary groups of ITT and clinical-evaluable groups were comparable in the Oritavancin, both the arms, as well as Vancomycin when sex, and ethnic origin, and age was concerned.

When you look at the clinical outcome or success rates in this study, I just highlighted the clinical-evaluable population of 3 milligrams per KG dosing, because we know that most of the patients in 1.5 milligrams per KG did not really get the level dose, so, I will just look at the 3 milligram per KG column for the

 

outcome.

And there the cure rates was 73.4 percent compared to 75.4 percent in the Vancomycin group. And the point difference is minus 1.9. And the confidence intervals barely made the 15 percent.

As far as organisms were concerned, this was a much smaller study. And we have fewer organisms. But methicillin-resistant Staph did much better in this study than the previous one. But Strep pyogenes also did better in the Oritavancin 3 milligrams group. And -- but the numbers are very small.

Since we were -- we have been talking this past two days about categorizing the chronic -- the complicated skin and skin into different infections, I just would like to sort of bring to your attention that most -- most of the patients were divided into these three groups. And the outcomes were the same as if you would combine them together. So, there was really not much difference, except that there were more major abscesses in the larger study on -- than in the smaller study. So, that basically gives you an outline of the efficacy.

 

And moving on to safety, I really do not have much to add to what the sponsors has already mentioned. And there were two Phase 2 studies, in which 1,173 patients were treated with Oritavancin, and 590 patients with Vancomycin. And when you look at the deaths, and this was also discussed by the sponsor, that most overall the majority of deaths were related to the underlying medical conditions, because the patients really -- were very sick, as when they were entered in this study.

There were some serious adverse events that occurred in this -- also the numbers were the same as whatever the sponsor had presented, like 9.1 percent of patients in the Oritavancin group, and 11.4 in the Vancomycin group.

I have listed some of selected serious adverse events. This occurred in less than 1 percent of patients. Usually we do not label this, but this was very evident that there were some adverse events that happened more in the Oritavancin group than in the Vancomycin. And I just did this as an exercise to sort of let you know that there were more infectious kind of adversity actions in the Oritavancin group. But when you

 

look in detail as to how many of those patients got osteomyelitis. And I went through the data and realized that most of those patients were very complicated. One of the patient had MRSA lipidemia, would have osteomyelitis. There was -- most of the patients were drug abusers. There was a group B sepsis patients with hepatitis. There was a beta vascular disease patient with insufficiency. He had developed gangrene and diabetes mellitus. So, there were -- these were patients who really developed these complications based on their underlying disease.

As far as discontinuations of drug was concerned, in the largest study, ARRI, the discontinuation rates were comparable with Vancomycin. And this table gives you a detail of -- that most of the discontinuations were because of lack of efficacy.

In the same way, in the ARRD Study, the discontinuations were comparable across the treatment groups. And here also, because the numbers are smaller, lack of efficacy was the -- sort of stands out as one of the reasons for discontinuation.

There was a special interest in the IV

 

phlebitis ADR based on the initial Phase 1 studies that were done with Oritavancin. And -- because in that -- in those -- a couple of Phase 1 studies, basically more than 90 percent of patients develop IV phlebitis, or -- the company went on and did a separate Phase 1 single-center, randomized, double-blind study, where they studied two different doses of Oritavancin. They were separated by 14 days. So, there would -- to one group they would give 200 milligram doses, and then followed by a dose of 800 milligrams. And this 800 milligram was divided into two doses of 400 milligrams. And 15 healthy men were enrolled in this study, and 13 completed the study.

The -- when you look at the ADRS that were reported, in this study there were three subjects who experienced injection site phlebitis after receiving the 800 milligram dose. And then there were two subjects who experienced injection site reactions, excluding the phlebitis, but they had edema, and erythema swelling and tenderness. And this happened after the 200 milligram dose.

And there was one patient that just I think he just -- the IV site was just bad, I guess. And this

 

occurred after -- during the infusion of the first of the 800 milligram dose. And two of the subjects experienced the histamine-like infusion reactions after the first exposure of 800 milligrams.

So, when you look at this study that was very well done, it didn't really give us any additional information than we -- what we already knew. And based on this I just wanted to give you an idea of what the treatment emergent ADR of this IV infusion phlebitis in the Phase 3. And then you look at that are -- phlebitis was noted in, like, 1.6 percent of Oritavancin patient, compared to 1.5 percent of Vancomycin patients. And the infusion site, pain was reported in 1.7 percent of Oritavancin patient, compared to 1.9 percent of Vancomycin patients. The only thing that was different in the Phase 3 study was the Vancomycin patient had more pruritus reported in the database. So, basically, this is something that we can definitely address in labeling.

So, that really concludes my talk. And the issues for discussion for today's Oritavancin NDA is, does the Study ARRI independently provide evidence of the efficacy, of the effectiveness of Oritavancin for cSSSI,

 

the primary outcome of 95 percent versus 99.89 -- 99.875 percent confidence intervals for this study?

I want to discuss the outcomes for patients with known baseline pathogens, particularly MRSA. The second question would be: Does the second study, ARRI -- ARRD independently provide evidence of the effectiveness of Oritavancin? And then to discuss the primary outcome and the weight-based dosing regimen used in this study.

And the third question would be: Does the data provide safety and effectiveness of Oritavancin for the treatment of complicated skin and soft tissue infections?

I would like to thank the team in my division who helped me put this thing together. Thank you very much.

DR. RELLER: Thank you, Dr. Moledina.

We're now open for questions for either the sponsor or for the FDA. Dr. Bennett.

DR. BENNETT: Dr. Moledina, can I ask you about your Slide 16? Can we put that up, please?

In this slide it shows that the difference in the response rate to Oritavancin and Vancomycin for MSSA

 

is only 2.4 percent difference, with the favor being Oritavancin. But in the MRSA it's the other way around, with a 12 percent difference in favor of Vancomycin.

Can we also look then at Slide 21? Because although the numbers are smaller, we see the same thing; and that is, although there are two doses of Oritavancin, the difference in MRSA is 22.5 and 17.1 percent in favor of Vancomycin.

So, the question is: How do you evaluate Oritavancin for the subset of MRSA? I've already said I'm not thrilled about subset analysis, but this is a subset of specific interest. So, am I missing something?

DR. MOLEDINA: I mean, that's why when I presented I told you that all the numbers were jumping around. There was -- there's no consistency. There is really no -- because in one study, in the ARRI Study, the MRSA did much worse in the Oritavancin group, but when you look at the ARRD Study, MRSA did much better. I don't know. Maybe the investigators are from different sides. I don't know. But -- I don't know the reason why this -- I don't know the reason for the outcome. Maybe the sponsor can help you.

 

DR. BENNETT: So, it is --

DR. RELLER: Dr. Bennett.

DR. BENNETT: So, it is your opinion that the Oritavancin performed equally well in the MRSA subset? That's a question.

DR. COX: I mean, I think, too, I mean, that's one of the questions that we actually wanted to hear some discussion from the committee on. I mean, if that's okay.

DR. RELLER: Dr. Bennett put his finger on the issue right at the outset. And we just need to hear, what gives?

Dr. Fleming.

DR. FLEMING: Well, I just -- just to reinforce, that he's getting at one of the issues that I was noting. And he's right, it's an issue where it's a subgroup. It's a small number, but MRSA is of real interest. So, it is certainly less problematic when you're delving into something that you would have in advance specified to be of keen interest. It is a 12 percent difference in the study that has the larger sample size. And actually it's a 7 -- I mean, pooling

 

the two dose arms, it's 50 percent against 57, so, it's also a 7 percent difference there. So, I had the same question. I don't know what to make of this, in terms of how reliable it is. But it's certainly a suggestion that, for MRSA, Vancomycin might look -- certainly trending better.

DR. RELLER: Dr. Septimus, then we'll come back to a response by Dr. Parr, and then on the other side, Drs. Follmann and Kauffman.

DR. SEPTIMUS: I'll follow up on that and ask whether or not there were any analysis of MICs between the groups that might explain some of those differences. And then I would also ask another interesting difference on -- I think it's Slide 44. We looked at the response for Group B Strep and Group A Strep, and there was some interesting variations in response to those organisms as well, and whether the sponsor had any comments as to what those differences were. I think it's on Slide 44, I believe.

Yeah. As you can see, Group B Strep 86 versus 67, group A is 66 versus 78. Interesting differences, and I wanted to know if they had any explanation for

 

that.

DR. RELLER: To keep track of these items, let's hear from Dr. Parr next.

DR. PARR: I think this is a summation of the -- the question that we started to entertain, which is from the briefing document -- the FDA's brief document, Table 6.5, that points out what Dr. Fleming noted, that there's a 12 percent difference in the ARRI subgroup for MRSA.

We were surprised by this finding. When we've looked at nearly 7,000 Staphylococcus aureus strains, half of which are MRSA and half of which were methicillin-susceptible, there was no indication, that, based on a potency measure, there would be an anticipated difference in the efficacy.

When we were doing animal experiments for target attainment, understand how much drug was required in order to treat successfully methicillin-susceptible Staph, or methicillin-resistant Staph, we again did not see a difference in the amount of drug necessary to treat the animals if they were methicillin-resistant. The first column in this graph is a methicillin-susceptible

 

type strain, 13709. The next four columns are methicillin-resistant Staph aureus strains, with the last two being Vancomycin-resistant Staph aureus strains.

The height of the bar indicates the area under the concentration curve in mice normalized to exposures in humans. That would allow you to provide a static dose a one, a two, or a three log killing.

And, as you can see, this methicillin-susceptible strain requires as much drug as the methicillin-resistant strains, perhaps more in some cases. Incidentally, on this slide, the actual exposure in humans would be about up at the yellow line at the top. So, it was unanticipated to us that we would see the results that popped up in the analyses.

We are convinced that this is an imbalance that was seen in the table is due to a protocol specified failures being unusually low in the Vancomycin MRSA subgroup in the MITT population, which was on that table for MRSA.

Overall protocol driven failures could be attributed to patients who did not receive surgical intervention in -- under 48 hours following enrollment

 

into this study drug start.

In general, for the population overall, 50 percent were seen to be disqualified as failures for this purpose. In the case of Vancomycin, the data are 29.4 percent.

Due to the randomization, the power given to the Vancomycin numbers is magnified. And should the imbalance based on this protocol rule be in harmony with the rest of the study, the difference would shrink to 4 percent.

To give you, then, the data underlying the assumption that they were imbalance overall, this is the ITT analysis of failures. And, again, based on this protocol-driven role, they -- it was balanced between Oritavancin and Vancomycin in general, but not as I just showed you with respect to the MRSA subpopulation.

There is also an underlying medical explanation for the imbalance. And I'd ask Dr. Etienne to elaborate on that.

DR. ETIENNE: Thank you, Dr. Parr.

So, Dr. Parr explained that there was a lower than expected number of MRSA cases on Vancomycin who were

 

coded as failures because of their first surgical intervention being done right outside -- or outside the 48-hour window.

And this raises a couple of questions. What was the surgical condition of those patients at baseline? What was the relationship between the surgical condition of those patients and the timing of the intervention?

So, what I'll -- I'll walk you through those relationships in the entire study in general, and then I'll walk to the MSSA subpopulation. And we'll look at the MRSA's population to finish this.

Okay. Okay. Perfect. Thank you. So, this is Study ARRI in its entirety. And, as you can see, approximately 15 percent of all patients were coded for failure, because their first indication -- their first surgery was done after 48 hours, after the beginning of study drug.

So, this rule is applied regardless of whether the surgery was justified -- or what was planned or unplanned. And the other important thing to realize, that this rule is not limited to the ITT population, that

 

proportion, 15 percent, is carried through all the populations, the -- including the CE population.

Now, when we look at the entire list of patients who were coded as failures for that reason, and we look at their surgical condition at baseline, we realize that half of them, approximately, had a condition at baseline that justified a surgical intervention.

Now, you know, this was not done by case-by-case review, this was done programmatically, taking into account the information coded by the investigators.

And we are talking about real indications for surgery, the presence of moderate or severe devitalized tissue, or the presence of moderate to severe purulent drainage.

We then looked at the population of MSSA patients, and you can see that that relationship is maintained in that population. Approximately half the patients coded as failures have a surgical condition at baseline that is a -- is an indication for surgery.

The symmetry is kept here, but when we go to the MRSA population, we lose that symmetry. And we have 17 patients in the early group, versus two patients in

 

the Vancomycin group, who really have three things in common. They have a condition at baseline, which is an indication for surgery. They're coded as failures because their first -- you know, their first indication -- their first surgery is done after 48 hours. And they are coded as failures because of that rule.

So, the bottom line is, that this rule was systematically applied in the entire trial and had symmetrical consequences in the entire Phase 3 population, except in the MRSA group where it had unintended consequences.

DR. RELLER: We'll come back to Dr. Fleming, because earlier we had -- is it related to this specific issue? Yes. Then go ahead.

DR. FLEMING: It is. And you can tell me if you want to come back to it.

DR. RELLER: Right.

DR. FLEMING: I -- what's possibly underlying this is even a more fundamental issue. And I'm really struggling with the definition of the primary endpoint, which is very much a part of what these slides are trying to get at. So, you tell me whether you want to discuss

that right now or wait a moment.

DR. RELLER: Go ahead.

DR. FLEMING: Okay. Obviously the primary endpoint is very key. It needs to be clinically relevant. It needs to be interpretable. But it's particularly key in a noninferiority trial, because the justification of the margin is specific to what the endpoint is. We talked about that a great deal yesterday. And IDSA had defined a set of A criteria that were all very specific to looking at, judging resolution of the disease, and directly measuring resolution of symptoms, et cetera. And the justification of the margin is, therefore, based on using an endpoint that is, in some real way, similar to the endpoint that you used for evidence-based formulation of the margin. That's one major issue.

Another major issue is, it needs to be very relevant and interpretable. The -- we see variations of the idea, say. And it's looking at actual resolution of symptoms, direct measurement of resolution of symptoms. This endpoint I've looked at over and over and over again, trying to really get the best sense of what it

 

is. And it's in the FDA -- the best place where I see its definition is in the FDA briefing document on Page 15. It wasn't really presented in detail by either of the presentations today. And it's got three fundamental components on Page 15 of the FDA briefing document.

If a patient was given a systemic antibiotic, with activity against Gram-positive pathogens at any time, that's a failure. So, a specific antibiotic with activity against Gram-positive.

Second, if any procedure was performed to treat a primary study condition, but it had to have started more than 48 hours after initiation of therapy, then that counts -- something that goes before 48 hours and repeated after 48 hours doesn't count -- or if it's missing then you're a failure.

So, the endpoint seems to be, basically, do you need rescue antibiotics at some point for Gram-positive, or do you need an intervention but it has to be for the primary clinical condition? It can only be counted if it's after 48 hours. It's a -- my trouble -- the trouble that I'm having with this is, it in some sense represents the clinical condition, but it's surely

 

a surrogate for resolution. And it's a surrogate that could be very misleading. I remember back to my days more than 15 years ago with NIAID sitting on data monitoring committees looking at PCP prophylaxis and HIV, and looking at agents like Bactrim that didn't look very good when you used these measures, because they were very potent, but couldn't be tolerated by everybody. So, if you used time to discontinuation measure, you would have thought it was not a very good intervention.

And there are some differences. They're not profound. But when you look at the reasons for discontinuing, people are discontinuing somewhat more often on Oritavancin because of lack of efficacy. So, they're discontinuing because of lack of efficacy.

As the sponsor pointed out -- and they're right -- there's more discontinuation for adverse events on Vancomycin. So, people are discontinuing for different reasons. It has a little bit of that flavor of that Bactrim scenario, but it leaves me incredibly confused about how to interpret it. To me it's a proof of concept measure. It's giving me a sense, but it by no means is measuring directly, what is the difference in

 

these two resolutions in resolution of the clinical condition? Much like the FDA worked hard to try to achieve, and IDSA tried to -- worked hard to try to achieve, and some of the rest of us who did literature reviews as well.

So, two things. First, I don't know how to justify a margin using this endpoint.

Secondly, this isn't a direct measure, as other measures that we would look at, that's directly looking at resolution of symptoms. So, I guess one positive is, maybe there isn't a problem with MRSA. I don't know. I can't interpret this measure clearly.

DR. RELLER: Dr. Etienne, can you connect the dots here? I mean, we see a disproportionate falling into the categories you described, but how does that specifically relate to the greater failure, specifically in methicillin-resistant, as opposed to methicillin-susceptible Staphylococci?

DR. ETIENNE: Well, I -- we haven't done -- the difference we observe in the MSSA subgroup is quite small, right? So, the difference that is perplexing is in the MRSA subgroup. And I can only share Dr. Fleming's

 

perplexity about the use of those rules. But those rules are not -- the first measure of outcome is the resolution of signs and symptoms, which is included in the investigator defined clinical outcome. It is only in two situations where those rules may interfere, so to speak, with the judgment of the clinician. And those two rules make sense, but they do not reflect -- they don't -- they do not always reflect clinical practice. I mean, the rule of concomitant antibiotics use, for instance, is not error proof, in the sense that another antibiotic may be prescribed almost by accident.

And, similarly, the rule -- the surgical window rule is not error proof either. I mean, the logic behind the rule is that, since the patients are expected to be treated surgically within 48 hours, if they are treated surgically after 48 hours, something may have gone wrong with that patient or the patient may have deteriorated. And that rule is to catch those patients deteriorate. And the reason why you put a limit on that window, is to try to equalize a variety of practices that -- and surgical response teams -- or the response of surgical teams across -- in a multicentered trial.

 

But was this rule a little too strict in this case? The data would suggest that, yes. And it had symmetrical consequences overall, and asymmetrical consequences for the MRSA subgroup.

DR. RELLER: Before Dr. Goetz and Dr. Alston, we had two questions over here on the right, Dr. Follmann and Dr. Kauffman, who were waiting to speak.

DR. FOLLMANN: I have a couple of comments. The first relates to, you know, the issue of whether there's a difference in chair as a function of the baseline pathogen, in particular MRSA. So, I noticed the same thing you had said, Dr. Bennett.

And, if you could bring up the Slide 16 of the FDA, I could make the point more easily. It was mentioned earlier, I think there's a 14 or so difference in the cure rate for MRSA. If you look at the line below it, there's like a 20 percent difference in the cure rate favoring Oritavancin. And if you do statistical tests of those, there's a P of .07 for the MRSA test of whether there's a difference in cure rates, but there's a P of .01 for the pathogens just below at the pylotaneze (ph).

So, when I did that I thought, you know, I was

 

inclined to think this is just subgrouping safari basically, and I didn't really know what to make out of it. So, that's my comment regarding the baseline pathogens.

I have two other comments I wanted to make. One thing, I guess, gets to, you know, ultimately the provable question and it relates to whether we have one study or two. And related to that is, how can we combine ARRI and ARRD when the dosing is so different? And, so, I think the FDA did an interesting analysis where they compared the doses that were actually achieved in ARRD and tried to match them up with a dosing in ARRI.

And on Slide 10 they showed that over 50 percent of the doses, the 3.0 milligram per kilogram dose, which we see on Slide 10 here on the bottom, over half of them were outside of 20 percent window. So, to me my inclination is to think, you know, dosing does matter. And, so, this makes it rather hard to use ARRD in support of the dosing used in ARRI. So, I don't know if anyone wants to comment on that, but that's my impression, basically. So, I'm doing it more like a Phase 2 study of a related kind of compound really,

 

because dose I think is part of the whole package.

DR. FLEMING: Could we comment on that? I'd like --

DR. RELLER: Please.

DR. FLEMING: I'd like Dr. Ambrose (ph) to talk about the dose.

DR. AMBROSE: Hi. My name is Paul Ambrose. I'm a PKPD consultant from the Ordway Research Institute and the Institute of Clinical Pharmacodynamics in Albany, New York.

What you noted on that FDA slide is a difference between ARRD and ARRI, where between 10 and 15 percent higher dose on milligram per kilogram basis irons out on a flat milligram basis rather and D versus I. However, dose is a very imprecise measure of drug exposure.

And if we take a look at Slide 14, please, to illustrate this point. There we go. Push the button. So, what we're looking at is from the population of pharmacokinetic model, which included 360 infected patients. And if you -- data stratified a couple of different ways, but you're looking at AUC on the Y axis

 

on day one of dosing. And you've got the two patients laying -- weighing less than 110 kilograms on the left-hand side, using the 200 milligram fixed dose in red; and a 3 milligram per kilogram dose in the blue. And you can see, when you look at it as exposure relative to dose, the data closely overlie each other.

If you look at higher -- higher weight patients, those greater than 110 milligrams, and you dose on a fixed 300 milligram basis, what you see is that box splot basically looks very similar to the ones further over to the left.

As you go further right, this is if you dose 3 milligrams per kilogram, you know, increasing shows actually you bump -- you know, since clearance changes, the exposures get higher on a 3 milligram per kilogram basis. But my point, basically is, the 3 milligram per kilogram fixed dose, when you consider inner patient variability in pharmacokinetics, is not all that different than the 200 milligram fixed dose.

DR. FOLLMANN: What is the sample size for this, by the way?

DR. AMBROSE: 360 patients overall in the

 

population pharmacokinetic analysis.

DR. FOLLMANN: I have one more comment. This relates to the 99.875 confidence intervals that the FDA talked about and calculated for the last Study ARRI, I believe. And I think -- there wasn't much discussion about this, but I -- my sense is that this is a try -- this is an attempt to take one study and give it the weight of evidence of two studies, which is not often done. I think typically the FDA, and people who are approving drugs like to see consistency across studies. And I think having two separate or independent studies provides a level of evidence beyond what you get, even from a very small P value, a very tight confidence interval, that you get in a single study. There's just more variability, in some sense more reproducibility when you have two separate studies.

On yesterday, yesterday I -- Dr. Laessig talked about under what one conditions one study could be viewed as sufficient for approval. And paraphrasing her, she said, one study with a highly reliable treatment effect on an important clinical endpoint might be considered as providing sufficient evidence based on a

 

single study.

And, so, just to refresh everyone's memory, I think that, you know, ultimately on question three is what we should be thinking about, highly reliable treatment effect on an important clinical endpoint. And, you know, to the confidence interval you get from that wide alpha 99.875 still is outside. You don't include zero. So, that's the comment I have.

DR. RELLER: According to our schedule, it would now be time for the public hearing. There being no speaker in the open public hearing, we'll continue with the questions and the comments.

Dr. Kauffman.

DR. KAUFFMAN: So, I think when Dr. Moledina started, she said, in essence, in Study ARRD, the 3 MG per KG dosing is what we should consider to be equivalent to what happened in ARRI. It's about 200 milligrams. And the 1.5, then, is a lessor dose and not what the company is aiming toward.

So, if you look at just those data, then, in fact, the MRSA is a little bit better than the Vanco, and the Oritavancin study is a little bit better than the

 

Vancomycin. The numbers are really tiny, however.

But the other thing I wanted to point out was, that it looked like the endpoints are different. So, it was the investigator defined clinical outcome for ARRD, which is symptoms -- resolution of symptoms and signs. And then it's the sponsor-defined clinical outcome for ARRI which put in this sort of bizarre, as far as I'm concerned, surgery intervention more than 48 hours. I can conceive of a lot of reasons that the surgeon doesn't do it until after 48 hours, even though they plan to do it before that. Certainly in our hospital we see that all the time. So, I think that hurts you actually by having that as a failure.

DR. RELLER: Dr. Goetz.

DR. GOETZ: Yeah. My questions are related, again, to the surgery. So, there's sort of two ways of looking at this. There are those people who plan to have surgery and then didn't get it within the first 48 hours, but then at least to what's -- the question is how you define planned surgery, because there are also patients in whom we think we're going to need to do surgery who it turns out do better than expected and don't need to do

 

surgery.

So, if we're going to look at the surgery as being the cusp upon which this rides, I think we need to look at both at both categories of patients.

And the related question that I have is, that I understand we have prespecified endpoints and we need to live and die by them sometimes. But I wonder if there are any data that you have, if you were to change the window to 72 hours or something of that sort, a little bit of leeway, does that balance things out altogether? I recognize the statistical weakness of that, though.

DR. ETIENNE: With regards to changing the window retrospectively and undoing the consequences of that rule, this is not simple to do, for the reason that the application of the rule by the investigator effects the conduct of treatment. So, we cannot undo this and recalculate what would have happened with a more -- a broader window.

Now, I don't know whether I made myself completely clear about the surgical condition at baseline. What is -- what I would -- what I tried to get across, were that those patients, before starting study

 

drug, had those surgical characteristics.

DR. RELLER. Okay. Dr. Goetz.

DR. GOETZ: I understand the characteristics, but I guess the question I'm asking -- I mean, I assume that the case report form captured an intention to do surgery at entry into this study, or is it a retrospective reading of what the patient looked like that you're using to determine?

DR. ETIENNE: It's a retrospective reading. The case report forms did not capture whether the treatment was planned or not, so, we can only assume. We can only -- the percentage of patients, the 15 percent of the entire population coded as failures are coded as failures whether the surgery was planned or unplanned. Okay. And those characteristics are measured -- captured before study drug is started.

DR. RELLER: Dr. Alston.

DR. ALSTON: I think this is just a comment. I think what we're looking for and what we need are MRSA drugs, because for MSSA and for beta hemolytic Strep we have beta-lactams.

And I think MSSA and MRSA have become

 

different diseases, in that MRSA characteristically forms abscesses which require surgical drainage. And, so, because the MRSAs in this day and age are going to need surgery, this gets back to my point that I tried to make yesterday and this morning, is that I think this is a problem of study design, and not a problem of statistics, that these patients need surgery at some point, and when they ended up getting surgery determined their outcome. And because the numbers are so small -- I think it's 154 MRSA patients got the study drug -- I think you ended up with peculiar small numbers. And I think it's a clinical issue, not a statistical one. And I think it's because MRSA behaves differently than MSSA.

DR. RELLER: Dr. Fleming.

DR. FLEMING: Well, I was just thinking along the lines of what Dr. Goetz was talking about in terms of refining the endpoint. Actually I was thinking more in line of, did you collect data that was directly getting at resolution of symptoms that would allow us to assess, maybe as a supportive outcome measure, the kind of measures that IDSA was looking at, FDA was looking at, that isn't an endpoint driven by when you -- whether you

 

get Gram-positive antibiotics or surgery after 48 hours, or indeterminate? Did you collect direct evidence about resolution of clinical condition that the patient is specifically trying to address?

DR. MCALEM: Good afternoon. My name is Jill McAlem (ph). I'm the clinical director for Targanta Therapeutics. At the time that these studies were conducted I was an employee of Eli Lilly and Company, and actually ran the ARRD Study in the US affiliate for that company.

And regarding your question about what signs and symptoms were collected. I think if you put up Slide 739, 740. And while we're waiting for this slide to come up, there were signs and symptoms that were required for the definition of wound, cellulitis and abscess. And they are coming up on the slide now. Some of these were signs, obviously some were symptoms. But the disease categories that we included, as you know, are wound infection, cellulitis, and major abscess. And we looked for the resolution of the pain, the erythema, the localized swelling that was present at baseline.

These are the definitions that we used. And

 

in order to be considered a cure -- if you -- can you pull up 727, please -- in order to be considered a cure, there were specific definitions that we're required in order to meet the definition of cure. And these were assessed by the investigator. And in both studies they were very similar. There had to be complete resolution of drainage, pain, edema, fever, erythema, tenderness, et cetera. We did allow for some serious drainage to be considered a cure, or some granulation tissue in the ARRD Study, which is the study of question.

And then they also looked at the presence or the need for surgery. So, the investigator also indicated whether or not surgery was required within the 48 hours. They could code the patient as a failure for that as well. If they missed it, that's when we went back and added it. And that's why we had so many patients in that failure group.

Does that answer the question?

DR. RELLER: Dr. Kauffman.

DR. KAUFFMAN: Can you show us results using the investigator defined clinical outcome?

DR. MCALEM: Sure. Sure we can. Dr. Hartman

 

will show you the results.

DR. HARTMAN: May I ask which study you would prefer to see, the IDC-1 or would you like to see them for both? May I remind -- I'll remind you, that for Study ARRD, our primary outcome was the IDCO --

DR. KAUFFMAN: Right. Yeah.

DR. HARTMAN: -- which we shared in the core presentation. And then for ARRI it was the sponsor-defined clinical outcome.

DR. KAUFFMAN: It's ARRI one that you haven't given us those data.

DR. HARTMAN: Okay.

DR. FLEMING: But the results that you've shown us thus far are for your use of antibiotics that are Gram-positive, or use of surgery after 48 hours driven outcomes.

DR. MCALEM: So, the here -- here's Study ARRI. These are the outcomes for all four patient populations of ITT, CE, MITT, and ME, using the investigator-defined clinic welcome. And these outcomes are consistent across the populations and are consistent with what we saw also looking at it with SDCO. Because

 

of the way we define SDCO where we can do those overrides, where if they've missed, you know, defining somebody as a failure because of the surgical intervention, or if they accidentally start an antibiotic and we were able to see that and we overrode those, the sponsored-defined clinical outcomes will be slightly lower just by that definition than the investigator-defined clinical outcomes. But they are similar.

DR. KAUFFMAN: Do you have that broken down by organisms, then?

DR. MCALEM: The IDCO or the --

DR. KAUFFMAN: The IDCO. Yeah.

DR. MCALEM: Let me see if we have a slide on that.

DR. RELLER: And, while looking for that, it would be of interest to see the successes and failures in the MRSA by MIC of the Staph aureus, if that be available.

While looking for that we'll entertain Dr. Septimus' query.

DR. SEPTIMUS: You want me to entertain or --

DR. RELLER: We shall listen attentively.

 

DR. SEPTIMUS: I'm glad we came back to the MIC. But I wanted to get that -- couple of issues. One is the incision and drainage in surgical intervention issue. There's two ways to look at that. One there was a delay in a more definitive therapy, which resulted in a lower response rate, or that the patient didn't respond well in the first 48 hours and got worse. So, you can look at that from both sides of the coin.

And I want to get back to -- and I know that Dean said the same thing. I'm looking at Group A Strep, Strep pyogenes, and I mentioned this question earlier, and also Group B Strep, which there also are some differences between the two arms.

And I'm also looking at -- let me -- this is Slide 44 of the sponsor, and maybe I'm not reading this correctly. But it looks to me like there actually may be almost as many Group A Strep as there are MRSA isolates in this study. So, it is somewhat of a weighted amount on Streptococcus in this study versus some other skin and soft tissue studies that I've seen in recent times. And I don't know whether that -- whether the sponsors want to comment on that. And also what the differences were in

 

Group A Strep and Group B Strep between these two drugs.

DR. PARR: So, with respect to the MRSA versus Group A Strep numbers, the -- you have to remember the time that the studies were done. They were conducted between '98 and 2002. And the incidents of MRSA in these studies was around 20 percent. In our more recent Phase 2 studies we're running 50 to 60 percent. So, it has to do with the demography of the period.

DR. HARTMAN: May I address the rest of Dr. Kauffman's request a little while ago about looking at the outcomes by IDCO, the investigator-defined clinical outcome by pathogen?

DR. RELLER: Please.

DR. HARTMAN: I only have two slides to show you. Since the IDCO was not the primary endpoint, and the SDCO was, I have only the two slides here. So, these are the IDCO outcomes for Staph aureus overall, which are similar. And then I can share with you the IDCO outcomes for MRSA as well.

Now, not surprisingly these are going to be very similar to the sponsor-defined clinical outcomes, because if you recall, the definition of the sponsor-

 

defined clinical outcome is based off of the IDCO. And we just have a -- it's a conservative review and revision to overcome any inconsistencies in the way we had asked -- or the way we defined failures -- or for -- directed them to define failures.

So, if they had missed any surgical interventions that possibly had occurred after 48 hours, or the concomitant antibiotic for use for primary study indication, those were the overrides that we deemed to failures. So, you'll see very similar outcomes here.

Something that made -- that I would like to point you to, though, are the microbiological outcomes. And these are a slightly different way of looking at outcomes.

So, whereas the SDCO and the IDCO are a clinical evaluation, we do have a patient microbiological outcome that we evaluate patients on. And that -- it primarily takes into consideration just the microbiological outcome. And when there are no microbiological results or -- to be had, then the SDCO would play into it. It's in this microbiological outcome by pathogens that you see a more similar result between

 

the two groups.

This was presented earlier by Dr. Etienne in the core presentation. And you can see here on the MRSA, when you look at the microbiological outcome, which doesn't take into account that SDCO as much, the outcomes are much more similar for MRSA.

DR. PARR: And we have also now located the MRSA by MIC data that was requested.

DR. RELLER: May we see it?

DR. MOAK: My name is Greg Moak (ph). I'm the senior director of biology at Targanta.

On the screen now, what we're looking at is the sponsor-defined clinical outcome, and also the pathogen-level outcome for Staph aureus. This is the MRSA subset of all Staph aureus, as a function of Oritavancin MIC at baseline for the MITT population. The orange columns provide the pathogen eradication rates, and the blue bars provide the clinical response. We can see that there is no significant trend of outcome by Oritavancin MIC. And this is quite consistent with MSSA, and also Staph aureus as a whole. We see the same type of relationships when we look at the different

 

populations, namely ME population, and also when we look at IDCO.

DR. RELLER: Exactly. Do you have the same plots? Which of these are -- this is MRSA, but these are the Oritavancin MICs. What about the Vancomycin MICs?

DR. MOAK: So, we've not plotted Vancomycin MICs by the same extent. These are the Oritavancin -- this is the Oritavancin treatment arm. But, if you wish, what I could show is the outcome as a function of Vancomycin MIC. Was that what you were interested in?

DR. RELLER: Yes.

DR. MOAK: So, what we're looking at now are the outcomes, here both the sponsor-defined clinical outcome shown as the cures, and also the pathogen-level outcome shown as the eradication. Little N, large N, and percent. The percent values being in orange. The two data columns to the left present the Oritavancin treatment arm, and the two data columns to the right present the Vancomycin treatment arm.

What we see is that there are no substantial changes in outcomes for the Oritavancin-treated patients as a function of Vancomycin MIC.

 

DR. RELLER: Limited by the small numbers at two, and even fewer at that point, so, that this looks like the wow-type distribution of MICs in most of the European and US studies. I mean, these are -- look like garden variety Staphylococci without any of the more recent problematic strains in the mix.

I understand it's all Staph aureus, but we don't see the less susceptible Staphylococci with sufficient numbers to give any hint that Oritavancin may be more or less effective as the MICs creep upward.

DR. PARR: That's right. In the clinical studies that were conducted, the highest Vancomycin MICs we saw were two micrograms per mill. So, representatives of the VISA subgroup, for example, were not members of either populations treated by Oritavancin or Vancomycin.

DR. RELLER: Right. These numbers reflect exactly the so-called wow-type distribution of Staphylococcal isolates in -- at least in Europe and the United States -- in the more recent -- so that -- basically what we do not have for either Vancomycin in these trials, nor for Oritavancin, is the most challenging organisms would be one way of looking at it.

 

DR. MOAK: If I may, what I could indicate is that there is -- Oritavancin does show significant in vitro activity against the hetero-VISA and also VISA strains.

As Dr. Parr had mentioned, we weren't lucky enough to encounter those strains during the Phase 3 studies, but a number of studies that were released at ICAAC/IDSA this year by collaborators of ours have shown significant activity against those strains.

DR. RELLER: Thank you. Dr. Bennett.

DR. BENNETT: Now for an easier question for the company, and that is: Are we sure that the dizziness was not vestibulitis from vestibular damage? Patients confuse vertigo with dizziness. Dizziness is a very difficult word to pin down, even talking to the patient.

But let me return to the old days when Streptomycin was being used, and the patients who had vestibular toxicity from Streptomycin got bad vertigo. And then vertigo went away, even if their vestibular apparatus was totally destroyed, and they didn't notice that actually until they got up in the night to go urinate and then ran into the door because they had lost

 

their vestibular control. So, vestibulitis can be very severe and permanent and just manifested as dizziness.

So, the way you tell this, of course, is do we have nystagmus? Oh, yes, look at the patient's eyes. So, we -- anytime we do 20 P values something's going to pop up. So, the weakness is saying that dizziness was significantly more common in the Oritavancin as a lot of P tests were being done. So, my question is: Are we sure that that's not vestibulitis and nystagmus?

DR. MORIARTY: Thank you. I'm Susan Moriarty, Targanta Therapeutics.

Again, we were very concerned about this significant difference in dizziness in the Oritavancin treatment group. It's something that we had not seen in -- prior to Phase 3 or since Phase 3.

What I can tell you, is that each of these patients complete case report forms reviewed. And I could find absolutely no indication of true vertigo or vestibular or inner ear toxicity. I'll show you here how the investigators described these patients. And, you know, dizziness is, unfortunately, a rather vague term for a lot of people. And it is difficult to tease out

 

just exactly what the symptom is and what it might represent.

The terms actually used by the investigators, the patient's investigators, were a combination of dizziness, light headedness, and giddiness, all of which code to dizziness preferred term in the MedDRA Coding System. I would like to point out, that when we looked at dizziness, as far as related adverse events, that there was no significant difference between the Oritavancin and treatment groups when we looked at those events that were considered by the investigator to be possibly related to study drug.

None of these events were serious adverse events. None of them led to discontinuations. And here you're looking at the Oritavancin group. I can show you the Vancomycin group in just a minute. Eighty percent were described as mild, 20 percent were described as moderate. Ninety-one percent of them resolved within seven days. Three percent, one patient, had intermittent mild episodes unrelated, considered by the investigator, for about 25 days. Six percent, or two of the patients, had ongoing, both mild, and both considered unrelated by

 

the investigators. And when I looked at when these events occurred, it was really a -- throughout the study period, but most of them occurred while the patient was still hospitalized. And I know that we all have seen a variety of different causes of dizziness, even bed rest causing dizziness, especially dizziness that resolves, you know, within a relatively short period of time.

In addition, I can also tell you that, throughout the rest of the Oritavancin development history, there has only been one incidence of vertigo reported in the safety database. That was a Phase 1 patient and it last -- it was mild and lasted for less than three hours. Thank you.

DR. RELLER: Dr. Nelson.

DR. NELSON: Thanks, Dr. Moriarty. This is for you, too, Dr. Moriarty.

We seem to have moved off of efficacy. So, I'll talk for a moment about -- at least for a moment about toxicity and toxicology.

You had mentioned something, I guess, that I thought was interesting. And I was hoping maybe you had a little data. In -- you know, in the earlier drug that

 

we talked about today, there were clear signals that there were issues with the kidney and with the heart. The kidney seemed to be pretty reasonably easy to evaluate. And I think that the testing you would have done would have found acute kidney injury. But I'm still stuck on the fact that assessing QT is a very difficult thing to do, particularly given the nature of the susceptible population and how hard you have to look to find them.

So, I know you said that there was no difference, but I'm not sure if that meant that there was just no statistical difference, if it meant that there was not one single individual who prolonged his or her QT. And I don't know if you had any specific data about that.

DR. MORIARTY: We do for the Phase 1 QTc trial -- the thorough QTc trial. If you would like to hear about that, I'd --

DR. NELSON: Was it not part of the clinical trials, the ARRI, or D -- you didn't follow QT on those patients?

DR. MORIARTY: We did. If I could have the

 

core slide on QT. We actually have a rather extensive, I think, safety database regarding QT changes. I will get this slide up from the core presentation in just a minute. But we did examine around 350 patients on Oritavancin. And a comparable number -- with a two-to-one randomization throughout our clinical trials, comparable number of Vancomycin patients. And there was no evidence of QT prolongation with Oritavancin in those patients, no evidence of arrhythmias that might represent torsade or other ventricular arrhythmias.

As far as outliers, I'm trying to remember. There was just no signal there. I -- I'm sorry, I don't remember the specific numbers for the patient trials. We can give you more specific numbers for the Phase 1 trials, but I know that we worked with Dr. Morganoff (ph) on that report, and that we found no evidence of QT prolongation caused by Oritavancin.

DR. NELSON: Right. I mean, I just hope you understand why I'm asking, because this is the kind of syndrome that, you know, the vast majority of people don't have. So, if you just look at the large means, or, you know, even means with any sort of statistics around

 

it, you're not going to find it but one person or --

DR. MORIARTY: Right.

DR. NELSON: -- two people out of a group might have it. It might be one out of a 1,000 people. And if you don't look at that individual, you're going to miss the syndrome. And, again, that's something that we really need to know.

DR. MORIARTY: And I can tell you that that was done in this study. I cannot give you exact numbers, but I can tell you that outlier analyses were performed as well, and the conclusion at the end of the study was that there was no evidence of QT prolongation.

DR. RELLER: Dr. Kauffman, and then Hilton, Cross, and Guiterrez.

Dr. Kauffman.

DR. KAUFFMAN: So, my main concern in reading through the information I had gotten in terms of toxicity, is the fact that this drug looks like it lives forever and has a long half-life. And you describe in rats, dogs, rabbits accumulation of cytoplasmic granules in a variety of different cells, including macrophages, which ultimately disappeared.

 

And the question is: Is that drug that's accumulated in there, and what's the long-term toxicity of stuffing your macrophages full of something that's not metabolized away? And maybe -- and do you have enough data in humans to say this is safe?

And I'm wondering then if Jack Bennett, after you answer, could comment on Amphotericin which sounds sort of similar to me, in that it lives around for a long time, slowly excreted in urine. But I'm not sure it accumulates in macrophages.

DR. RELLER: I'm glad Dr. Kauffman asked that question, because if it got to me I was asking exactly the same thing. And for the pharmacologists, as well as the toxicologists, are there -- what are the -- is there any other drug like this, I mean, the volume of distribution of 100 liters staying there seemingly in almost perpetuity? What are the precedence and what are the implications, as best as we know, with what is a short follow-up time after therapy that we see in the documents?

DR. PARR: Would you like to speak about the clinical or the toxicologic implications first?

 

DR. RELLER: Your -- presenter's choice in the order, just as long as we cover the questions.

DR. PARR: So, Dr. Freidman -- or, sorry, Dr. Polace will talk about the so-to-speak phospholipidosis, and histiocytosis, and the implications.

As he's coming forward, it is interesting to note that Oritivancin, when accumulated in macrophages, is active as an antimicrobial and is more active than other compounds that are accumulated into those kinds of cells.

DR. POLACE: Good afternoon. I'm Guy Polace, consultant toxicology for Targanta. And I -- what I would like to do is just try to convey to you the significance of these -- what is being described in the animal studies as the macrophages, with the presence of eosinophil granules in their cytoplasm.

I have here a slide that speaks to the significance. As you said, indeed, one of the hallmark in this compound in animals is the presence of macrophages with enlarged cytoplasm with eosinophil granules. And we looked as this and we looked at this

 

ultra structurally. And we see that these eosinophil granules translate into large secondary lysosomes that contain lamellar membrane inclusions and can preform electron-dense material. Now, the fact that there are these lamellar membrane inclusions is indicative of the presence of phospholipidosis in these cells.

And we also know from published literature on macrophage cultures, that in vitro, these secondary lysosomes with -- that we see with Oritavancin are associated with high concentrations of Oritavancin. So, there is a combination that getting together of the phospholipidosis is in the high concentrations of Oritavancin.

Now, there are several drugs on the market that show phospholipidosis. And there is a body of opinion that says that the presence of phospholipidosis in itself is not evidence of toxicity. It is an adaptive cell of process. And as a reaction against intracellular concentrations of drug.

Functional or toxic effect can arise as the result of either excessive accumulation of phospholipids or -- and that is what many people believe to be the case

 

in these circumstances -- the intrinsic properties of the drug at high concentrations.

Now, to your question about in the anti-infective area, I would mention two compounds that are being -- are currently on the market, and one is Azithromycin, that it causes such a kind of effect. And another compound that I would like to mention also is Chloroquine, which causes phospholipidosis and has high volumes of distribution.

What I should emphasize here, is that we are talking about a very short course of treatment. While in the animal studies, like the dog study that is referred to in the package, the toxicology package, we actually give a daily dose during 90 days. So, there is a big difference when you compare cumulative doses.

Could I have Slide 24? On this slide here you see I simply calculated the cumulative dose in the dog in that 90-day study that we have in our toxicology package. And this leads to a cumulative dose of 4,000 milligram per kilogram, and compare this to the cumulative dose over the treatment course that is being proposed, which is rather around 20 milligram per

 

kilogram.

So, there is a huge difference here in the amount of drug that has been given to the animals. And looking at cumulative dose is not as appropriate given the excretion that results are low in dogs. So, we are entitled to study and compare cumulative doses.

Now, if we go back to the two-week study that we have done in dogs with four-week reversibility, we still have a factor of 10 between the cumulative dose in man and the cumulative dose in that study. Then you see that there is, indeed, reversibility of the histiocytes, the presence, and the size of the macrophages, with the eosinophilic granules. And we only have at the end of the reversibility a minimal presence in liver, spleen, and bone marrow.

And what is also important, is that under those circumstances, the perivascular inflammation at the injection sights are no longer present.

I hope this answers your question.

DR. KAUFFMAN: Have you done any studies on macrophage function?

DR. POLACE: We have not done studies on

 

macrophage function. We have -- in fact, we have not done in vitro studies on these, or ex vivo studies on the macrophage function.

DR. PARR: Susan -- or Dr. Moriarty would like to add a bit there.

DR. MORIARTY: I wanted to try to answer the clinical portion of your question.

We -- given this compounds tissue penetration and long residence time in the body, we looked very careful for any evidence of toxicities associated with that. And after extensive analyses, we have found no evidence that that has adverse effects on the safety profile of the drug.

Let me first review with you the analyses that we did, looking for any evidence of liver toxicity. The -- one of the primary organs of concentration, primarily within macrophages -- tissue macrophages or kupffer cells is in the liver. And, so, we did look very closely at the liver.

If I could have 826, please. First I'll show you the standard laboratory analyses that were done. And, as you can see, Oritavancin and Vancomycin really

 

show no significant changes in the degree of change to the maximum high value from baseline of the hepatocellular enzymes.

And then when we look at alkaline phosphatase and bilirubin, we again see no evidence of hepatotoxicity with Oritavancin administration.

In looking at the liver, we also did the screening that I mentioned in the opening presentation, looking for any evidence of patients that might have drug induced liver injury as represented by meeting Hy's law or Hy's criteria. We did that also for Phases 1, 2 and 3. And we found no patients who met Hy's law criteria. All patients who met the screening criteria -- which I mentioned were relatively broad in order to be very sensitive -- they all had underlying liver disease at study entry, and none of them in Phases 1, 2, or 3 had clinically relevant changes in their liver enzymes, the hepatic transaminases, or the bilirubin.

In addition, then, we looked at a vulnerable liver population. We defined a vulnerable liver population as those with significant underlying liver disease at study entry, and patients who had significant

 

abnormalities with their liver labs at study entry.

And we found no evidence of any increased liver toxicity in those patients represented by laboratory analyses, or by adverse events.

In addition, I'd like to go to the long residence time in the body and the general adverse event analyses we have done with regards to that. If I could, again, remind you of -- Core Slide 56 -- where we show the time to onset of adverse events, and the fact that we don't see later adverse events with Oritavancin, and we don't see any evidence of adverse events starting to occur later in this study.

In addition, I'd like to show you the late post study drug period. If I could have Slide 934, please.

The late post study drug period was days 37 through 90. And as you can see as represented by adverse events, we see no indication of later adverse events occurring in the Oritavancin-treatment group compared with the Vancomycin-treatment group, nor do we see any evidence of real differences in what those adverse events might be.

 

One other point I would like to make, is at the end of the study period, comparable, almost identical percentages in patients in the Oritavancin and Vancomycin-treatment groups had ongoing adverse events that were considered by the investigator to be possibly related to study drug, with Oritavancin group having 2.9 percent, and the Vancomycin group having 2.7 percent ongoing adverse events possibly related to study drug.

So, in all of these extensive analyses, we have just not seen any indication that Oritavancin's long residence time in the body, or the organs where it resides in the body, that there is any adverse effect of that.

DR. RELLER: Dr. Hilton.

DR. HILTON: I wanted to come back to a couple of points that were made earlier. First, Dr. Bennett's point about the ARRI/MRSA rate being higher in the Vancomycin group, and the reverse direction in the ARRD group.

So, I'm looking at the FDA Slides 16 and 21. And there's a 12 percent difference in one direction in one, and 12 percent in the other. And it occurred me to

 

that ARRI sample is much larger. In the ARRD sample, if we look at the 3 milligram per kilogram arm, if there were just two fewer events, 8 out of 16, that rate would go down to 50 percent and the whole trend would disappear entirely.

And then I tried to reconcile those two slides with the Industry Slide Number 44. And the FDA slides are in the MITT population, and the industry slide is in the ME population, so, it's a subgroup of MITT. And it combines all the ORI data into one pool. And since it's dominated by the larger ARRI study, again, that difference just disappears and washes out. The imbalance equalizes kind of. And, so, I think that we have the explanation. And I think it's just mainly driven by small numbers in the ARRD study. So, that was one loose end that was bothering me that I wanted to reconcile.

And then a second one that I wanted to address that Dr. Follmann brought up was about the 95 percent confidence intervals. And I'm looking at the FDA Slide 20, and they made a strong case for using only the 3.0 milligram per kilogram arm in that study. And I think that industry also made a strong case for doing that when

 

they showed the dosing slide a couple of several presenters back. So, if everyone is agreed that only the 3.0 milligram per kilogram arm is relevant and we can just disregard the 1.5, then why not use a 95 percent confidence interval there? Then you get a narrower confidence interval and you're further from the 15 percent margin. So, just a thought that we might consider.

And in connection with Dr. Follmann's remarks, it goes to the point of, do we want to look at these as two independent studies that are independently giving evidence, or do we really want a pool of cross studies?

So, looking at them independently, and both groups independently saying this is the more important arm to focus on, one possibility is to think in terms of a 95 percent confidence interval there.

DR. RELLER: Dr. Cross.

DR. CROSS: I had two questions. One is: You said that your in vitro and your animal data showed efficacy against VRE. Apparently you didn't see any VRE cases in your two clinical studies?

DR. PARR: In the two Phase 3 clinical studies

 

we did not. We have open label Phase 2 bacteremia study dosing on a different schedule that we successfully treated VRE.

We also have VRE data from an ascending pyelonephritis model in rodents, where we show activity where Vancomycin does not. But we -- in these studies, VRE was not encountered.

DR. CROSS: And my second question is: You had, apparently, some number of patients, who in addition to having Vanco were switched over to Cephalexin. Is there any difference in the outcomes with the Vanco arm in those who had only Vancomycin versus those who switched over to Cephalexin for over three days, or for some period of time, more than one day?

DR. PARR: As Dr. Hartman approaches the podium, the rule was, for MRSA, a requirement of Vancomycin, obviously, for confirmed methicillin-susceptible Staph aureus, following three days of administration of IV Vanco. At the physician's discretion, they were possibly switched to the oral medication.

DR. CROSS: Well, it's important, with regards

 

certainly to MRSA, but I think your data on the Strep pyogenes and the Group B Strep is also a bit puzzling why, first of all, you had such low response rates and how it was a positive in one arm and not in the other. So, I was just wondering whether the Cephalexin therapy may have had a role in those really puzzling results.

DR. HARTMAN: It's difficult to tease out how Cephalexin played in. So, the only way to really -- to approach is -- because, I mean, all patients received this -- or most -- the majority of the patients switched over to Cephalexin. Eighty-five percent of our patients had an IV-to-oral switch. And, so, if you are of the belief that it is active, then you have -- we can't divide out the outcomes, then, and negate that.

If you are of the belief that Cephalexin is a placebo and it's not offering any advantage, then it would be our overall outcomes, which show similarity.

In trying to pick this out, though, we did try to look at outcomes by IV use over -- by total duration, and I did not see any difference in the IV use between Oritavancin and Vancomycin, in terms of the outcomes.

DR. PARR: With regard to the possibility of

 

Cephalexin as a placebo, I'd like Dr. Ambrose to talk about the PKPD exposures in the patients that were administered the Cephalexin drug.

DR. AMBROSE: Hello again. Let me start off by sharing with you the in vitro activity of Cephalexin against methicillin-susceptible Staph aureus and Group A Streptococci. And what you can see in the red bars are the MIC distribution for S. pyogenes, and in the yellow bar MSSA.

And what one can see is the MIC distribution for Strep pyogenes is essentially one or less. And for MSSA it's 16 or less in this collection of isolates. And I note that there -- they always -- well, the cSSSI susceptibility break point for these organisms base is 8 micrograms per ML. So, 94 percent of the MSSA would be considered susceptible, and 100 percent of Strep pyogenes. But let's bring forth a little bit of PKPD and look at that data in a different kind of a way.

What you're looking at is the concentration time profile of Cephalexin administered to 12 healthy volunteers following a 1 gram dose. And that's the black line. In preclinical animal models, what one finds for

 

Streptococci, is you need approximately 30 percent time above MIC, and for Staphylococci about 25 percent time above MIC for stasis.

And, so, if you look at the red line, which is the MIC 50 slash 90 value for Strep pyogenes, you can see all patients would achieve this particular time above MIC threshold. If you look at the MSSA MIC 50 value again, at 25 percent of the dosing interval again, all of the patients would be predicted to achieve this particular PKPD threshold.

If you look at the MIC 90 value, you can see the majority, but not all, hit this particular time above MIC threshold 25 percent time above MIC; however, it's important to remember there are very few isolates at an MIC value of 08. So, these PKPD data would suggest Cephalexin dose, that one gram every 12 hours is not a placebo.

DR. RELLER: Dr. Gutierrez.

DR. GUTIERREZ: My question was the same as Dr. Kauffman's, so, I'll pass.

DR. RELLER: Dr. Fleming then Dr. Goetz.

DR. FLEMING: Just returning for a moment to

 

Table 7.3, Page 29 of the FDA document. Looking at SAEs, I always have the most interest in understanding the more serious events. And it's already been noted that, where there seems to be an excess is in infectious-related processes. We note here that sepsis is 7/3. That's just a slight excess. But septic shock 5 against 0, 4 against 0, osteomyelitis 5 against 0. And if we go back two pages earlier to the deaths, we see that there -- one of the deaths occurred in the patient with septic shock. Sepsis, having occurred in advance of death, occurred once in Vancomycin, four times in Oritavancin. And, so, there's an excess of 5 against 1 also in occurrences of sepsis or septic shock in advance of death.

Have -- in all of our discussions today have we got any insights about this?

DR. PARR: Just a little additional comment. The -- remember the -- we should remember the randomization at 2 to 1.

DR. FLEMING: That's right. So, I am definitely factoring that in.

DR. PARR: Yeah. Okay.

DR. FLEMING: That's why I said, when shock is

 

7 against 3, that's just a modest increase --

DR. PARR: Sure.

DR. FLEMING: -- so -- .6 against .5. But the osteomyelitis and septic --

DR. PARR: Right.

DR. FLEMING: -- shock cases are 9 against 0, and the deaths are 5 against -- the deaths occurring where you had prior septic shock or sepsis --

DR. PARR: Right.

DR. FLEMING: -- is 5 against 1, which is not a five-fold, but a two-and-a-half-fold increase.

DR. PARR: Correct. Yeah.

DR. MORIARTY: I'd be happy to address that, Dr. Fleming. We looked again very closely at these patients to describe what -- just what exactly was represented by this adverse event term of septic shock. And what we found were, indeed, that there were four Oritavancin patients who had a serious adverse event of septic shock. Two of these were apparently related to Gram-positive organisms and two were not.

First for the two that were not. One of these cases had septic shock due to a gangrenous colon. And,

 

so, that's not only a polymicrobial disease process including Gram-negatives and anaerobes, but it also involves necrotic tissue and sepsis on that basis.

The second one was a Gram-negative bacteremia on day 6, despite being on Aztreonam.

Now, if we move on to the Gram-positive situations. The first patient is a patient with severe diabetes mellitus at study entry. She was treated with Oritavancin, 201 milligrams on day one for cellulitis of the lower leg. She had debridements on day one and day two, telling us that even though her diagnosis was cellulitis, that she obviously had necrotic tissue and possibly a necrotizing fasciitis, but certainly had a very severe infectious process well on its way by the time she entered our clinical trial. She did just get the one dose of Oritavancin. And then on day two, after her second surgical debridement, developed septic shock, as we can see happen in these patients, postoperatively. And that resulted in her death.

The second patient is a younger gentleman who was a IV drug abuser and a skin popper who had a very large shoulder abscess from skin popping. The abscess

 

grew methicillin- sensitive Staphylococcus aureus and blood cultures were negative. He developed hypotension after surgical drainage. And, unfortunately, there was a fatal medication error when Dopamine was ordered, but Nitroglycerin was hung. And, so, this medication error actually contributed significantly, I believe, to this patient's demise and death.

Now I'd like to move on to the osteomyelitis cases. And I'd like to go to the general discussion of osteomyelitis first, if we could have -- I'd like to discuss all of the osteomyelitis cases together, because we did see an imbalance in the Oritavancin and the Vancomycin groups, with regard to osteomyelitis. There was one Vancomycin patient with acute osteomyelitis, which gets coded just a little differently than osteomyelitis. But basically we had -- altogether we had 12 patients in the Oritavancin-treatment group with treatment emergent osteomyelitis. None were considered to be possibly related by the investigator. Unfortunately, none had imaging studies reported at study entry or any time greater than one day prior to the event of osteomyelitis being reported.

 

I believe that these cases represent the clinical difficulty with establishing a diagnosis of osteomyelitis at the beginning of a patient's presentation, rather than a failure of study drug.

We see that of those 12 patients with osteomyelitis, six with -- and all of these were likely contiguous osteomyelitis by their descriptions -- six were diagnose on or before day seven. And the ones that we know of their imaging studies, one had an MRI done on day two, one had an x-ray on day five, and one had an x-ray on day six. And given the length of time that it takes to see x-ray changes, plain film changes, the -- all six of these surely had osteomyelitis at study entry.

An additional four had contiguous osteomyelitis diagnosed or were reported between days 8 and 14. Again, none of these patients had imaging studies reported at baseline or any time more than a day prior to their adverse event being reported. One of these was diagnosed with an x-ray and bone scan on day 13. I believe it's most likely that these patients also had their osteomyelitis at study entry, but went unrecognized. As we know, that is a clinical problem.

 

There were two patients with osteomyelitis reported later in this study. And I believe that both of these patients most likely had osteomyelitis earlier on. They weren't diagnosed. And the study drug that we administered in this trial wasn't meant to cure osteomyelitis on its own without surgical intervention.

Now, the -- would you like to hear more in detail about the SAEs? I can go into that as well, what specifically they were. But basically they were serious adverse events included in this 12 patients. And the serious nature was with regards to -- leading to more prolonged hospitalization in four of the patients. And in one of the patients who had diabetes in a lower leg, complicated skin infection at study entry, the serious indication was that the patient had some disability from that.

Have I answered your question? Are there any other?

DR. RELLER: Owing to time we'll take any -- we'll take the three persons who have already been recognized waiting for questions or comments, Dr. Goetz, Miss Thomas, and Dr. Cross. And then we'll move to the

 

question. Dr. Goetz.

DR. GOETZ: My question actually follows up on Dr. Fleming's question. In regards to the osteomyelitis, I'm interested in pathogen identification of the cases where osteomyelitis arose in the patients receiving Oritavancin. And I also note on that same slide, 26, that if you -- when it adds up, the cases of cellulitis, abscess, sepsis, abscessed limb, and osteomyelitis in the Oritavancin versus Vancomycin patients, there are 35 such instances amongst Oritavancin patients, and 11 in Vancomycin. Granted, randomization was two to one, so, we'd expect to see some imbalance, but this is essentially three-fold.

My questions are related to the identification of the pathogens causing these serious infectious complications amongst the patients who received Oritavancin.

DR. MORIARTY: Yes. I can address both of those questions for you.

First, with regards to pathogens, if we could go ahead and put up the SAE osteomyelitis slide. Actually I can tell you that the five patients who had

 

serious adverse events of osteomyelitis have methicillin-sensitive Staph aureus, MRSA.

The third patient, no pathogen was reported.

The fourth patient, it occurred post bunionectomy, and it was methicillin-sensitive Staph aureus.

And the fifth serious adverse event, osteomyelitis patient, had MSSA after a flip puncture wound.

In the patients who had later onset osteomyelitis, that fifth patient I just mentioned, was one of those. And, so, it was MSSA after a puncture wound. And I think clinically one of those situations that unfortunately we see happen from time to time when, again, the inoculation of the bone isn't recognized at the beginning.

And then the other patient had a Gram-negative pathogen in combination with Gram-positive at study entry. If we could -- I'm sorry, I would like to have the -- it's either 910 or 913, the patient with klebsiella pneumoniae. But we did have one of those patients with late onset osteomyelitis, who had

 

klebsiella pneumoniae isolated from his wound at study entry, and then again when osteomyelitis was diagnosed. Unfortunately that patient received no Gram-negative therapy.

DR. RELLER: Miss Thomas and Dr. Cross.

DR. THOMAS: I was just wondering if you had any data on how many patients contracted C. diff in your study. This is a huge problem. And it seems to be really susceptible in MRSA patients.

DR. MORIARTY: Yes. We did look at clostridium difficile. As far as adverse event occurrence, identical percentages of Oritavancin and Vancomycin patients developed pseudomembranous colitis or clostridium difficile infection during this study period. So .5 percent in each study group. In the Oritavancin group, there were six patients with seven events of pseudomembranous colitis, two were mild, four were moderate, one was severe and consider unrelated to study drug. Onset was anywhere between day 5 and 48. And all of these patients had received other systemic antibiotics prior to the onset of clostridium difficile.

And as you can see an identical percentage,

 

half as many, because of the two-to-one randomization, an identical percentage of Vancomycin patients developed evidence of clostridium difficile infection. And, again, those -- the onset of illness in the Vancomycin group was 22 to 23 -- I'm sorry, 22 to 32 days. And, again, all had received other systemic antibiotics. And, so, cause and effect with study drug is somewhat uncertain.

DR. RELLER: Dr. Cross.

DR. CROSS: Following up on Dr. Fleming's point in Table 73, if you take all the SAEs from cellulitis to septic shock, you end up with 39 in the Oritavancin group versus 9 in the Vancomycin. And I think a possible common theme there, is that if you had macrophage dysfunction caused by the granules, then one can have both Gram-positive and Gram-negative, or fungal infections makes no difference, which just emphasizes the -- a point made by Dr. Kauffman, that it would be important to have some in vitro macrophage function test, looking at least at uptake and killing of bacteria in macrophages exposed to the Oritavancin.

And, secondly, to see whether or not stimulation macrophages with a stimulus will induce the

 

same type of cytokine response, TNF, or anything of your choice as untreated macrophages.

DR. MORIARTY: Let me address first the clinical question of any imbalance in infections in the Oritavancin group, any evidence of immune dysfunction. First I'd like to show -- at least in our clinical trials.

First I'd like to show you that there was no imbalance under the system organ class of infections and infestations, and although you see some imbalances when you look at each individual preferred term. Again, of course, this study is not powered to equal those things out, you know, completely. And when we look at all of the infections and infestations, we can see that comparable percentages of Oritavancin and Vancomycin-treated patients were reported with an adverse event of infection and infestation.

With regards to immune function under the system organ class of neoplasms, there have been malignant -- excuse me. We see a significantly higher percentage of Vancomycin than Oritavancin patients with an adverse event in that category. I tend to think that

 

that's probably a result of doing multiple tests, and you'll eventually finally get something that's statistically significant.

Under the high level term of fungal infections, which is under the infections and infestations, we looked for any evidence of disseminated fungal infections or endemic mycoses. The endemic mycosis was a coccidiomycosis case in the Vancomycin group.

In the -- under the high level term of Canada infections, we saw, again, comparable percentages of Oritavancin and Vancomycin patients. We did have one patient in the Oritavancin group who had Canada bloodstream infection. He had multiple risk factors for that, abdominal surgeries, a colonic fistula, hyperalimentation for a long period of time, malnutrition, other antibiotics, all those things.

And then under microbacterial infections, there was one patient in the Oritavancin group who had presumed disseminated tuberculosis, according to the investigator. But this occurred in day two. And, so, it could not have been associated with Oritavancin use.

 

Dr. Parr, did you want anyone to comment on -- thank you.

DR. PARR: That sounded good to me.

DR. MORIARTY: Did that address your question?

All right. Thank you.

DR. RELLER: Dr. Fleming has a comment on this line.

DR. FLEMING: A very quick comment. Just if that slide could be back up. It's certainly relevant to look at all AEs that are infections, and infestations, but sometimes we can miss the most important things when we're dominating this by mild adverse events. That's why the other tables that were really focusing on the more serious adverse events that were in the infectious categories is very relevant.

DR. MORIARTY: Yeah. I agree. And also I would like to point out that among all of those individual preferred terms under infections and infestations, osteomyelitis was significantly different in the Oritavancin and Vancomycin-treatment groups. And that's why we looked so carefully at when those cases

 

occurred, how they were diagnosed when we had that information to put it together. And again came the conclusion that the vast majority of those were almost surely present at study entry.

DR. RELLER: Dr. Cox, do you have -- do you wish to present the charge to the committee regarding questions?

DR. COX: Sure. Thank you, Dr. Reller.

I'll try and do somewhat sort of approach, just some comments and then we'll walk through the questions.

I want to start just by thanking all the presenters, and all the discussants for touching on a lot -- different, you know, issues related to the drug, and talking about -- and giving a lot of good information for the discussion.

We heard about data on efficacy. We discussed the issue of the different dosing regimens, talked about Study ARRI, which had a fixed dose regimen, and also ARRD, which had the weight-base dosing. And there was also some discussion about, you know, different noninferiority margins. You'll notice this will come up

 

in the questions, too.

For study ARRI, we just briefly touched on the issue of the 95 percent confidence interval versus a 99.875 percent confidence interval. And for ARRD there was some discussion of 97.5 versus 95 percent confidence intervals.

Also briefly noted was the different noninferiority margins for each of the two studies. We also had some discussion, too, on the issue of MRSA, and then also on the endpoints that were utilized in the studies.

With regards to safety issues, we also talked some about the issue of infections in the overall population.

So, now moving to the questions. Question 1, it really is asking the question of, you know, does Study ARRI, is that study alone a win? So, this is not the safety and efficacy question with regards to, you know, have they provided the overall database to support safe efficacy? This is just looking at this single trial. Is this single trial in essence a win?

So, our question is: Does Study ARRI

 

independently provide evidence of the effectiveness of Oritavancin for complicated skin and skin structure infections? Please vote yes or no.

In your response, please discuss the following: We brought up the issue in the discussion with regards to the strength of the evidence here, and also it's in relation to the primary outcome for the study. And then we've also asked if, following the vote, if there could be some discussion with regards to baseline pathogen, and specifically note MRSA.

Any questions on that question? If not, I'll go on to two. So, that's in essence thinking about ARRI in the setting of when you have -- you know, in essence the default here is, if you had two studies and this was for one of them, would this one independently provide evidence? And that we include the question -- also the discussion about the 99.875 confidence interval so that folks can discuss what weight of evidence this study might provide.

The second question asked is: Does Study ARRD independently provide evidence of the effectiveness of Oritavancin for complicated skin and skin structure

 

infection? Please vote yes or no.

Again, this is just asking specifically in reference to this one study. And we ask that you discuss the primary outcome. And the question specifically cites the 97.5 percent confidence interval, any comments related to the 95 percent confidence interval would certainly also be welcome. And that came up in the discussions here today. And we also -- in your discussions, if you can comment on the weight-based dosing.

And then the last question, Question 3 -- this question gets to the overall issue of demonstrating safety and effectiveness, from the overall database. So, that would be looking at the collective evidence from the two studies. And I will just make a comment, too, as Dr. Laessig and her slides presented yesterday, it is possible for the agency to consider one adequate and well-controlled study and confirmatory evidence. And, you know, typically when we are doing that, we are looking at statistically compelling study, it's multicenter and internally consistent across all the centers.

 

And then after you vote, if there are any specific labeling issues, if the vote is yes. If the answer is no, if you can provide comments on additional data or studies that would be needed.

So, those are the three questions and we look forward to your advice. Thank you.

DR. RELLER: Question Number 1, may we have the activation of the -- please vote.

All set. We'll vote -- lock in the vote. Results, please.

The results are 11 yeses, 6 nos, and 1 abstention.

We'll start at the left for supplementary comments regarding your vote.

Dr. Katona.

DR. KATONA: Well, I think that the study met the noninferiority margin that it was designed to do. But certainly the Staph aureus was somewhat bothersome, and what was it statistically significant difference. There was a small number of people. They did get less drug. We did have some MIC data. And we -- I don't know what to make of the delay in surgery. But that was

 

somewhat bothersome, because that is really the key issue that we're trying to address here above and beyond the other drugs that were in the study itself.

DR. RELLER: Dr. Alston.

DR. ALSTON: I voted no, because I think treating complicated skin and soft tissue infections in this day and age is treating MRSA, and I'm not sure that was shown.

DR. GOETZ: Similarly I voted no. My concern is, that in the study if I added up the numbers and they differ across the various tables, but there were 470 MSSA, 160 MRSA, at least according to one of the tables -- I think that's table -- Slide 44 presented by the sponsor. Considering that the majority of the isolates that we're now dealing with in complicated skin and soft tissue infections are MRSA. The study, while technically well-performed, is not an answer of today's question. And I'm concerned that the very wide confidence limits around the results with MRSA that were found here, do not support use of this drug today with our current patient population.

DR. RELLER: Dr. Fleming.

 

DR. FLEMING: I voted no. I start with the fact that I struggled greatly with the definition of the primary endpoint and understanding the primary endpoint. It's critical that the primary endpoint provider capture the essence of what it is that patients are trying to address, the resolution of the clinical condition that the patient is specifically trying to address. And I had a great deal of difficulty in interpreting that.

Also it deviates significantly from the historical evidence that we used to set up margins. So, technically being able to justify the 10 percent margin is also problematic. We need to address the separation of the subcutaneous abscess or major abscess, but in this case it doesn't alter the conclusions that I would derive from this.

The MRSA results are obviously complicated to interpret. There's been great discussion, Dr. Bennett from the beginning in pointing out the recognition of this trend, but pointing out the need for caution and subgroup analyses, as Dr. Follmann has also done. But it's not just any subgroup. It's certainly a group of keen interest. I'd call it hypothesis generating. And,

 

in fact, I think the entire trial is hypothesis generating. It serves as a proof of concept supported trial to another very good trial that I would hope could give us more insight about the MRSA aspect of this.

I worry some. The safety profile looks quite favorable. I do worry about the infectious complications results that are serious that do seem to be in excess. The trial was done in '98 to '02, and I think that is part of what also is complicating its interpretation.

One last point that I guess is fairly apparent, the concept of essentially using 000625, strength of evidence of two trials. I think Dr. Follmann has appropriately pointed out reasons for caution about that. Two independent trials is certainly more persuasive. But I do believe -- I do believe that you could have a result that is highly compelling statistically, but it's got to be highly compelling clinically, and highly compelling statistically, and internally consist. And the results can't be ignored from the other trial, which look less favorable than this trial. An absolute difference is against Vancomycin until we had a clarification of the IDCO, and those

 

results are a lot less favorable than their primary endpoint.

So, many issues of concern in interpreting this trial that lead me to say I wouldn't view it as one of two adequate, well-controlled trials. But I could be persuaded that it would be a supportive trial with a second high-quality study done with an adequate sample size and a strong endpoint with results that could also provide us more insight about MRSA.

DR. LEGGETT: I voted yes, having considered the same factors as those who just preceded me, but looking at the confidence intervals, which were well within the limits, whether it's 95 or 99. And also justly regarding a subgroup safari is just that, as noted by Dr. Follmann. And I thought the drug was safe, as well.

DR. RELLER: Thank you. Dr. Bennett.

DR. BENNETT: I have nothing really to add. I voted yes, because I thought the overall weight of evidence was that the drug was effective.

DR. RELLER: Dr. Lesar.

DR. LESAR: I voted yes, but I have nothing to

 

add to previous comments.

DR. RELLER: Dr. Nelson.

DR. NELSON: Yeah. I voted yes. And I think the main reason was the question actually asked about the overall effectiveness of the drug, not necessarily about its MRSA effectiveness. If the question really did ask about MRSA, I would be much less comfortable. I mean, I know there was some explanations for the findings, although they are explanations and not necessarily proof. And I think I would go back and try to look for more proof that MRSA is -- which is really the target organism, I think, that we're probably looking at. I think there needs to be a little more proof that it actually is more effective.

But in the overall picture, I think that for cSSSI, I think it seems to be -- it seems to be effective.

DR. RELLER: Dr. Septimus.

DR. SEPTIMUS: I voted yes with some reservations. This is actually a very attractive drug wound, one looks at dosing, and toxicity, except for some of those infectious complications, which I really don't

 

think is related to the drug.

It certainly meets the noninferiority confidence intervals. I'm still a little concerned about the Strep. I'm not sure that I ever got that question answered.

And as far as the MRSA is concerned, it would be nice at some point to go back, or start today with MRSA and do a really in depth evaluation of this drug against MRSA alone.

DR. RELLER: Miss Thomas.

DR. THOMAS: I voted yes. I would have liked to have seen a larger study. I was a little perplexed by the MRSA result being low as it was, but I can understand that this was done years ago.

The osteo rate is a concern -- osteomyelitis, but I know that that is hard to diagnose.

DR. RELLER: Dr. Cross.

DR. CROSS: I voted no. I also agree, it's a very attractive drug, and I think overall it showed a efficacy for cSSSI. However, again, in my case I'm bothered by the MRSA. And the fact of the matter is, that, if anything, the MRSA has become more resistant to

 

Vancomycin. And I don't think in this clinical trial we really even tested the more difficult cases of MRSA. Some -- until we have more of that data, and since this really is directed towards MRSA, we have to cover that empirically, that I came down on the no side.

DR. RELLER: Dr. Hilton.

DR. HILTON: I voted yes, because the question did not focus on MRSA. If it had, I would have voted no.

And based on this morning's discussion, I'm curious to know if pregnant women were eligible. And I'm hoping that the sponsor is going to be alert to what we learned this morning in the other study.

DR. RELLER: Mr. Levin.

MR. LEVIN: So, uncharacteristically I voted abstaining, because as the discussion went on I -- it might be the hour or it may be this is beyond my pay grade -- but I find -- I found myself more and more confused. That probably should be a no vote, because I was not convinced on the yes side of the equation. But given the option to abstain, I really -- I just couldn't get behind any of the other two buttons with great conviction.

 

DR. RELLER: Dr. Weinstein.

DR. WEINSTEIN: Like Dr. Nelson, I based my vote for yes on the overall issue of efficacy for these infections. But had it come down to only MRSA, I would have voted no.

I think the data presented, perhaps, because of the study design, simply don't convince me that there's noninferiority. And I think we need data from contemporary isolates and contemporary studies.

DR. RELLER: Dr. Follmann.

DR. FOLLMANN: I voted yes, because I thought the overall cure rates reliably show that the Oritavancin was reliably noninferior to comparator.

I had concerns, though -- my comments pretty much echo Tom's. I thought the endpoint was suboptimal and in future a better endpoint could be used.

You know, I noted that, you know, about 40 percent of the patients had abscesses, and that has issues or consequences, both for the endpoint they used here and for the margin that we discussed yesterday.

I view this as one study. I don't view it as, you know, having the weight of evidence of two studies as

 

I mentioned before. And then I'm inclined to think that the MRSA results are murky and that, you know, it's more like an hypothesis-generating thing that could be looked in future studies as Tom suggested.

DR. RELLER: Dr. Gutierrez.

DR. GUTIERREZ: Well, I voted no. And like the others on the panel that voted no, I really struggled with this. Because, you know, this is a very attractive drug and I like the safety profile, but I just in this day of complicated skin soft tissue infections being mostly MRSA, I just couldn't be convinced that it was noninferior to Vancomycin. And, so, I -- you know, I really hope that the sponsor will pursue further studies looking at MRSA in particular, because I think it is a very attractive drug.

DR. RELLER: Dr. Kauffman.

DR. KAUFFMAN: I voted yes, because I thought that was the answer to the question. It did indicate -- it provided evidence for the effectiveness overall for complicated skin and soft tissue infections. I'm very concerned about the MRSA data, and I feel that they clearly need to have more information for us to use it

 

for that. And that really is going to be the driver in the future for using drugs other than beta-lactamase for skin soft tissue infections.

DR. RELLER: I voted yes, but with full recognition of all the reservations that have been expressed by most of the people with the yes votes, and causing those with the no votes to vote no.

Question 2: Does Study ARRD independently provide evidence of the effectiveness of Oritavancin for complicated skin and skin structure infections. Please vote yes or no.

The vote is closed.

Results.

UNIDENTIFIED SPEAKER: One person didn't vote? Okay. Somebody didn't vote.

UNIDENTIFIED SPEAKER: Should we vote again?

UNIDENTIFIED SPEAKER: Should we all vote again?

DR. RELLER: So --

UNIDENTIFIED SPEAKER: Can they vote again?

DR. RELLER: So, we'll -- we need to verify the vote. We could consider this a recount. Please vote

 

again.

So, the voting result is 8 yes, 10 no, 0 abstentions.

We'll go in the reverse direction.

Dr. Kauffman.

DR. KAUFFMAN: I voted no in the -- for this study, because I thought the numbers really were too small. I think you inherited a dose finding study and then tried to make maybe a silk purse out of a sow's ear. I don't know. But you were sort of stuck with small numbers. And the only data that probably is relevant or -- is the 3 milligram per kilo dose. And then you get down to very tiny numbers within each of those subsets. So, I didn't think it really proved a point.

DR. RELLER: Dr. Gutierrez.

DR. GUTIERREZ: I also voted no. Again, I thought the numbers -- I agree with Dr. Kauffman, the numbers were small, and really were only looking at the 3 milligram dose.

DR. RELLER: Dr. Follmann.

DR. FOLLMANN: I voted no for similar

 

reasons. I thought the margin of 15 percent was too large. I, you know, had questions about the endpoint. I echo the issues that were raised earlier. I think in some sense it inherited an underpowered study and I wondered what you could do about that, because it's not as if you designed a large study and then made a margin of, you know, 15 percent, or didn't make a margin of 15 percent, or were right on it. It's as if you designed an underpowered study. But, you know, I don't think that changes really anything. It's just an underpowered study.

The -- in terms of the 97.5 percent confidence interval issues, I'm inclined to think that's more of a technical point. And I would probably be okay with a 95 percent confidence interval, thinking that we're more interested in the 3 milligram dose. So, I would focus on that if I was going to align the two studies. And I think that's all I have to say.

DR. RELLER: Dr. Weinstein.

DR. WEINSTEIN: I voted no for the same reasons, mainly the inadequate number of observations.

DR. GOETZ: I voted no, and ditto to the

 

previous comments.

DR. RELLER: Mr. Levin -- Dr. Hilton.

DR. HILTON: I was the person who didn't vote on that first partial round. I just couldn't make my finger go to any particular button. And now I've sort of pinpointed what my dilemma was. I think it's the 15 percent noninferiority margin that was bothering me so much. So, I did vote yes, but I think everything worked pretty nicely for a 15 percent margin, but I'm actually not content with the 15 percent margin.

So, I agree with Dr. Follmann's comment, that it's basically an underpowered study. But -- can -- with good results.

DR. RELLER: Dr. Cross.

DR. CROSS: I voted yes with reservations. I, too, feel it's underpowered. We have to really discard the low dose and -- at the 3 MG per KG dose. I think there's a signal there, but in and of itself it probably isn't enough to support anything.

DR. RELLER: Miss Thomas.

DR. THOMAS: I voted yes. I did think it was a small study, and the margins were maybe problematic,

 

but I thought it was a fairly good design of a study.

DR. RELLER: Dr. Septimus.

DR. SEPTIMUS: You'll get that. I voted yes at reservations for the same reason that Dr. Cross mentioned.

DR. NELSON: I voted yes. And I wasn't particularly feeling strong about my decision either. And I had some concerns. But, again, I was being a stickler for the question. I mean, they did find what they set out to find. Yesterday's discussion about the noninferiority margin of 10 percent didn't really come up today as being the definitive answer as what our baseline was going to be. And they did fine within their range at a higher confidence or at a higher statistical probability than 95 percent. So, I think they did find what they were looking for.

I would agree, though, that -- I mean, small numbers are fine, as long as they are -- if they're statistically, you know, reasonable, and they seem to be. So, I'm not so concerned about small numbers, but, of course, I would like to see more numbers, regardless to increase, you know, the confidence I have.

 

DR. RELLER: Those are the comments of Dr. Nelson. Dr. Lesar.

DR. LESAR: I've been trying to consistency in the way I formulated the answer. I voted again yes, but with more reservations. I think they have been expressed. But, again, more reservations but -- so, yes.

DR. RELLER: Dr. Bennett.

DR. BENNETT: As always, Carol Kauffman says everything I wanted to say, so, I'll just say it over again. That is, I think it's underpowered. I don't like the 14.1 percent confidence interval with the registration dose of 3 milligrams per kilogram. Two smalls, not enough cases of MRSA, 16 cases of MRSA treated with the registration dose of Oritavancin. So, underpowered and not convincing.

DR. RELLER: Dr. Leggett.

DR. LEGGETT: My thoughts exactly, except I would like to point out that they did follow the noninferior margin that was dictated at the time.

DR. RELLER: Dr. Fleming.

DR. FLEMING: While I agree the results are underpowered and makes it less reliable, the question

 

we're asking is: Does this provide strength of evidence of a positive trial? And we spent an entire day yesterday going through, with I thought great clarity, the challenges of defining -- justifying any margin under any circumstance greater than 10 percent, unless you have a huge safety advantage and other factors along those lines.

And even at that, 10 percent as a margin is a difficult one in this setting, because the endpoint is so different from the kinds of measures that were used to justify that margin. Using a 10 percent margin, the study fails on both arms. It fails on ITT, MITT, CE, even without adjusting for multiplicity, even without adjusting for, we need to take the abscess patients out to see how the results stand. You don't even meet the 15 percent margin when you do that. So, the results are what they were, as they said it was designed. It's a result from a Phase 2 screening trial. And part of the reason that these results are unfavorable, though, is not only the small sample size, but the trends are slightly in the wrong direction in this trial. They were at least slightly in the right direction in the other trial.

 

So, with the results -- with the estimate slightly in the wrong direction, and with the limited sample size, the confidence intervals don't even consistently exclude 15 percent, particularly when you leave the major abscess patients out of the analysis.

So, for multiple reasons, this, in my view, is not a one of two adequate, well-controlled positive trials.

DR. RELLER: Dr. Goetz.

DR. GOETZ: I voted no. I have really nothing to add to the prior comments.

DR. RELLER: Dr. Alston.

DR. ALSTON: I voted no and I have nothing to add.

DR. RELLER: Dr. Katona.

DR. KATONA: I voted yes. I think the study barely met the criteria that it was designed for. I didn't have a problem with the 15 percent. And overall I think it accomplished what it was supposed to have accomplished. They did get more drug in this study. Staph aureus issue wasn't quite as prominent.

DR. RELLER: As in the previous question, I

 

voted yes, but I did not disagree with the reservations, while the other yes votes.

But additionally, I was influenced on this particular one by, you know, what our discussions were yesterday, but yet at the time that it was done, the 15 percent was proved in a matter of consistency.

We'll move to Question Number 3.

The voting is open. And Question Number 3 is: Do the data presented demonstrate the safety and efficacy of Oritavancin for the treatment of complicated skin and skin structure infections? Please vote yes or no. And this is a comprehensive question that encompasses considerations from the previous two questions correct, Dr. Cox?

DR. COX: Yes. This is essentially, you know, has the -- you know, the two-study standard -- and we talked about how you can do that with one study -- but has that -- in essence, has that standard been met?

DR. RELLER: So, a decision on balance. Please vote.

Voting is closed.

Results, please.

 

The results are yes 8, no 10, 0 abstentions.

Dr. Katona.

DR. KATONA: I voted yes. I think the Staph issue is the one that I'd really like to resolve and get more data on to see where we are. Obviously these trials were done a long time ago. The bugs were slightly different. But I think they did accomplish what they set out to accomplish, and I'd just like to have more data on the Staph.

DR. RELLER: Dr. Alston.

DR. ALSTON: I voted no and I think you need an MRSA study.

DR. RELLER: Dr. Goetz.

DR. GOETZ: I voted no, thinking that I could not see how I personally could approve the use of this drug for treatment of MRSA infections.

DR. RELLER: Dr. Fleming.

DR. FLEMING: I voted no based on the issues raised in my responses to the first two questions. I would, though, think that one additional trial that was conducted in modern time that would give us a reliable answer with -- I would like to see a -- an endpoint that

 

is more nearly aligned to addressing resolution of clinical conditions that patients are seeking to have addressed, and also giving us more insight about MRSA will be invaluable. So, I would recommend that one additional quality study be conducted.

DR. RELLER: Dr. Leggett.

DR. LEGGETT: I voted yes, because I think in balance they answered the question satisfactorily.

DR. RELLER: Dr. Bennett.

DR. BENNETT: Push the right button. I had a very unenthusiastic yes. I think that the problem here is it's extraordinarily expensive to do these kinds of studies. The question -- it's not a wonderful drug. We don't have wonderful information, but in the balance, if -- do we think this is worth another several million dollars to do it modern? I thought probably not. I thought we probably had enough.

DR. RELLER: Dr. Lesar.

DR. LESAR: Again, I voted yes to -- trying to be consistent in my thinking. Again, with great reservations, but safety profile looks very good, and doesn't seem -- it seems to reduce my concern about the

 

balancing and effect, other than the MRSA, which I do have tremendous concern about.

DR. RELLER: Dr. Nelson.

DR. NELSON: You know, in the first two -- I voted no. In the first two studies there was a very specific question about the studies, not about the big picture. I think in the big picture the drug ultimately doesn't really show to do what it's purported to me to do. And, although the safety profile does look good, it certainly -- compared to other drugs we've talked about. There are some lingering issues. And the words here are, does it demonstrate safety? And I certainly think it demonstrates that it's not terribly unsafe, but I'm not sure it's actually demonstrated that it's completely safe. There is still lingering questions that I have.

DR. RELLER: Dr. Septimus.

DR. SEPTIMUS: I voted a soft yes. Again, answering the question, looking at safety and effectiveness. I think it's, again, attractive because of some of the safety and dosing issues we've already talked about. If you're asking me specifically about MRSA, I would say no. But in answer to the general

 

question I would say yes. And I'll just echo what I said before in others, it would be nice to have this study updated with MRSA.

DR. RELLER: Miss Thomas.

DR. THOMAS: I voted yes. And I just wanted to say I echo Dr. Katona's comments.

DR. RELLER: Dr. Cross.

DR. CROSS: I voted no for the same reasons that Dr. Goetz did, even though they technically fulfill the noninferiority, I think you do need something that covers MRSA better.

DR. HILTON: I voted yes because MRSA wasn't the stated goal.

DR. RELLER: Thank you, Dr. Hilton.

Mr. Levin.

MR. LEVIN: I voted no, and I have nothing to add.

DR. RELLER: Dr. Weinstein.

DR. WEINSTEIN: I voted yes for all of the same reasons that Dr. Septimus did.

DR. RELLER: Dr. Follmann.

DR. FOLLMANN: I voted no. I thought we had

 

one study that would, if coupled with another study done in the modern era, would, I think, provide evidence. But I think the ARRD is just dose-finding study. It doesn't really add.

DR. RELLER: Dr. Gutierrez.

DR. GUTIERREZ: I voted no because of the MRSA issue.

DR. RELLER: Dr. Kauffman.

DR. KAUFFMAN: I voted no, echoing what Dr. Follmann said. But I would really like to encourage the FDA to encourage the company to do a trial that involves a lot of Staph cases, especially MRSA, and then to do some tox data in terms of those macrophages. It might be a wonderful drug, we just need to have more information, I think.

DR. RELLER: I voted no. And the context of that was the on balance question. And it's interesting, in one reviewing the votes, there are multiple votes on this question where there are differences between Question 1 and 2 and Question 3. And that to me sends a very strong signal, that people want an effective drug, but we just haven't seen enough evidence with what the

 

contemporary problem is. And I do not necessarily see inconsistency, what it is, is the consistent message that we need more information to be perfectly comfortable on the question of toxicity, but most importantly on the efficacy of this drug as a drug that is started empirically in serious questions in the hospital, and for that, in practical terms, requires a drug that is of demonstrated effectiveness against MRSA.

And, also, I think a follow-up study that would provide that assurance should be done with a single, appropriate dose so that we have the numbers to have the adequate comparisons.

Dr. Cox, do you have a clear -- or clear enough message from the committee?

DR. COX: Yes. Thank you, Dr. Reller. And I'd also like to thank the committee, too, for all your work over the course of the day, and your comments and advice.

DR. RELLER: I realize that we are 25 minutes over time, but given the half an hour late start, in trying to be fair for sponsor and hear full discussion, I'm pleased that we've been able to provide what I hope

 

is -- useful information to the agency. We now stand adjourned until tomorrow morning at 8 a.m.

 

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NATALIA KORNILOVA
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