PETER KOWEY: Can I have SA-7.

BARTH RELLER: Please introduce yourself also, for the record.

PETER KOWEY: Sure. I'm sorry. I'm Peter Kowey, I'm a cardiologist from Philadelphia. Could I have that up, SA-7 please. No, that's not the one I wanted. It was from the QT package.

While we're looking for that, in regard to your question, I don't think that we can make any meaningful interpretation of a difference between those two numbers that you just saw from day one to day four. There's a lot of variability in the measurement.

The slide that I was going to show you, and if we can find it I'll put it up, is the numbers of patients who actually exceeded a 500 millisecond value for QTcF. It is extraordinarily rare for patients to experience torsade. And obviously -- yeah, that's the slide, you can put that one up. It's obviously -- the thing that we're all sort of dancing around here is what is the liability if this drug to cause torsade. And as you've heard from the presentations, I think it's pretty clear that this is probably a risk that is

fairly close to what the risk might be for moxifloxicin, an already marketed antibiotic.

The most compelling piece of data, I think, from this entire data package, and it's a very, very well refined data package I must say, is that there are vanishingly few patients in the categories that we really care about, QTcF, for any of these categories with iclaprim who exceeded a critical value of 500 milliseconds. And not exceeding 500 milliseconds, as far as I'm concerned, means that this drug -- it's virtually impossible to develop torsade with a QTcF less than 500 milliseconds. And this is, I think, the most reassuring thing that we have.

In addition you saw all the data on the Delta 60 millisecond changes. They weren't really any different between the comparator and iclaprim. So I think the composite of data here, and it's a, as I said, a very refined data set, would lead me to the conclusion that is torsade possible? It's certainly possible. Is it likely in patients that are treated with the recommended doses, I think that probability is pretty small.

KHALID ISLAM: Thank you.

BARTH RELLER: Dr. Fleming has a question for the speaker.

THOMAS FLEMMING: Torsade, as you point out correctly, is not common. Obviously this is an area of great challenge, because we have a bio-marker but as is the case with so many bio-markers it's certainly giving us an awful lot of uncertainties. But to look at the data and reflect on the fact that we're not seeing torsade, and I don't know that this is what you're saying, that this is greatly reassuring, just remember the rule of three. The rule of three would say in a trial with 300 people all you can do is rule out that the rate is more than one percent.

We'd be in deep trouble if the rate were one percent. So these trials are obviously seriously underpowered to be able to really look at the actual occurrence of the clinical consequences that an elevated QTc would make us worry about.

PETER KOWEY: Tom, I couldn't agree with you more, and that's the reason why we deal with the surrogate, is because real clinical events are so very,

very rare in clinical development. You can count on the fingers of one hand how many times I'm sure you've seen that actually occur in a data set of this size. I mean it's very, very rare.

So we use the QT, and I think that's fine. But it has to be put in some kind of a context, especially for a drug that clearly has a QT effect. There's no doubt here that this drug prolongs QT interval. And it does it in a dose dependent way, it does it in a concentration related way. It's perfectly understandable, and I think the interpretation of the data are very clear. The question is, at the end of the day, in this particular data set of these patients being treated for this term of therapy in this particular fashion, with co-morbidities and other QT prolonging drugs, and they did receive other QT prolonging drugs, there were no cases of torsade. And in addition, as I pointed out, there were no extreme outliers of greater than 500 milliseconds, a smathering of them but very, very rare.

So I agree with you, Tom. I think you have to take it all in context.

BARTH RELLER: Next was Dr. Follmann.

DEAN FOLLMANN: Just to elaborate a little bit more on the QT discussion. So the dosing for this drug is from seven to ten days in the trial and yet the QT evidence that you have is either based on a single dose or within the trial you looked at day one and day four. So I was wondering if there was any QT data that was after 10, 14 or more days that would reflect what was seen in clinical practice?

KHALID ISLAM: Yes, coming back a minute. We were talking about the QT effect and also we discussed something about higher doses of iclaprim being used and the number of -- or the duration of therapy. So so far we experience with both .8 milligram per kilogram as well as 1.6 milligram per kilogram doses. In our Phase 2 trial we used both of those sums. We didn't see any QT issues that arose in that context. And the duration period in the Phase 2 study was ten days and in the Phase 3 studies they've gone on to 14 days.

We also showed that actually when we did Phase 1 pharmacokinetic studies we went up to four times the therapeutic dose, it’s the current therapeutic dose.

And within those doses we know that there is no accumulation of the drug with time. So we do not expect an accumulation of the QT effect.

And coming back to what you were just asking, we do not have experience which exceeds 14 days. When we discussed with the FDA, both us and the FDA felt that it was better to collect the data on day one and day four as you might risk losing data as you went further out in time, because maybe patients drop out from therapy, maybe they discontinue, maybe they don't turn back -- come back for test of cure visit.

So in agreement with the FDA we felt this would give some idea, some feel around the QT change, which we see on day one and day four, because this was a better way to collect the data. And I don't know if you want to --

DEAN FOLLMANN: But you don't have the data at day 14?

KHALID ISLAM: No, we do not because we've not collected that data. We know that there is no accumulation of the drug after marked for administration. And therefore we believe that day one

and day four actually pretty adequately represent the type of changes that you might see.

PETER KOWEY: Just so that -- these studies are extraordinarily difficult. And what people try to do with these things is intensify the measurements at time points when they believe that the drug has its maximum liability and that's C-MAX. Whether it's true in every case or not, we've all chosen to believe that it's all about C-MAX. And so the comfort here is that there is intensive sampling around the time when you would have achieved your maximum concentrations.

Doing more sparse sampling at later time points, as Khalid points out, can lead actually to misleading information rather than really getting the truth. So I don't have any problem with the way this was done. That is sampling intensively at times when you expect the patients to have their maximum QT effects.

LEWIS NELSON: There's only one -- it's Lewis Nelson. But the only time that C-MAX would be the right time to measure QT is when it's the parent compound that causes the problem. And I guess my

question really goes back to the fact that metabolites don't necessarily have the same pharmacokinetics as the parent compound. We really don't know that there's not a metabolite that's slowly building up, that's a potassium channel blocker, that's going to not really show itself for four days, eight days or even a week after accumulative dosing. And that's kind of where my question was coming from.

KHALID ISLAM: I'll also take back something that I said. I told you we only measure on day one and four, my apologies. We did measure on additional days, if there were QT changes seen and/or if there was potential ConMed that were given. So we do have some information regarding other days. Obviously it's not as extensive or as intensive as day one and day four.

BARTH RELLER: At this juncture I'd like to ask if anyone in the audience had intended to speak at the open public hearing. Please come to the microphone and introduce yourself.

JAMES FLOYD: I'm James Floyd, I'm a physician and researcher at Public Citizen, a nonprofit public interest group based in Washington, D.C.

BARTH RELLER: Dr. Floyd, thank you. You had signed up and I wanted to outline the confines of the open public hearing. And since you have announced yourself, I will read the following statement.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product and if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have such a financial relationship.

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The FDA and this committee place great importance on the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the topic before them. That said, in many instances and for many topics there will be a variety of opinions. One of today's goals is for this open public hearing to be conducted, and as I mentioned, in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy and respect.

Dr. Floyd, thank you. You have three minutes. Please, we look forward to your presentation.

JAMES FLOYD: Thank you. I'll be brief. No conflicts of interest to declare. I'm sure this will be discussed later when the advisory -- in the advisory committee, but I just want to make a few comments about efficacy which haven't been brought up yet. And also, I don't know if I've heard it yet this morning but that this drug did not meet non-inferiority criteria just

explicitly based on criteria set up by the FDA and by the sponsor in co-primary end points in both studies.

And more worrisome, I think the upper limit of the confidence (inaudible) for effect size was less than zero. This drug was actually worse than the active comparator.

Now also one thing confounding things was the higher rate of concomitant antibiotic use which I don't think was mentioned as well, but is in the FDA briefing document, up to 40 percent in the iclaprim group, which if anything biases towards a finding of non-inferiority. However, we saw that the upper bound is actually less than zero and this drug is worse than the active comparator.

There are some safety signals that have been brought up as well that are -- have been discussed and will be more fully discussed. But I'm thinking, as an internist who is a hospitalist and takes care of cellulitis frequently in an in-patient setting, for a drug that has been shown to be worse than the active comparator, I can't think of a scenario where I would use this as empiric therapy.

And I think some people have brought up the scenario of this is, you know, another drug in the arsenal or a drug of last resort. And in that case it might be reasonable to use, if every other drug that's been shown to be more effective either does not work or there's a contraindication for using it. And in that case that should be the indication for the drug.

But to justify its use as empiric therapy for soft tissue infection, I don't think this drug meets the criteria for efficacy. And also there are concerning safety signals that doesn't make this a better safety profile. So those are my only comments. Thank you.

BARTH RELLER: Thank you, Dr. Floyd. The open public hearing portion of this meeting is now concluded. And we will no longer take comments from the audience.

The committee will now turn its attention to the address -- continue addressing the task at hand. The careful consideration of the data before (break in recording) as well as the public comment.

Our list of inquirers are Dr. Cross,

Wiedermann and Steckelberg, in that order. Dr. Cross.

DR. CROSS: I'd like to follow up on a concern that Dr. Bennett mentioned about myelosuppression. In the briefing document that we received it lists the target organs in the toxicology studies and does not mention the bone marrow. However further down it's pointed out that there were a decrease in the white blood cell count in rats, at four weeks.

A concern is one it's not clear in that document what multiple of human dose were used in those studies and for how long and whether it is single or multiple doses. I wonder if you might address that please.

KHALID ISLAM: Thank you for the question. Actually the doses that were -- that the animals were exposed to in the full week IV study, around 30 milligram per kilogram. So as in a human exposure that would turn out to be around three to six times roughly. We've also done studies by the oral route for 13 weeks and we've also done studies in marmosets. Again, we didn't see these effects. And also the no observed effect level is always around three to six times in

these animals, with respect to the human therapy dose.

DR. CROSS: And was the bone marrow actually examined histologically?

KHALID ISLAM: We did full histological examinations and this was not -- this is past -- any effects that are seen are those that are being seen much higher above the (inaudible). But we did not -- this was not noted by the study director at the time.

BARTH RELLER: Dr. Wiedermann.

BERNHARD WIEDERMANN: Yes, thank you. This is back on the QTc controversy, trying to get a little clarification here concerning two slides. First on sponsor slide 51, there's been some discussion to imply that iclaprim's profile in QTc is similar to moxifloxicin with moxifloxicin having a four to six millisecond increase. I'm wondering, is that -- you know, that ball park is referring to, at least with iclaprim, the delta, the difference between iclaprim and linezolid, is that number for moxifloxicin also compared? Is that a delta compared to linezolid to some other drug or is it an absolute increase and really shouldn't be compared to these numbers here?

KHALID ISLAM: The moxifloxicin number is actually from the PDR and it's for oral moxifloxicin. The IV number is around nine milliseconds, that's what we worked with from the PDR. We did not do the drug comparison. Obviously this is in comparison to linezolid. But moxifloxicin has been used in quite a lot of trials.

We did look at the NDA data, accrued data and compared that with our dose dependent increases in QTc. And on that basis we actually get almost a super imposable graph with respect to IV iclaprim and oral moxifloxicin. Again, I'm taking the data from the NDA from moxifloxicin and our data from our ECG studies. And that went up to four times the therapeutic dose. So that should literally overlap. However, I'd repeat again, we didn't do the direct study so what I'm referring to is literature data compared to our dose dependents.

BERNHARD WEIDERMANN: Okay.

PETER KOWEY: Peter Kowey again. Just so that we're clear, it is the delta of the delta for moxifloxicin as a placebo. The central tendency

effects that we're talking about are in the same range, absent this comparison with linezolid. The other thing that's very comparable with the moxifloxicin data or the outlier data, the categorical data, so the delta 30's and the delta 60's and the 500's, all of that really -- if you go back and look at the moxi data it looks very similar to what you see for this.

BERNHARD WEIDERMANN: And that was actually my second question, slide 52.

PETER KOWEY: You can put 52 on.

BERNHARD WEIDERMANN: If you can put another column there for moxifloxicin, because I'm much more interested in not the group mean of increase but how many patients are at risk. So do you have numbers available for moxifloxicin, if you just duplicated another column on this table?

PETER KOWEY: I don't have the exact numbers, but they would look almost super imposable. If you -- again, a lot of this has to do with the concentrations of the drugs that are -- of the drug that's used in the experiments. And one of the things that we've learned from the thorough QT designs is that, again as I said

earlier, it's all about the concentration. But supra-therapeutic concentrations of moxifloxicin do about the same thing that you see here.

You saw data, for example, as Khalid pointed out, at fourfold the concentration. And it's the same thing with moxifloxicin. The concentration effect is exactly the same. But at the therapeutic dose that's recommended for moxifloxicin, these outlier data look very similar. I can't say that they're identical, but they're very similar.

BERNHARD WEIDERMANN: Thank you.

LEWIS NELSON: Can I just ask a follow up question to that? Lewis Nelson. In the -- and you might have said this and I just forgot. People were excluded if they had a QT on their cardiogram of what, 400 milliseconds, did you say that?

KHALID ISLAM: Yeah, the exclusion initially, in stage A, up to 200 patients in the ASSIST program was that the baseline QTc ought not to exceed 470 milliseconds. They would then not be included in the ASSIST Program, for the first 200 patients, after which the DMC removed that criteria.

LEWIS NELSON: I mean -- I guess maybe this needs to go in -- stated, those are the people who, if they prolonged their QT more than 30 milliseconds would have been in the 500 and above range.

KHALID ISLAM: Correct.

LEWIS NELSON: So you took out a substantial proportion of patients at risk for developing the complication of note, right. Now there are probably some people who were less than that, had to have the potential to prolong beyond 500 milliseconds. And those would be the people that are truly the outliers, the people that go from 400 to 600 milliseconds. And those are the rare cases of people that we probably have to be aware of.

BARTH RELLER: I had overlooked Dr. Kauffman in the queue, so the order now will be Kauffman and Steckelburg, Fohlmann and Lesar.

KHALID ISLAM: May I just make one quick comment. One, we've just put you up some data regarding patients who had baseline QTc's and QTcF's that were included in these trials. As you can see that's probably representative of the general

population.

Two, I'd just like to make one quick comment. Regarding QT, we will be discussing, with the FDA, having appropriate cautionary language within the label. So we actually point out that this is a drug which has a QT effect and obviously we'll be discussing, in the label, how best to manage that QT effect. So we're not trying to say it is not a QT prolonging drug. We're saying it has a QT effect and we're telling you that the QT effect is similar to that of oral moxifloxicin.

PETER KOWEY: Just to make sure you understand that, we were very concerned about your question. Your question is right on. And that is if you exclude people with a lower -- with a higher QT then obviously you can miss the signal. And that's why what was built in the program was an opportunity to open up the aperture after the first 200 patients.

And when we didn't see anything we let people in that had any QT interval. So there were -- I think the distribution of QT for the entry patients was pretty much characteristic of what you would see in a

hospitalized patient population. But an excellent point about the 500 milliseconds.

BARTH RELLER: Dr. Kauffman.

CAROL KAUFFMAN: Well I continue to be struck by the differences geographically. Across the board the data are much better coming out of Eastern Europe and Russia and some of the countries in the area around Russia. And I'm just wondering, was -- PAREXEL is an international corporation and the monitoring was the same throughout the world? And did the Data Monitoring Safety Board look at this and say, what's the difference here, why is it different here than it is in the States and Canada? Any comments on that?

KHALID ISLAM: Maybe Wayne can -- Dr. Dankner could answer for PAREXEL. Would you like to answer?

WAYNE DANKNER: Yes, PAREXEL is a global company, but PAREXEL did not monitor the Eastern European countries in this particular trial. This was done by another CRO called PSI which has extensive experience in that region of the world and has worked with the investigators on multiple trials in this indication in the past. PAREXEL monitored the U.S.

sites in this particular trial.

In ASSIST-2 it was a different CRO that monitored the U.S. sites and PSI again monitored the Eastern European sites for that ASSIST-2 Trial. But again, PSI uses -- they have their SOPs just like other large CROs do because they all have the ability to be investigated by any regulatory authority throughout the world.

CAROL KAUFFMAN: So was there any concern of the data monitoring board that there were these differences in different places? Or how did they explain that? Or how do you explain that?

KHALID ISLAM: Well as also the agency pointed out, we do not know why there are these differences. They're obviously there. We look carefully to try and identify perhaps some differences in the medical care setting and the medical procedures that are used in Eastern Europe with respect to the U.S.

But we didn't see any obvious explanation for the differences in the cure rate. I think this has happened a few times in a few other trials. The monitoring was done very carefully and we have followed

all of the patients very carefully. But we do not have an explanation, just as the agency.

BARTH RELLER: Dr. Steckelberg.

JAMES STECKELBERG: Most of the discussion has been about staphylococci and streptococci, but I note there are some enterococci isolettes in the Phase 3 studies. And I can't find the slide in the book, but I think you showed some data that for enterococci the results were actually pretty good. But this is a folate antagonist and for other folate antagonist, because enterococci are oxytroths (ph) you don't really expect an in vivo response.

So have you an explanation for that, as to whether these were maybe not causative enterococci or there's something different about iclaprim or the self-resolve maybe their abscesses.

KHALID ISLAM: Okay, can you put the slide up for me, please. So this is actually the data on the on the enterococci again. The numbers are small, so please care of that. The difference is, for linezolid and iclaprim, again are in the same region as you would see, for example for strep pyogenes. Somewhere half

way between the strep pyogenes and staph aureus.

The actual E. faecalis strains, and maybe I'll need to ask Dr. Jones, probably distributed in different infection types and maybe Dr. Jones can comment on that.

MARK JONES: I think two brief points with regards to enterococci. There is some considerable heterogeneity of the DHFR in enterococci. So one can get something like biomodal distribution, in terms of in vitro activity. But in terms of the clinical cure, many of the enterococcus considered as baseline pathogens were also present with staph aureus. So to your question, there is potential to cure isolettes, but many of them are in conjunction with another significant gram-positive baseline pathogen. Excuse me.

BARTH RELLER: To follow up on Dr. Steckelberg's question, which is one that I wished to ask, going to the ability of enterococci to do an end run around DHFR in using preformed folate, and the discrepancy between in vitro and physiologic clinical response, do you have a counterpart for enterococci for

your strep pyogenes slide EE-69? So for strep pyogenes EE-69, one had a category of the kinds of infections that harbored streptococcus pyogenes. And related to Dr. Steckelberg's query, it would be of interest to see that for enterococci.

(Off microphone conversation)

KHALID ISLAM: Slide up, please. Is that the correct slide, Dr. Reller?

BARTH RELLER: This is strep pyogenes. So this exact breakdown but for those infections attributed to enterococci that the number was even -- about half of the strep pyogenes but greater than all of the rest of the streptococci in the aggregate. There were 15 cases.

KHALID ISLAM: Yeah.

BARTH RELLER: It's -- the total numbers and the outcomes that were nearly 100 percent that Dr. Steckelberg pointed out was slide 8 of the FDA presentation. But that was the total numbers, it did not break it down by category of cSSSI, as you have here for pyogenes.

KHALID ISLAM: Yeah, could you put up CC-16.

The actual number of strains that were present are actually quite small. We do not have the breakdown of them, we didn't try to break them down in the different wounds types, if that helps.

BARTH RELLER: Because the question would arise whether those enterococci that were so successful, where it does not make, to my knowledge, physiologic sense, may all have been drainable abscesses. We'll continue in the order of those requesting to question. Dr. Follmann.

DEAN FOLLMANN: So I wanted to talk a little more about the margin, which was raised by Dr. Alexander. And I'd like the FDA's slide number five brought up. And while it's being brought up I'd like to offer a brief comment.

So in superiority trials it's comment that a benchmark is to have two P values less than .05, to provide some level of evidence that the treatment actually works. And all that's not a hard and fast rule. You always have to look at each set of studies to feel comfortable with it. You know, it's somewhat context independent, you can start of take that from

one setting to another. Non-inferiority trials I think are a bit different, and even if you meet a particular margin that was a priori specified, you have to reexamine the assumptions that went into that in a way that I think is just shakier and less reliable than in a superiority trial.

And specifically this, I think gets to the choice of margin now. In the documents we saw earlier, the margin was chosen to be 12.5 percent based on an assumed cure rate of 85 percent and based on some other justifications. And in this trial now we see, you know, dramatically greater cure rates for the protocol population, one of the two co-primary end points.

And so if you look at this slide here, in the pre protocol population analysis you see cure rates of, you know, very high in the linezolid group for both studies, 99 percent or 95 percent. And I think, you know, you can't sort of just automatically just say well they met their margin of 12.5 or 10 percent. You have to interpret it in the context of the cure rates that were achieved for that study. These are very high cure rates and it makes you think that, you know, 12

percent or a 10 percent margin is quite liberal for a study like this.

So the point I'm making really is just that I think the margin of 12 or even 10 percent has to be interpreted in the context of the cure rates we see for this study.

BARTH RELLER: Dr. Follmann, this is an opportune time. I wanted to ask you, Dr. Hilton and Dr. Fleming what your view is on Dr. Wei's thesis that the comparator chosen should or might influence the NI margin selected. Dr. Follmann, Hilton, Fleming.

DEAN FOLLMANN: I would say in principal, that you know, the comparator can be factored in when you chose a margin. And if you play that game though you have to accept that you could meet the margin and be demonstrably inferior to that. And you have to really believe then that you're within an acceptable tolerance of inferiority and that the drug that you are interested in offers some substantial advantage in some other way over the comparator.

So I do accept different margins for different comparators. But, you know, you still have to

interpret it in the context of that study.

BARTH RELLER: Dr. Hilton, any comment?

JOAN HILTON: I don't have the slide in mind right now, but I think that the sponsor showed that the comparator chosen was better than vancomycin, on average. And so it was a good choice of a comparator.

But Dr. Valpavil (sic) also pointed out that there was considerable uncertainty in the comparator. And we do worry about the constancy assumption over time. I think the sponsor did the best they could with that choice.

BARTH RELLER: Dr. Fleming.

THOMAS FLEMING: Well this is certainly a very key issue. And I think there are a number of facts that we need to revisit. We had a great discussion two days ago to really try to go through the complexities. And I don't think there's a need to revisit all those issues.

But just to remind you of a couple of key thoughts that were very important, the IDSA assessments attempted to formulate what a margin would be. And we had much discussion, as Dr. Follmann has also alluded

to, in the fact that what's an appropriate margin is certainly situation specific. The margins that were put forward by IDSA are inherently based on their analysis on trying to understand what the effective and active comparator is. And they were assessing it in non-randomized trials.

And that creates an awful lot of uncertainty about whether there's bias. There's confounding between the penicillin and the no treatment group. There's also, as we were discussing a couple days ago, a lot of issues about effect modifiers. If we're looking at what the effect is of an active comparator, it depends on whether or not there's emergence of resistance and what's the impact of that on the active comparator's effect. It depends on co-morbidities. And in the historical evidence there was a lot of evidence of pneumonia, meningitis, bacteremia that certainly can influence overall success rates. And it depends on supportive care, as was indicated in the open public hearing. When there's a lot of concomitant antibiotics that are available, that can certainly influence outcome. Now one approach here was to define

those patients as failures.

The definition of the end point also matters. And this is what Dr. Follmann was getting at. When the IDSA assessments were done, that was done in a setting where the assessments of benefits were based on shorter term assessments. And the longer you follow someone the more likely there will be resolution. And so the magnitude of the difference, when you have longer follow up, will be less.

And as in the per protocol analysis, you're excluding people that didn't get four days of treatment, that didn't have at least seven doses. They have no major protocol violations. You're looking at a very pristine situation. There was -- there's no direct way to say that what IDSA did would tell us what the magnitude of effect would be of penicillin against no supportive care, again no antibiotic care, in that context.

And when you have these very high response rates there's an assay sensitivity issue. It is -- to allow a 10 percent margin in that setting is giving a considerable risk of allowing a therapy through that's

not effective.

Now specific to the point of the attempt by the sponsor to say should the margin be larger because linezolid is the control, I want to compliment the sponsor or choosing an active comparator that is among the arsenal that we have that is very effective. And maybe it is somewhat more effective. The data that was put forward to indicate that linezolid is more effective than vancomycin, we certainly need to have an opportunity to independently carefully scrutinize that evidence. There's not established analyses, to my knowledge today, that would establish that linezolid would beat vancomycin. And Thamban was pointing out some of those issues for caution, open label studies, etcetera. These things need to be reassessed.

But let's suppose that we said that linezolid was a couple percent better than vancomycin today. That's not the key issue in the margin, using the historical margin evidence we had before. The question is does that mean that it's better than penicillin in the pre 1950's when there wasn't resistance? We were looking, when we were using the IDSA data, we were

establishing what the margin was based on what penicillin did in a non-resistant setting, against no treatment.

And so the question of relevance here is if you're going to have a bigger margin, does that mean that you're concluding that linezolid is better than penicillin? If you can't say that then there's no basis for justifying that the margin should be even larger.

And there's also the clinical relevance issue. And it's again, somewhat coming back to Dr. Follmann's point. What is an acceptable increase beyond what you could have? How much worse are we willing to be? And I always -- as I was saying two days ago, I always like to turn the tables around and say, if you could be five or ten percent better, would that be really important. And most of us, I think, would say it would. To justify any margin greater than ten percent, then I think is very problematic.

This group did come to a consensus that while the margin should depend on the given setting, a general sense was ten percent would be the margin that

would be the upper limit of what's acceptable. The FDA, prior to that discussion, when they were discussing with the sponsor, indicated -- suggested a ten percent margin. Sponsors typically want the biggest margin possible, it allows for a smaller trial, it increases the chances of being successful. But in essence, the critical issue here is the margin has to be sufficiently rigorous that we're not losing a meaningful level of benefit.

And the FDA guidance, in 2007, a lot pointed out that even if there had been an agreement to a 12.5 or a larger margin historically, those are off the books. It has to be justified based on the science of today.

I guess my last thought on this is that it is -- when post hoc analyses are done to try to justify a larger margin when a result is problematic -- and this is not uncommon, a margin is set, it's not met, results are problematic. If post hoc analyses are viewed as persuasive, then there's real risk to the integrity of non-inferiority. If we're going to be able to use non-inferiority as an option to a superiority trial, it is

critical to maintain the integrity of those non-inferiority analyses.

So, in essence, I think the key issues here are that if linezolid is better than vancomycin, it's very appropriate that it was used as the active comparator. If in fact it's better it doesn't justify a bigger margin unless you can say linezolid is better than the historical agent, penicillin, when there wasn't resistance, in terms of the evidence used to establish that particular margin.

I guess there's one last thought. And it's somewhat related to this so I might mention it at this point. And that is one might say, in fact for instance we had slide -- slide five, looking at these results relative to the prespecified margin, and I view that as ten percent as the justifiable margin and as Dr. Follmann points out, that even is a very liberal margin, I would think for the per protocol analysis, these data are essentially not addressing or not meeting that margin. And the same is true if you do the analysis that is -- using the sponsor data and their analysis, when you leave out the major abscess

patients, in both studies we didn't meet the ten percent margin. But there's also evidence here that there's worse -- that you're worse. Tree of these four are ruling out equality.

And so there's not only considerable concern about establishing non-inferiority, but the estimates are suggesting that you have a considerably lower success rate. And the confidence intervals are suggesting, at least providing considerable evidence, that you may be worse.

One could argue well, okay but an agent still could be used even though it's worse than another agent. I suppose because in settings for example when you would have MRSA and you couldn't use linezolid, then this would be an option. But what scientific data do we have indicating that this is effective in a specific cohort of patients when other available MRSA agents, including linezolid are contraindicated? That would be, I guess I'm kind of jumping ahead to future studies, that would help us answer the question if it's worse, and there's considerable evidence to suggest it is, and it's not met the non-inferiority margin, might

there still be a role? Well what we need is a study when it's contraindicated to use this agent, or others that may be better, to find out if it provides a role in that setting. And those data haven't been presented. In fact that study hasn't been done.

BARTH RELLER: Dr. Hilton, and then we'll have the last question from Dr. Lesar. And I'm assuming it's directly related to the statistical issues. Yes, Dr. Hilton.

JOAN HILTON: I liked the point that Dr. Follmann made, and I just wanted to put it in more quantitative terms. If we have a delta of non-inferiority margin of ten percent, and a baseline response rate of 85 percent, that translates into an odds ratio that's less than two. But if we have a baseline response rate of 95 percent, which is more typical here, then that translates into an odds ratio of 3.35 percent.

So those numbers escalate when we change the non-inferiority margin to 12.5 percent and for 85 percent response rate it's an odds ratio of 2.15 and for 96 percent baseline response rate it's 4.0. So

four times the odds ratio is what we're thinking about when the margin is 12.5 percent. So I think just quantifying it just helps make his point even stronger.

BARTH RELLER: Thank you, Dr. Fleming.

THOMAS FLEMING: Just one sentence on that. I agree with Dr. Hilton. And in fact if you do that calculation, when it's 99 the odds ratio is ten. We're saying it's fine to have a tenfold increase.

BARTH RELLER: Dr. Lesar.

TIMOTHY LESAR: In order to continue having continuity of thought, my question was actually on QTc, so I'll withdraw.

BARTH RELLER: Therefore we did not intend to totally take a break -- I mean to totally miss the break. We will take a please, only 15 minute break to stretch, refresh the oxygen supply to the brain for getting across the goal line in the next hour.

(Break)

BARTH RELLER: Dr. Laessig, the deputy director, will make some remarks before we launch into consideration of the questions themselves and any residual queries that need to be taken before the -- or

addressed before the vote. Dr. Laessig.

KATHERINE LAESSIG: Thank you, Dr. Reller. So this is basically to take a few minutes to recognize two our committee members who are rotating off at the end of the month, Drs. Kathleen Gutierrez and Bernhard Weidermann have served on the AIDA committee since 2006. And their commitment and service to this committee has been beyond reproach. They have really complimented the committee with separate and unique experience and expertise. And during their years of appointment their professionalism and guidance have really been vital to our regulatory review process.

They have allowed our division to provide safe and effective products for the treatment of infectious diseases to the American public in a timely manner. And in appreciation of their service the agency would like to provide them with plaques, which Dr. Kim is handing our right now. And we are extremely appreciative of the work that you've done and have valued your opinions greatly. Thank you. Back to you, Dr. Reller.

BARTH RELLER: Dr. Cox, would you like to

present the charge to the committee regarding the questions?

EDWARD COX: Sure, thanks Dr. Reller. I'll start out by thanking all the presenters and discussants at today's morning session. There's been much information provided, both on the safety and the efficacy. And I just want to touch on a couple of things.

With regards to efficacy, we've had discussion on the confidence limits for the study results and where they fall. We've also talked about the non-inferiority margin. There was also discussion on the issue of comparator. And discussion of different categories of skin infections within the overall category of complicated skin and skin structure infections. And as -- we've also had a fair bit of discussion too on safety issues. And we've talked about safety data overall, including the size of the safety database, and also had considerable discussion on the QT effects.

So with that and all the presentations and discussions that we've had so far as consideration for

the questions, we have two questions that we'd like to get the committee's advice on. The first one, if I have it up, yeah.

So the first question is, did the data presented demonstrate the safety and effectiveness of iclaprim for the treatment of complicated skin and skin structure infections. We're asking you to vote yes or no.

And if the answer is yes, are there any specific issues that should be addressed in labeling? And if the answer is no, what additional data or studies are needed? And as always I need a rationale that supports your yes or no, that would also be very helpful and much appreciated.

Our second question. Should there be any limitations on the use of iclaprim? Please vote yes or no. In your response please discuss the following: The comparative outcomes for iclaprim and linezolid from the Phase 3 trials; the specific clinical situations where iclaprim should be used and the basis for any specific restrictions.

So those are the two questions that we have

from you and we look forward to your advice. Back to you, Dr. Reller.

BARTH RELLER: Thank you. We'll have a brief period for any residual questions that were not addressed this morning, including we have retrieved the teratogencity data, that question was raised as well, and we have that on that. But first a question from Dr. Weinstein.

MELVIN WEINSTEIN: So as I've listened to the discussions this morning something has sort of troubled me and maybe sort of crystallized as I was walking out of the room for the break. The information that we've looked at over the last couple of days has suggested that vancomycin, which is the comparator that has been used in other trials, has an efficacy rate of somewhere in the range of 70 to 80 percent. And it seems to me that those are the kinds of data that are being shown for iclaprim. And yet what we've -- what I've heard is that because the comparator used in these studies was not vancomycin, was linezolid, that this drug that's been presented this morning is inferior.

And clinically it seems to me that it probably

-- had they chosen vancomycin as the comparator, we wouldn't have been having a lot of the discussions this morning about inferiority that we have been having. And so I just would like to hear some discussion from my colleagues around the table about that issue.

BARTH RELLER: Any takers?

DEAN FOLLMANN: Well, I think it's fair to say that we just don't know. We saw very high cure rates in the study and what that's due to, because of the relative superiority of both drugs compared to vancomycin or just because the study was done when there was a lot of use of other antibiotics or done in Eastern Europe, we just don't know. And so it's a fair speculation, but you know that things might have turned out differently if vancomycin had been used as a comparator, but we just don't know.

BARTH RELLER: Dr. Leggett.

JAMES LEGGETT: One thing that comes to mind, now as we are talking about that and we talked about it and that I noticed was on Tuesday was that we're sort of suddenly talking about these newer trials as somehow being better than the -- at that point talking about

better than the older trials, pre, you know, 18th century that we talked about using penicillin and sulfa. And the immediate thought to me was, well those are the same trials that came before the FDA within the last ten or years. And I can't ever remember a trial being so pristine and pure that we then suddenly say, okay that drug is so much better.

So I was left with the fact that sure, linezolid may look a little bit better, in those three or four trials that were shown. But that doesn't necessarily mean that it -- it certainly wasn't shown that it was statistically better. And then each of those trials, in my mind, probably had the same give and take as we're facing here. So it's not -- it's as if it were sort of standing a little bit on shifting sand. And I wouldn't really say that, oh clearly if they had chosen vancomycin that we would have been okay with it. I wouldn't -- I just -- that doesn't compute, to me.

BARTH RELLER: Dr. Septimus.

EDWARD SEPTIMUS: Just one other variable in that is the test of cure, as I remember, in this

particular trial was 7 to 14 days after the completion of therapy. And how does that compute into the results?

BARTH RELLER: May we have the teratogenicity data that we left unfinished before the break.

KHALID ISLAM: Thank you. Put this slide up, please. So these are some of the studies. We looked at the repertaxin in rats, we don't have any affect on fertility. In terms of teratogenic effects we have seen somewhere around five, six times the human exposure dose, some effects in rats and mini-pig by the oral root. And -- but they're very similar to those known for the folate class, trimethoprim.

As you know, trimethoprim, you do use trimethoprim in pregnant women. You need to take care not to use it in the first trimester and I believe this is very similar as teratogenic effects for this drug. And so I think that the agency was suggesting Category C and I think that would be reasonable, that's what trimethoprim is. Our pleasure.

Can I also just take the occasion, Dr. Reller, to make one more comment? If that would be helpful?

BARTH RELLER: Please.

KHALID ISLAM: Thank you. Could I just have the U.S. population data, please. Thank you, yes slide up. We were discussing the differences between Eastern Europe and the U.S. Or European countries, I'd just to mention that we've had somewhere around eight to nine of these study sites that have been audited by regulatory authorities. And we have not had any notification to tell us that there was something wrong with those sites.

This is just to show you the U.S. data. And as you note, always iclaprim in the yellow bars compared to linezolid in the green, this is just the combined data of only the U.S. population with respect to what we are looking as primary analysis. We also noted the differences, we specified the differences for why we consider our patients to be cured and did not feel that the FDA analysis is necessarily coherent with our analysis, but there are differences.

So I just wanted to share that data with you so that you can keep this in mind. Thank you very much.

BARTH RELLER: Thank you. It's time for the vote, and then we'll go around the table for any amplification, clarification of why one voted as they are about to vote. Electronically, are we set? Question number one, do the data presented demonstrate the safety and efficacy of iclaprim for the treatment of complicated skin and skin structure infections? Please vote yes or no. The buttons are flashing.

We have one monitor that is not working, Dr. Katona's. It's okay now? Has everyone voted? The vote is locked in. The results when we -- the results are yes, two; no, 16; abstentions, zero.

We will go around the table this time on the left side, but counter-clockwise. Dr. Septimus. Your vote and rationale or any comments that you wish to make, not compelled to make but wish to make.

EDWARD SEPTIMUS: I voted no. I'm concerned about our non-inferiority margins that we agreed to a couple of days ago and the analysis of the data. I'm also concerned about the differences between the European trials and the North American trial. I'm cautious about the Group A strep data as well. There's

some safety signals that we've already talked about. And concerns about unintended risks with long term risk, as Dr. Bennett discussed. So for all those reasons I voted no.

BARTH RELLER: Dr. Nelson.

LEWIS NELSON: I voted no as well. I think that the efficacy data is a little bit concerning in terms of the non-inferiority margins as well. I'm also obviously concerned about some of the safety signals. And what I'd like to see, if this drug comes forward again, is some, you know, risk assessment and management plan rather than just kind of a promise that they would be dealing with that issue when it arose, and perhaps some sort of scientific evaluation, on a different basis, to show that both QT and hepatic issues, and a little bit more about this developmental toxicity which we just heard about, is going to be handled.

BARTH RELLER: Dr. Lesar.

TIMOTHY LESAR: I voted no. Again, my primary reason was that if the measure of non-inferiority was the target that was not met and also some concerns

related to the potential risk of rapid infusions of this drug.

BARTH RELLER: Dr. Bennett.

JOHN BENNETT: I voted no. If I was reaching for a dihydrofolate reductase inhibitor I would probably pick trimethoprim-sulfamethoxazole. Four years of experience, cheap, available orally and IV. Yes, some people are allergic to it, but it's not the only option for patients who have complicated skin and soft tissue infections. And so with what we've heard about the issues about safety and about the possibility of it being, for example, ten percent worse, I think there are many other options that would be preferable. So I would not pursue development of this compound any further.

BARTH RELLER: Dr. Leggett.

JAMES LEGGETT: I voted no. I don't believe that efficacy was shown to be sufficient. In regards to safety I think the drug is reasonably safe, even considering all the QTc and other aspects. But it's primarily on the basis of lack of showing efficacy.

BARTH RELLER: Dr. Fleming.

THOMAS FLEMING: I voted no. I think with all the discussions that we had justifying a context for margins, the ten percent margin would be as large as I could justify, particularly in settings in the per protocol analysis for reasons that Dr. Follmann clearly laid out. The data -- when we look at the data for ITT or per protocol analyses in both studies, they're not meeting this margin. And in fact when you pull out the patients with major abscesses you're still not meeting the margin.

What's problematic is that in fact there is suggestions, with many of these analyses, ruling out zero that you're actually inferior. Also when we look at MRSA, and numbers are somewhat small, but the data are suggesting that you are having a higher failure rate, or a lower success rate. And the degree of that -- the magnitude of the difference in success rates between iclaprim and linezolid is actually somewhat larger when you look within the MRSA subcategory than when you look within the entirety of the data set. So this sense of being less effective also applies in the MRSA category.

From the safety profile, numbers are small, but there were six deaths against two. And again it's an imprecise science as to cause, but suggestions that two of the cardiac deaths, two of the renal deaths could have been related.

And QTc is certainly an issue. It's very difficult to know the exact consequences of elevated QTc but those issues are also influential. So it's not a setting where I can say there's safety issues that are favorable and that in some sense could argue for adjusting the margin.

Regarding if your answer is no what additional data or studies are needed, I commented before the vote that given considerable evidence suggesting an inferiority of iclaprim to linezolid, what would only be left would be -- or what would be an obvious place to potentially go would be to understand the effect of iclaprim when existing agents, such as linezolid for anti-MRSA would be contraindicated. Can we -- can a future study be done to say in settings where you couldn't use other therapies, like linezolid that would be thought to be more effective, that here's where you

have the Allen wrench. The Allen wrench could be used in those settings.

But for all I know today you might put that Allen wrench where it's the only thing you can use and it might not have the right bit, it might not work. So it remains to be shown if you can find circumstances where other options that could be better are contraindicated, that this one would do the job. And that could be addressed in a future study.

BARTH RELLER: Dr. Goetz.

MATTHEW GOETZ: Yes, I also voted no. Going over my reasons, they're similar to those that preceded. I'm concerned about the lower bound of the non-inferior RE limit being set in 12.5 percent. And the study clearly exceeded, in my view, the boundary of -10 percent that we discussed several days ago. I'm concerned as well by the evidence that suggests that the agent may be inferior in that several of the outcomes that were looked at, the upper bounds of the 95 percent confidence limits was less than zero, favoring linezolid. In particular in that regard, I'm concerned about the lesser outcomes seen in people with

cellulitis or Group A streptococcal infections who receive iclaprim rather than the comparator agent.

The safety signal did not trouble me as much, but clearly more data are needed, because rare outcomes are very difficult to evaluate in studies of this size.

Thinking about what additional data or studies are needed, if development of the drug is to proceed, in my view, it may have a role for staphylococcal infections, although the point estimates don't favor the drug at this time. The confidence limits are broad enough, I think, it's potentially a valuable agent in that regard. It'd be difficult for me to imagine exactly how a study would be done, because I would really, at this point be reluctant to include people with Group A streptococcal infections or cellulitis, unless I had convincing evidence that cellulitis was not to due to Group A streptococci.

BARTH RELLER: Dr. Alston.

KEMPER ALSTON: Well it reflects my utter inability to predict, because I thought this was a no-brainer. I think it improves on an existing drug class, doesn't request the use of sulfa, it has the

potential for oral administration. I was impressed by the comparator being linezolid. I liked that the trials were recent, with recent microbiology. I liked that the trials were identical and could be pooled. The drug seems safe to me, and we have decades of experience with trimethoprim.

And, you know, looking at this clinically and not statistically, we're used to having drugs on a gradient of potency. And while I wouldn't use this or trimethoprim sulfa in a patient with a life-threatening bacterimic streptococcal infection, I think this has a role just like trimethoprim sulfa has a role. We're happy with the relative lack of potency with vancomycin, we understand the superiority of beta lactams, but I don't think that means we can't use those drugs.

And I like that using an older drug class with an older target would allow us to protect and preserve newer drug classes with newer targets, like linezolid, for when they're really required.

So looking at it purely clinically and not statistically and not getting bogged down in its

comparison to linezolid, I'm comfortable if it's even in fact inferior to linezolid but I'm not sure that doesn't mean there's not a clinical role for it.

BARTH RELLER: Dr. Katona.

PETER KATONA: I voted no. You know, I don't have a desire to have absolutes in non-inferiority margins. But I do think that it came below what we would have expected. And even looking at the subsets, when you look at the kind of thing that was treated, or the bug that was involved, it all seemed to kind of fall into place. But at the same time, you know, it's very hard to have a non-inferior margin that's acceptable when you've got a 99 percent cure rate in your comparator, which I understand.

Linezolid and vancomycin, I mean I'm willing to accept that there's -- that linezolid may have a non-inferiority with vancomycin, but I'm not sure I can accept that it's a better drug than vancomycin. But I'll accept the fact that they're close.

But I was concerned with the fact that you were looking at diverse populations here. You know, each of these diverse populations were in small numbers

and they had divergent results. And that was somewhat bothersome to me in terms of interpreting the information.

And also, in terms of the organisms, the ASSIST-1 didn't have very good data for MRSA and there wasn't particularly good results for strep pyogenes and that may be a factor of the cellulitis association that Dr. Goetz mentioned, but that was also a negative for the whole thing.

I won't go into the side effect issues, because I think that's been covered by others. But that's my comments.

BARTH RELLER: I voted no. I have physiologic reservations about interpreting the outcome with enterococci not getting even close on the subset of streptococci, so that leaves staphylococci. And I was not persuaded along the lines that Dr. Katona presented and Dr. Goetz, particularly that there was sufficient -- that the drugs are different. That is linezolid and vancomycin are different, I'm not persuaded that one is superior to the other, they're just different and therefore complimentary. And as a consequence, that

there was sufficient comfort in departing from the ten percent non-inferiority margin.

As far as additional studies, one option would be versus vancomycin and clear this issue. The other would be if this drug is taken forward as an oral agent, then this question of linezolid could be addressed again. And I must say that I was made -- I was a bit uneasy about the lack of explanation about the Eastern European results. Dr. Weidermann.

BERNHARD WEIDERMANN: I also voted no and I won't necessarily reiterate as for many of the same reasons as has already been expressed. I would just mention I'm certainly not opposed to a post hoc fudging of the margin. But in my mind I started with a ten percent margin in mind and there were too many fuzzy things surrounding this which have already been commented on for me to fudge the margin. So that's what I stuck to and that resulted in my no vote.

BARTH RELLER: Dr. Kauffman.

CAROL KAUFFMAN: I voted no but not without lots of consternation. I was back and forth many times during the morning, because we clearly need new drugs

for staph aureus, for MRSA. And I guess in the end I thought that the analysis by the FDA and the analysis by the company, probably in the middle was the truth, because I think some of those cases actually were cures that the FDA didn't believe were. But it still ended up that most of the confidence intervals didn't cross zero and were just skewed to one side.

And the company was evidently told that a ten percent margin was suggested highly by the FDA, but still persisted with a 12.5 and I think then they didn't make it. So in the end I voted no.

BARTH RELLER: Dr. Gutierrez.

KATHLEEN GUTIERREZ: I also voted no. I did go back and forth throughout the morning too. And, you know, some of my issues I think were the same as maybe Dr. Alston's. I liked the fact that there was the potential for an oral preparation and that, you know, we do need new drugs and that possibly this might be something that even we could use for less complicated skin and soft tissue infections.

However I think I -- you know, in just looking at it in comparison to linezolid I -- you know, I felt

it was an inferior drug.

BARTH RELLER: Dr. Follmann.

DEAN FOLLMANN: I also voted no, primarily because I thought, you know, the non-inferiority margins of 12 or 10 percent were too large for this study where we had such very high cure rates. And I think, you know, it's unfortunate that the study just didn't -- wasn't a very sensitive assay to see if there was a non-inferior difference between the two.

And I didn't see a -- you know, there's also concern that linezolid might actually be superior to Iclaalarpim (sic). So I voted no.

BARTH RELLER: Dr. Weinstein.

MELVIN WEINSTEIN: Like some of the others I went back and forth over the course of the morning. In the end I voted yes because I thought there might be situations where the drug could be useful.

BARTH RELLER: Dr. Davis -- excuse me, Mr. Levin.

ARTHUR LEVIN: I voted no because of the margin concerns and because of the safety signals in a very small population. And we've seen a lot of

experience -- we've had a lot of experience where safety, when the drug gets out on the market then many thousands of people are exposed, these safety issues -- unfortunate safety issues have proven to be a problem.

BARTH RELLER: Dr. Hilton.

JOAN HILTON: I voted no because of the overall results as well as the pathogen specific results. But I feel there's encouragement in the ASSIST-2 data set which had a larger fraction of patients with MRSA than the ASSIST-1 did and showed better results in that population. So I think that there's still hope for this compound.

BARTH RELLER: Dr. Cross.

ALAN CROSS: I also voted no. Like Dr. Kauffman, I felt that the disputed cases would put the data somewhere between the sponsor and the FDA's conclusions. However I was most disturbed by the discrepancy between the Eastern European and the North American data. And as a result I really didn't have full comfort in the quality of the data. And that coupled with the evidence here that it was probably inferior to linezolid tipped me over.

I do think that it's a potentially valuable agent and I'm not as concerned about the toxicology, except I would like to see a bit more information based on what we know by trimethoprim sulfa, in terms of further bone marrow toxicity.

BARTH RELLER: Dr. Steckelberg?

JAMES STECKELBERG: I voted no and agree largely with what Dr. Reller has said. However, I guess I'm not that worried about the margin or the margin of discussion, although it's very interesting in the theory. The way that it's set up is really to test whether this compound preserves 50 percent of the effect, using wide margins of patients treated when Theodore Roosevelt and Calvin Coolidge were President, compared to some treated when Franklin Roosevelt was President and then taking a very precise 50 percent of that to come down at 12.5 percent of the effect versus ten percent. And frankly -- and so there's a question of whether or not we've actually met that non-inferiority margin. But what that would show is that this drug is different than placebo, using penicillin in historic controls.

And to be -- you know, okay so maybe it's questionable whether it met that. I really don't have any question, in my mind, that it's more effective than placebo. To me the question is is it as effective as the comparator. And so I'm more concerned about the point estimate. And I do see a worrisome pattern that there are lots of point estimates in the overall analysis in the PP analysis that are somewhat less than the comparator.

Having said that, the argument was made that well had we chosen vancomycin, well first of all if vancomycin may be a couple of percentage points less effective than linezolid, which the sponsor finds important. But iclaprim is a couple percentage points less effective than linezolid, which is to be discounted. And that worries me a little bit, that kind of thinking. These are not usually transitive kinds of relationships.

So with respect to vancomycin, it may be true that had vancomycin been chosen as the comparator that then there would have been equivalence, and then it might be true that my vote would be different. But

that's different than data, and I think we have to make a decision based on the data that's submitted rather than supposition about what might have happened if it had been done differently.

BARTH RELLER: Thank you. In moving to question two, it's worth remembering the name of our committee, an advisory committee without authority for decision making. Consequently question two is relevant and we shall address it and vote yes or no.

Question two, should better be limitations on the use of iclaprim, were it approved? Please vote yes or no. The lights are flashing. Any changes? The vote is locked in. The results are yes, 15; no, 2; one abstention.

Dr. Steckelberg, you had the last word on the first question and the first word on the last question.

JAMES STECKELBERG: Well the primary -- two primary areas of concern would be microbiologically, and I'm not sure, for instance in the labeling where enterococci would fit, but I would have concern about that based on the physiology and the small numbers. And then I also have concern about streptococci.

BARTH RELLER: Dr. Cross.

ALAN CROSS: I voted no because I thought that while we reviewed the toxicology fairly thoroughly, I did not think that this drug represented a more toxic drug than others that we have discussed. And if we were to accept this based on its efficacy then I wouldn't see any further restrictions. I'd like to see more data on some of the microbiology. Our last two days I've been puzzled by the lack of efficacy against Group B strep and strep pyogenes. But leaving that aside, if one started with the premise that they showed efficacy then I don't see any further restrictions would be required.

BARTH RELLER: Dr. Hilton.

JOAN HILTON: My understanding is that most of the serious adverse events and deaths that were in balance between the two arms were due to patients underlying conditions. But I did hear a lot of concern about QT coming from the clinicians on the panel. And so I was -- I didn't feel that I was in the best position to make this choice, so I abstained.

BARTH RELLER: Mr. Levin.

ARTHUR LEVIN: So I voted yes. In sort of just thinking about the comments from the public session that I would think that if this drug were approved that the indication should be for use where patients are refractory or where other drugs are contraindicated, so it's the Allen wrench.

BARTH RELLER: Dr. Weinstein.

MELVIN WEINSTEIN: I voted yes and I had the same concerns that Dr. Steckelberg had about enterococci and Group A strep.

BARTH RELLER: Dr. Follmann.

DEAN FOLLMANN: I voted yes. I guess the reason is that I would think you would prefer to use linezolid first if you were considering either of these two antibiotics.

BARTH RELLER: Dr. Gutierrez:

KATHLEEN GUTIERREZ: I voted yes for the microbiologic reasons of not enough information on strep and enterococci.

BARTH RELLER: Dr. Kauffman.

CAROL KAUFFMAN: I voted yes again for the same reason that I think the data with streptococci

weren't very strong. And I would think there would be some limits put on it in terms of patients with -- on other drugs that influence QT or patients who have long QT syndromes.

BARTH RELLER: Dr. Weidermann.

BERNHARD WEIDERMANN: I voted yes as well and basically it would be -- if it were approved it would be for staphylococcal complicated skin and skin structure infections and probably leaving out the abscesses, although we didn't really get a thorough look in all classes about excluding abscesses; and then some obvious concern for use in pregnancy and some kind of warnings for the usual QTc issues.

BARTH RELLER: Dr. Reller. Yes, the same comments that Dr. Kauffman and previous people have made about streptococci and enterococci, just to emphasize the point for the record; and some kind of delineation of the importance of the QTc interval. Dr. Katona.

PETER KATONA: Since my name wasn't up there I'll just go right into the explanation instead of telling you how I voted. I'm not a big fan of

limitations, I mean I think that the more restrictions you put on something the more complex our job becomes. And there are off label uses for things automatically when something gets approved. So I'm not a big believer in putting limitations, with the understanding that there are QTc issues here and there are strep pyogenes issues here but those are more subjective than objective in terms of how you phrase a limitation and its use.

BARTH RELLER: Dr. Alston.

KEMPER ALSTON: I voted no, and I have no further comments.

BARTH RELLER: Dr. Goetz.

MATTHEW GOETZ: I voted yes. My concerns are, as has been previously elucidated regarding -- by others, the cellulitis issues, the microbiological issues with Group A streptococci and enterococci. As I think about how the drug might possibly be used, looking at the protocol I felt that there was not a demonstration of efficacy for complicated skin, soft tissue infections as a whole. But for the subset of staphylococcal infections there might -- complicated

skin and soft tissue infections due to staphylococci there might be an indication there. There should be some guidance about use of the drug in people with prolonged QT syndrome or medications of concern in that regard.

BARTH RELLER: Dr. Fleming.

THOMAS FLEMING: I voted yes. And I agree with comments that have been made before that there should be limitations in patients with long QT syndromes and where there's co-administration with drugs known to be prolonging QT syndrome. I do think there should be limitations to its use in refractory patients where treatments like linezolid would be contraindicated.

BARTH RELLER: Dr. Leggett.

JAMES LEGGETT: My thoughts echo those of people who've spoken previously.

BARTH RELLER: Dr. Bennett.

JOHN BENNETT: I'm reminded of when you're consulted by a surgeon about a wound infection and you say, I wouldn't give this patient antibiotics and they say, but if you did what antibiotic would you use? So

I have said that I didn't think this drug should be marketed. So now you say if it was marketed how would I label it.

And one of the things -- there are two things that I would be concerned about. One is there are strains of staphylococci, as shown on the sponsor's 17 and 18, that are resistant to 8, 16, 32, micrograms per milliliter so I might have said for susceptible strains of staphylococci in the labeling, not assuming that they're all susceptible.

The other is I'm not so certain that C is the adequate (inaudible) category, it might be X. Why? Because we have drugs of better known efficacy and safety. And so would you choose this if there was another drug? And I think no. So my understanding is that's the difference between X and C. So I don't have the answer to that, but I think that would deserve some more thought.

BARTH RELLER: Dr. Lesar.

TIMOTHY LESAR: I voted yes for many of the same reasons. Again, the issues related to the relative efficacy of this drug compared to other agents

and also related to the potential adverse events, particularly during infusions in a sick population on multiple drugs.

BARTH RELLER: Dr. Nelson.

LEWIS NELSON: Yeah, I won't comment on the microbiology, but I will stick to my original safety issues which includes, I think, that until it's much more clearly defined patients should have electrocardiograms before they start therapy and daily at least until therapy is ended with some criteria for when to stop the drug. I think liver function study should be monitored until we have more information as well.

I think the use in pregnancy categorization is very important. And I think we should, at the beginning, either contraindicate the drug in pregnant women or require -- at least require pregnancy testing prior to the start of therapy. And I think that we really need to get a better handle on potential drug interactions, knowing that it's a 3A-4 inhibitor means that there's going to be a host of drug interactions, most of which are well described already and need to be

laid out very clearly before the drug is given to anybody.

BARTH RELLER: Dr. Septimus.

EDWARD SEPTIMUS: I voted yes for the reasons discussed by Dr. Kauffman and Dr. Reller. I have little else to add.

BARTH RELLER: Dr. Cox. I think the committee has given a clear sense, with exposition, on their views on the two questions that you posed. Do you have any further comments before we conclude the meeting?

EDWARD COX: Thank you Dr. Reller and thanks to the committee. And I wanted to also give Dr. Laessig a chance to thank everybody. I think it's been a very productive two and a half days and we're very grateful.

KATHERINE LAESSIG: Yes, congratulations on making it to the end of 26.2 miles. We're sorry we don't actually have any medals for you, but at least you get to go home now.

But seriously, it was really invaluable. The discussion has been very thorough and thoughtful and you've really provided us with some excellent advice.

And I think it identified some issues that perhaps we hadn't thought about enough. So we will certainly take this back and consider it in depth.

So have a safe trip home. Thank you.

BARTH RELLER: I have one last request for Dr. Katona, for the record, from our designated federal official. Your vote on question two, since your monitor was not working? No, Dr. Katona is registered as a no.

(Off microphone comment)

BARTH RELLER: Excuse me? Question one also. Two nos. Dr. Katona no on number one, no on number two. Please revise the final summaries accordingly for the record.

Thank you very much. It is exactly 12 noon.

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