influence the labeling, is with the absorption of the drug orally, have very sick patients been looked at?

I mean the question for the clinician in the hospital always is: is your intubated patient that's really, really sick able to absorb an oral drug? And usually we just say no and give them intravenous, but do you have data on that?

I know data represented on the food, but I don't remember if things like tube feedings were looked at or antacids, calcium, the usual things that have influenced other drugs, and how strong are the data in those subsets?

And then the other question relates to that subset of individuals that seems to have low blood levels, and I'm curious. Do you have any information on what's going on with those people? Are they -- presumably they're different metabolically. Is there concern about patients?

How low can the levels be in somebody, and is there going to be a subset of patients that needs to be identified with MRSA bacteremia, for example, that would either need to have blood levels

determined? How confident are you that everybody that's sick enough is really going to have high enough levels?

Because according to the FDA analysis there are individuals that have quite low levels, relatively low levels.

DR. TARPLEY: Dr. Jungbluth will --

DR. MURRAY: And any reason to think that these, if they are hypermetabolizers, are they the subset that either fail or that get into toxicity problems, LFTs or whatever?

DR. TARPLEY: Let us organize a response because there were at least three questions there.

DR. MURRAY: Yes.

DR. TARPLEY: Thank you.

DR. JUNGBLUTH: Okay. I think part of your first question was the oral absorption in sick patients, and we don't have an exact bioavailability study conducted in somebody like this, but we have a large patient population. We've done pharmacokinetics in our Phase II studies, and there's over 600 patients included in that, and they would have received IV and

oral.

So we think that we have some pretty good data there that would suggest absorption is adequate, and the kinetics in these patients are similar to the profiles we have seen in the healthy volunteer data.

And did you have a second part to the absorption question?

DR. MURRAY: Any other specifics, two feedings, antacids, acid, anything --

DR. JUNGBLUTH: No, nothing specific like that.

DR. HAFKIN: To try and further answer that question, we could go through our analysis of response by APACHE score. It's very similar to Dr. Ross' analysis. We also have the analysis of patients on ventilators, and if you look at those lists of the patients that got the drug under controlled Phase III trial, there is not a fall off of efficacy.

So although the clinical database is not huge because we only have 2,000 patients in our database, at least for that very sick subset of patients, we have good outcomes.

CHAIRMAN RELLER: Dr. Leggett.

DR. LEGGETT: Yeah, I think there was a third part to Dr. Murray's question, and then I had a follow-up.

DR. TARPLEY: I'm sorry. Could you repeat the third part, please?

DR. MURRAY: The subset or the individuals that -- there seems to be a wide splay in the blood levels, and there are some individuals that really fall at a low range of blood levels. Do you know anything more about those? Do you have reason for concern that in very sick patients blood levels -- in some patients blood levels should be obtained because there may be an identifiable subset that has low levels that needs more drug?

DR. TARPLEY: Yes. The data that we showed today were at a fixed dose of 400 or 600 milligrams twice a day, and you saw that we were able to demonstrate very good efficacy. So we do not feel that it's necessary to monitor blood levels. You've seen the data in the sickest patients, as well, and the efficacy is quite, quite good.

CHAIRMAN RELLER: Dr. Wittes had a question.

DR. WITTES: Yeah, I want to circle back to 54 and 54(a), to the accounting. This is a two-part question.

The first part of it is sort of a confirm and the second is a question. I count 331 patients randomized in all, of whom 145 were in 54(a), 82 in 54, and the remainder still on the study. I assume the 145 in 54(a) were the first 145 randomized. I just want to confirm that.

And the second is the 82 in 54, are they the next 82 randomized? How did -- when the FDA asked for them, how did they specify which ones were to be looked at?

And let me tell you the drift of the question. The question is that as we're comparing the 200 to 600, is there a potential for bias in the information that we're seeing.

DR. TARPLEY: Dr. Oliphant will start the response, and we'll see if we can satisfy your question

DR. OLIPHANT: Slide up, please.

First of all, I should say that Dr. Ross' slide which demonstrated the history of these studies was quite accurate, and I think that told part of the story. This slide here may tell the rest hopefully. This is the key activities time line for Study 54(a).

On June 20th, Study 54(a) was closed to enrollment, and then July 22nd was our cutoff date for the case report forms that we were able to retrieve for completed patients, and that resulted in 79 patients in the 600 milligram group and 66 patients in the 200 milligram group.

DR. WITTES: Can I clarify something? Is this -- are those the first 79 and first 66 randomized?

DR. OLIPHANT: Not necessarily, no.

DR. WITTES: Okay.

DR. OLIPHANT: And then on August 3rd, 1999, we had a teleconference with the FDA to discuss the possibility of submitting the results of these 145 patients.

Subsequently, on August 19th, the database

was closed for Study 54(a). Treatment codes were unblinded, and then on August 30th, we did generate and present unblinded results.

Now, may I have the slide for Study 54? Slide up, please.

Okay. Now, Study 54 then, which was in effect a continuation, but was considered a separate study, as you see, it began enrollment officially on June 20th, which was the date of cutoff for Study 54(a).

Now, there were as you see in the footnotes some patients included in Study 54 who were enrolled prior to June 20th because their case report form data were not available at the time that we presented results for Study 54(a).

And December 27th, Study 54 was closed to enrollment. At that time we had the 186 patients, and in late December actually it was that we presented the data for those 82 patients to the FDA.

DR. WITTES: And then does that mean, again, that those 82 are not necessarily the next consecutive group? Is that right?

DR. OLIPHANT: I believe that those 82 are the next consecutive group, yes.

DR. WITTES: I guess I'm confused. If those are -- so that you determined by the 82 by date of randomization, but the 54(a) by date of case report form collection? Is that right?

DR. OLIPHANT: Well, if we can go back to the previous slide, the 54(a) time line, slide on, please. No, that's still 54. One, twenty-seven, I think. One, twenty-two? Yeah, slide on.

Okay. On June 20th, Study 54(a) was closed to enrollment. So patients who were enrolled prior to June 20th and as the second bullet point indicates, patients for whom we were able to retrieve case report form data from the field were included in our presentation of results for 54(a). So that's 145 patients.

DR. WITTES: Okay. Again, you retrieve when the entire -- that patient is finished, right?

DR. OLIPHANT: Correct.

DR. WITTES: So if somebody were recruited sort of late, like June 15th, and were still being

treated in July, I mean, sort of what I'm trying to get at, it seems to me there's a potential for a length bias in the last group of patients captured by the case report forms, and I think we need a handle of this in terms of a handle for the magnitude of what this could be in terms of looking at the comparison between the two doses.

Because I mean, we were trying to look at superiority in that, and therefore, if there's a potential for a bias in ascertainment, that would be difficult.

And then the other question is if you couldn't get the sequential ones for 54(a), why could you get them for 54?

DR. HAFKIN: Can I make a clinical observation on the CRF availability?

The patients with the longest follow-up are the patients with urinary tract infection, and because we demand six weeks of follow-up data. So there was, in essence, a bias against, in fact still going on in a sense, against urinary tract infection experience because the patient gets the same standard

length of therapy, but their follow-up goes on for weeks afterwards, whereas if you had the germ in the blood stream or interabdominal abscess, your acceptable follow-up period would be two weeks to three weeks.

The majority of patients that were pushed from 54(a) into 54 were urinary tract infections, and the majority of the patients that we have out in the field that you haven't seen from 54, the little interim analysis study, those will also be, in general -- there's a greater chance that they will be patients with urinary tract infection.

It is true that we wanted an experience with urinary tract infection, but at the present time, we're not actually asking the committee to judge where the drug is efficacious against urinary tract infection.

DR. OLIPHANT: May I just add one more point, Dr. Wittes? I believe I did misunderstand the second part of your question. Those 82 patients in 54 are not necessarily sequential, as well. We were asked by the agency late last year for additional

information on patients we had available in that study. So we had to cut off the database at that time. So those represent the 82 patients for whom we were able to get information at the time.

DR. WITTES: Thank you.

CHAIRMAN RELLER: Dr. Chesney.

DR. CHESNEY: This is totally switching gears, and I hope I'm remembering this correctly. In terms of adverse events, in the animal models there were some testicular changes. Am I remembering that correctly? And we're not worried about that in humans?

DR. TARPLEY: No, we are not. Dr. Petry can respond to that question from our Toxicology Group.

DR. PETRY: Actually we had some fertility changes in the male reproductive tox. studies, but we do not have testicular lesions. Rather what we have is a lesion in the epididymis, which as I'm sure you're aware is the site of sperm maturation. That lesion requires a relatively long onset.

Actually I believe I've got a slide

perhaps that would speak to that. Could I see T-195, please? Slide on, please.

We, in fact, required seven to nine weeks of administration, and it was completely reversible following another seven to nine week period of recovery. The time course of both the onset and the resolution of the effect correlated very well with this epididymal ductal epithelial hyperplasia.

Again, as I indicated, this is a site of sperm maturation. There was, in fact, no testicular lesion observed in these studies. We looked to see whether there might be some sort of a plasma testosterone phenomenon going on here because the epididymis is a testosterone dependent tissue, but we did not see that.

Additionally, we had no lesions in the canine reproductive tract. So on balance, we don't feel that there's going to be a risk for male reproductive issues associated with the compound.

DR. CHESNEY: You don't have any human studies though? I mean, we're extrapolating from the rat, and that's probably fine. I just want to be

reassured.

DR. PETRY: I have no human data to offer. You're correct.

CHAIRMAN RELLER: Dr. Soper.

DR. SOPER: As a follow-up to that, I notice that you relate mild fetal toxicity in rats at levels that are consistent with what would be used in humans, and that this was post implantation loss, and two out of the three women that were pregnant and were exposed to this agent suffered a miscarriage.

You relate the similarities of some of these findings to drugs like tetracyclines and quinalones, which we don't really use during pregnancy. Is this an agent that we need to avoid during pregnancy?

And what category drug will this be, pregnancy category?

DR. HAFKIN: I think I'll ask my colleagues from tox. to come, but it's our feeling that our drug should be Category C.

In terms of the rate of miscarriage, you're quite right. We had two miscarriages in very

early pregnancy in our clinical trials, but that's consistent with spontaneous miscarriage in healthy young women.

We have literature. We basically -- there have been a lot of reports of 50 percent, and that's basically what we're carrying forward.

DR. SOPER: The miscarriage rate is about 20 percent of clinical pregnancies, which is what you could relate to this observation. So --

DR. HAFKIN: Well, let me make the point. Everybody was pregnancy tested negative at baseline. So these were not pregnancies diagnosable at baseline.

DR. PETRY: Could I actually see Slide T-206, please? Slide on, please.

This does speak to what we've seen in our peri and postnatal development studies. There is a mild and it's a reversible decrease in the offspring body weight that classifies as fetal toxicity as these animals continue that resolves. There is an effect on pre-implantation or peri-implantation loss. That's not necessarily -- we've looked at this now quite in depth, and we don't see that when we rebreed those

males at 141 days.

It is a very mild effect in the fertility there. In contrast or by comparison, in a number of labs it would be considered within the historical range of controls, but because we've got a new class of agent here, we look at these very carefully.

Additionally there are some slight reductions in the pregnancy rates coming out of these animals. About 12 percent of animals didn't sire a litter in either of the breedings.

CHAIRMAN RELLER: Dr. Drayton.

DR. DRAYTON: I may be incorrect, but I think I recall reading that there were also developmental problems in the offspring, and I wondered whether they were physical developmental problems. Is that of concern in pediatric population?

DR. PETRY: We don't think that it is, no. The developmental delays that we see are sort of, again, a mild decrease in initial body weight, which resolves over time. There was a slight delay in pena detachment, which I don't see as a clinically significant issue.

CHAIRMAN RELLER: Dr. Lowy.

DR. LOWY: Regarding adverse effects, diarrhea was one of the more common findings in the clinical cases. Is there any information on the incidence of pseudomembranous colitis in the population of individuals who developed diarrhea?

DR. HAFKIN: Yes, we've done analysis. If I could ask you to look at S-169, yes, if you'd show that slide.

There was very little clostridium difficile diarrhea that was actually diagnosed in the study. Certainly there's no signal of increased risk with linezolid therapy.

CHAIRMAN RELLER: For a drug that doesn't get into the GI tract, why do you think this might be? Is it a motility issue? What's going on?

DR. HAFKIN: We really don't know. We'd have to speculate.

CHAIRMAN RELLER: Dr. Leggett.

DR. LEGGETT: Continuing with the VRE question, given an underpowered study looking at 200 and 600 for most of the things that were looked at, I

have a hard time understanding if 600 equals 200 equals placebo or placebo is worse than 200 is worse than 600.

In looking at ways of trying to get around that, I guess Dr. Chikami in the morning talked about historical data, and I was wondering if anybody knew of any sort of maybe comparable, if not exactly equivalent patient populations with other drugs against VRE.

And the second comment, trying to get back to Dr. Murray's question, in terms of responses, is it possible that the people with the bad diarrhea did not absorb drug as well? Can you correlate folks with increased incidence of diarrhea with those who failed?

And do you have any drug levels in other than volunteers? Is there any way to look at kinetic data combining 600 and 200 and trying to correlate that with ACU above MIC or time above MIC so that the folks with 200 who passed had better drug absorption, better drug levels than the folks with 600 who had terrible levels or the folks with 200 who had terrible levels?

So of a lot of questions, but all trying to get at another way to maybe convince us that this drug is efficacious.

DR. HAFKIN: I hear the three questions, and let me try and answer the first, and then we'll try and approach the second.

The estimates for mortality in VRE infection, enterococcal infection has been estimated by many people, and in fact, Barbara Murray just recently published in the New England Journal a review suggesting mortality of I believe it was 30 percent, but it may have been 40 percent in her review of the literature.

Other authors have suggested that mortality rates of 40 percent would commonly be seen, and indeed, there is additional data in compassionate use trials, such as ours which suggests that success rates of drugs that have active efficacy or active activity against VRE may actually be in the 60 percent success rate.

So in terms of historical controls for all comer kind of populations, another drug recently given

indication for VRE infection, I believe, had success rates in similar protocols of 60, 65 percent. I'm not an expert with that agent, but mortality rates have been estimated to be 30 to 40 percent in multiple historical papers. So I think that's one way.

Now, in terms of trying to help you understand the work we've done in terms of relationship between dosing and outcome, I'm going to ask my colleague from Pharmacokinetics, Ed Antal, to speak to that question.

DR. LEGGETT: Can I just jump in? I'm not quite sure I understand. If you said the traditional historical mortality rate, is that with treatment or without treatment of 30 percent?

DR. HAFKIN: Well, it depends on what kind of -- it is without treatment. Those are the estimates for without treatment.

DR. LEGGETT: Okay. Because what I see is a success rate of 67 percent, which sounds like 70 percent, which leaves 30 percent mortality, and that's with treatment, which is the same as without treatment.

That's the trouble I'm having.

DR. HAFKIN: Sure, and it depends on all comers and population ranks. Agreed.

DR. ANTAL: If I understood your question correctly about the relationship between, say, response or side effects in concentration or kinetics, we've looked at the Phase II databases, the database that we had accessible that had the most population pharmacokinetic sense. We use that as our basis.

We did see a relationship between AUC over MIC versus pharmacokinetic parameters. It was by no means 100 percent predictable. The relationship is there. There higher doses do have the higher tendency.

We looked to see if there was a rationale that one could say, for example, you know, a certain cutoff point that you wanted to be above or things of that nature. We didn't see it because I think that a lot of the failures that you're looking at are multi-factorial reasons. It's just not a question of a certain level of drug, but it's a lot of other things, too. So that's where we stand with our analysis right

now.

So is there a specific other question you have?

DR. LEGGETT: No, I was just thinking one thing. If you could get that subpopulation, maybe a small group of folks where you actually had VRE grow in the blood, you might be able to try to get a handle on it with a very small, hopefully a much smaller number of patient.s

DR. ANTAL: Sure.

DR. HAFKIN: Sure.

DR. ANTAL: Your other question about the safety, gastrointestinal, we saw no relationship between a low blood level and a higher incidence of gastric upset.

DR. HAFKIN: If I can jump in in one more way, there is a difference between success and mortality, and even in the low dose, we don't have mortality rates of 30 percent, and in fact, Dr. Ross' mortality analysis is particularly potent in that regard.

I don't remember David what slide you had

when you looked at the VRE study from the point of view of mortality.

DR. LEGGETT: It's page 14 of 18 of the FDA packet that we got put out, Table 3-10.

DR. ROSS: If you'd like, we can bring that slide up.

DR. CHIKAMI: Dr. Reller, may I make a comment?

CHAIRMAN RELLER: Please.

DR. CHIKAMI: In regards to the issue of trying to get a handle on historical information in this area, and I think this has come up in a previous meeting, and I am sure Dr. Murray can speak to this, but as we try to look at, one, mortality in this patient population, whether or not patients got treated, and if you look in the literature, most often patients got some sort of treatment, and it's very difficult to then sort of look at responses by whatever therapy was available.

But if one looks across studies, mortalities in the literature varies widely anywhere from 30 percent up to 70 percent. So the estimates

are quite imprecise as one might expect, given the large variability in the patients that are being reported in these studies.

To speak to the other issue in regard to other experience in, for example, compassionate use programs that have been used to treat VRE, there again one runs into the problem of how comparable the patient populations are.

In that other experience, in fact, the breakdown by site of infection was a little different, and moreover, given that that was a compassionate use program, not randomized controlled trials, the patients tended to be a little sicker.

Having said all of that, if one looked at, again, in two of those protocols, the overall mortality rates were around 50 percent in those trials, and the overall success rates varied anywhere from 46 to 56 percent. Again, very difficult to try and use those as historical controls, given the differences in the patient populations.

DR. HAFKIN: You know, I was wondering whether we should look at Dr. Ross' analysis of

mortality.

DR. ROSS: So for the MITT-VRE population, in the high dose arm, 16 out of 65 patients died, a mortality rate of 24.6 percent. In the low dose arm, 18 out of 52, 34.6 percent. In the bacteremic patient population -- so these are patients with VRE bacteremia at baseline -- in the high dose arm, four out of 18, that is, 22.2 percent and nine out of 16 in the low dose arm.

DR. HAFKIN: And if I could make one point, Dr. Ross' slides were prettier, but our analyses imply the same pattern of increased success or differentiation between the high dose versus the low dose, depending on severity of illness.

So the higher the MPM-2 score, which is the score that's based on vital sign and underlining morbidity, the higher the chance of mortality, the more effective the high dose becomes in relationship to the low dose.

CHAIRMAN RELLER: Dr. Murray.

DR. MURRAY: Yeah, I was just going to point out that the figure, the 30 percent that's

usually -- that figure that's quoted is from Edmond and Wincell for an attributable mortality to VRE bacteremia, which they defined, if I recall right, as either two positive blood cultures or one plus evidence of systemic infection with high fevers or low blood pressure. So that 30 percent figure is often quoted as an attributable mortality, although not all studies have shown that, but the definition of bacteremia has often varied from even one or two or with or without signs of sepsis.

So as Gary pointed out, it's extremely difficult to, without matching case with case, to use historical controls.

CHAIRMAN RELLER: Drs. O'Fallon and Wittes, do you have any comments you might make addressing the numbers of patients with enterococcal bacteremia and differences in outcome with what we have here for 600 versus 200?

DR. WITTES: The quick answer is no. I mean, I've actually opened up the table of numbers to do exactly that. It's very hard to answer without doing some calculations, but the numbers are small.

There's lots of different categories that are going on, and I'm still troubled by -- I'm still focused on the fact that we don't have a consecutive sequence, and I don't know how serious that is.

So I'm punting to Judy.

DR. O'FALLON: Well, I, too, was having trouble because of the enrichment study and trying to figure that out, how those numbers fit into the rest of them because, you see, the categories for me anyway, we've been asked five questions. When we look at these numbers in the one with 104 MRSAs and so on, they're grouped by disease. I mean all of the diseases are stuck together.

So it's hard for me to try to separate them out into the categories that we're being asked to do, and without more time, I can't tell.

I went through and looked at the original studies, and they were asking do you have enough people, and the answer is no, no, no.

But then to get to the enrichment study, but then they're all bugged together. All of the pneumonias are together and all the SSSIs are

together, and I can't break them out. So I don't know exactly what's going on here. I couldn't -- I don't know what the numbers are.

DR. CHIKAMI: Dr. Reller, may I make a comment?

I understand the comment that's made, but I think it relates to one of the issues that I raised early on at the beginning of the morning. That is, as we, the agency, and at the two public meetings have discussed with the advisory committee and members from academia and the pharmaceutical industry, one of the issues that is being faced is in doing a controlled trial for a specific site of infection, for example, pneumonia or skin, as they're traditionally done, one faces the issue that one could do a study which would demonstrate safety and effectiveness at that site of infection.

If one then wants to also get in the course of that study sufficient experience with a resistant organism, for example, MRSA or PRSP, it becomes very difficult, one, because of the epidemiology of some of these resistant organisms.

The other issue is an unknowable because, for example, even when studies are done in community acquired pneumonia, for example, in South Africa where there are very high rates of penicillin resistant Strep. pneumo., one finds in doing the studies that in the controlled trials you wind up with very low rates of pen. resistant Strep. pneumo. I can't explain that. I don't know why that is.

So that there is a problem in terms of for some of these agents being able to do controlled trials and get sufficient numbers of organisms to support effectiveness or for us to conclude that there is effectiveness.

Having said that, various proposals have been put on the table about how to develop that experience, and one of them is what was done in this development package, that is, to run a clinical trial specifically to capture those patients who have infections with resistant organisms.

In the context of a more traditional development program where you have large, adequate clinical trials that would support determining

effectiveness at a specific site of infection and then using that pathogen driven study to supplement that, now we understand, and this was some of the discussion that we have those meetings, there is an issue of how does one then appropriately pool that information or consider that information in making the determination that the overall development package demonstrates the effectiveness of the product for the site of infection and subsequently for the resistant organism.

What we've said is that in the course of those traditional studies, we would like to see a substantial amount of information of activity for the susceptible organism, for example, if it's pen. resistant Strep. pneumo. We would like to see in those studies a substantial amount of evidence for penicillin susceptible Strep. pneumo.

As Dr. Hafkin pointed out, there is the additional information both from in vitro studies and animal studies that suggest that the drug is as active against the resistant strains as it is against the resistant strains. Then one is left with a judgment about how much additional clinical information do you

need to draw the conclusion that it's effective for the treatment of those resistant organisms.

So that's sort of the broad brush strokes of where we are in trying to assess an overall clinical development package, and for these anti-infectives it's never just a single study or a single site of infection. We have multiple studies that look at the activity of the product at different sites of infections which may have a different spectrum of etiologic agents and may have different pharmacokinetic constraints in terms of getting the drug to that site of infection.

DR. O'FALLON: I wasn't arguing with the strategy. What I was saying was that it's difficult for me to use the data because the data from the enrichment study was not broken out according to the diseases that we were doing. They were lumped together, and the hospital based and the HAPs, the CAPs, the CAPs whether they were hospitalized or not, that's all jumped together. We don't have any way of knowing how it all goes.

You know, you're asking us to say that

those are all alike as far as the -- as far as this effectiveness is concerned for these specific bugs, and I guess we weren't as clear as we would have liked. When we, the FDA, did these analyses, we first took the view that, yes, we will look at the studies as they're designed, that is, a randomized controlled trial for a specific pathogen at different sites of infection and perform the analysis in that manner because that's the way the study was designed, understanding that eventually we would look at those subgroups of interest, that is, at the specific sites of infection, and try to make some assessment of the effectiveness for, for example, MRSA in the complicated skin structure infection.

And so that speaks to why the presentation was structured in the way it was, to look at the overall result to see if, in fact, understanding that each of these sites of infection may have a different prognosis or potential for outcome, but as a first cut, look at the overall result to see if the two agents are reasonably comparable, and then to look at the specific subgroups which were pre-specified, i.e.,

the site of infection at the time of entry into the study, to see if there's a consistency across those groups, that we can also attempt to estimate what the effectiveness was.

DR. O'FALLON: But the numbers are so small that I can't tell you whether they're consistent. I don't see that there's enough evidence there to help me. So that's my problem.

DR. MURPHY: I guess one of the issues here we're going to just lay out is that we have found not just with this company, not just with this drug that despite what we hear are significant numbers of resistant organisms out there, that if you expect to get a study in each one of these indications with enough resistant organisms, you're never going to reach that.

Fortunately, at this point in a way that's the bad news/good news at this point. And we are asking for you to then, as Gary said -- we know the numbers are small, and so we had the choice of either saying we are going to wait until we have enough in each category which we think would -- we're balancing

the risk of the time that will take to the time it would take to try to put pieces of information together.

And what you're telling us, you just still don't think the numbers are enough in the additional analysis, the enrichment pool.

DR. O'FALLON: I don't want to -- well, I don't feel like I'm an expert enough in this area to say that they are all alike, but you were just asking us one by one whether the efficacy is the same disease by disease.

And then we have 104 MRSAs in this class, and they're just thrown together and can't break them out.

Now, I'm going on the assumption that if you are asking for efficacy in five different diseases with the expectation that they could be different, then the effectiveness against the special bugs could be different in the different diseases, and I would say it would be very helpful for us to know what was the particular mix that we had in there, that is, how many HAPs were there, how many CAPs, how many SSIs.

CHAIRMAN RELLER: Dr. Murray.

DR. MURRAY: Yeah, and I just wanted to sort of muse philosophically for a moment. Again, part of this, I believe, is to establish whether a specific labeling can be added for a subgroup of a resistant type organism. We may not have any debate over whether the organism class or organism species -- whether the drug shows efficacy, but whether the efficacy is against a particular subclass of that organism.

And if one were content perhaps to label as Staph. aureus as opposed to the subgroup of methicillin resistant Staph. aureus, that the numbers would be fine for one and perhaps --

DR. O'FALLON: Nothing for another.

DR. MURRAY: Or that may not be the best example. So some of this has to do with how fine the subcategory needs to go, and I just wanted to go back to the VRE issue.

It is a tough one. As Dr. Leggett said, if we're not sure whether the 200 milligram dose is the placebo dose or if that's better than placebo, and

the trend is all in the right direction for the higher dose showing efficacy, and we would expect the 200 to have some efficacy, so I congratulate the company for having had the courage to do the study. They may have chosen a dose slightly too high at the 200 to be able to show a statistical difference. If they had chosen a lower dose, it might have been unethical because it might have been ineffective, but it's going to be tough to -- it's tough for me to know what to do with the results.

The trend is right, and is there any hope for larger numbers in the future or combining numbers and applying statistics, which hasn't been done yet? Can somebody address the concerns about losing the alpha?

As I recall, the second set of numbers hasn't been added in and analyzed statistically, and can we get any help? Are we going to get any?

CHAIRMAN RELLER: Dr. Wittes.

DR. WITTES: Well, I really think the first step is to make sure that the sequential ones are there in order. I don't imagine that that's going

to change things very much, but I think in the absence of knowing it, we've got to see that.

DR. MURRAY: Just for clarification for me now, can I ask? Now, this was a double blinded study. So both 200 and 600 -- I mean they were blinded and there was no placebo arm. So what is the ascertainment? I wasn't sure. I could understand in general why there might be a concern about ascertainment risk had there been a placebo arm perhaps, but in a double blind study are you still concerned about that?

DR. WITTES: Oh, absolutely, because I mean, I don't know the magnitude. I don't know whether we're talking about two patients or 20 patients. I just won't know.

But the concern is that you randomize, and what allows you to make the comparison is you're comparing like with like, and if you have one group that is the earlier randomized than the later, even if it's slight, or more importantly, I mean what I heard and I didn't even know this when I asked the question, but that it's the URIs that are -- the UTIs, sorry --

the UTIs that are the longer -- the ones that are in longer.

And if you look at the data, that's where the big difference is. Again, if you look at these very small numbers and you look at the lines, the line that has the biggest difference is that line.

Now, is it possible that the group in one of the arms -- that the group that is being plucked out of 54(a) and plucked into 54 is that different in some way because it took longer to cure them, because they were so much more complicated that the case report forms were harder to capture and so forth?

So it has nothing to do with the double blinding, and it has nothing to do with randomization. It has to do with essentially not following the randomization in a funny way, in an ascertainment way.

And then for 54, once more we don't know -- and again, I'm sure you have the numbers in there. It would be good to see them -- how many of the 54s are not yet analyzed because the data aren't in yet.

Once the data are all in, then it's easy. then we would know.

In terms of the alpha, I guess I'm less worried about that. Sorry about that.

DR. BRITTAIN: This is Erica Brittain.

There were, I think, 25 patients in 54 who were really 54(a) patients, but when I looked at them, put them into 54(a), it didn't really change the P value.

DR. WITTES: No, no, but that's right because there's something --

DR. BRITTAIN: Yeah. I just saw where they -- what their first dose day, June 20th, and when I threw those 25 back into 54(a), the result didn't really change

DR. WITTES: But we don't know who in 54 are in the future that we haven't seen, right?

DR. BRITTAIN: Definitely.

DR. WITTES: But you know, right?

(Laughter.)

CHAIRMAN RELLER: Dr. Hafkin, we'll wrap this tread up, and then Dr. Norden has another topic that he wants us to address.

Dr. Hafkin.

DR. HAFKIN: I can't explain some of the issue. The point I wanted to make was the point Dr. Britain made, which was we also got those additional 25 patients to put into our 54(a) analysis to answer that question, but let me go back even farther.

We're not, in a sense, happy either with the fact that we studied this disease for more than a year in more than 100 American referral centers, and this is what you've got. I mean this is an extraordinary -- this represents an extraordinary effort.

It is imperfect, but it is exciting to us because we believe that the drug works not only on the basis of these observations, which we think are very encouraging and certainly convincing to us, but also that it works for similar germs in the same sites.

So it's our feeling that this is not the only study that we're providing to you. We've shown you, we believe, that the drug is equivalent to really very good drugs for Staph. aureus and for Strep. pneumonia. We've bracketed, if you will, the sensitivity of organisms. The Staph. aureus germ is

much more resistant to the effect of antibiotics in a general sense than the Strep. pneumo., and the enterococcus is right in the middle.

So that on the basis of the laboratory studies we've done, on the basis of the clinical observations, we think we have a really good case to be made when that information is added to the information that comes. Although it's not perfect, it is the largest randomized blinded study of vancomycin resistant enterococcus done in the free world to date.

Maybe someone has got one that I don't know about, but it was an extraordinary effort by my team to put this data together.

Thank you.

CHAIRMAN RELLER: Dr. Norden.

DR. NORDEN: I just wanted to follow up on one other point that Dr. O'Fallon was making.

Dr. O'Fallon, it seems to me -- this is the point that Dr. O'Fallon was making -- it seems to me that we are given the information that you were asking about in terms of Study 31, for example. The MRSA, if I heard you correctly, we do under -- we do

know what diseases these patients had so that you can break them out separately.

What happens, of course, is the numbers just become smaller and smaller as you do it, but it's here. I mean, it's in Dr. Ross' analysis.

I'm sorry. It's page 34 of Dr. Ross' presentation.

DR. SOPER: Carl, correct me if I'm wrong, but that table is -- the data in that table is in addition -- the numbers are in addition to the Studies 55, 39(a), 33, 51 and 48(a). In other words, there's more patients added to that table than were studied in the comparative trials.

So when you go back and you actually find out how many patients were studied in a comparative community acquired pneumonia trial, there was one case of MRSA in the comparative community acquired pneumonia trial, five cases of PRSP, and the hospital acquired pneumonia, there's 22 cases of MRSA. So that might be able to make some decisions about that, but only two cases of PRSP.

In the uncomplicated skin and skin

structure infection, there's only one case of MRSA.

DR. NORDEN: You're absolutely right. No, I agree. I just was say that in the study, the enrichment study, if you will, if that's the phrase that's being used, that the data is here. I mean we have it, and I think the way the questions are phrased to us, I mean, the answer has to be, no, there aren't enough cases in community acquired pneumonia. No, there aren't enough cases, but if you pool them all together, which is one possible way to do it, the answer might be yes.

DR. SOPER: Actually as an adjunct to that, what you might want to do is add a sixth question, and that is that number five is infections due to vancomycin resistant enterococci. You might add number six, infections due to MRSA.

DR. MURRAY: Well, and then we get into the quibbles. If something were good for MRSA and hospital acquired pneumonia, would it not be okay for MRSA in community acquired pneumonia, but I think that gets into a final labeling.

We can answer certain questions. Are

there enough patients in a community acquired MRSA to say it's efficacious in that exact setting. The answer would be no, but that's different. To say that it would be approved or we would recommend it for nosocomial pneumonia due to MRSA and not community acquired pneumonia due to MRSA wouldn't be logical.

DR. CHIKAMI: May I clarify the intent of the questions? I think that we traditionally ask questions about each indication because, again, that's the way these drugs are developed. With the specific resistant organisms, PRSP, MRSA, we understand as you've all been discussing that we've had to rethink or relook at how, in fact, we can get that additional experience.

The intention of the questions was not to say within community acquired pneumonia did the sponsor collect sufficient evidence to support approval within that study. Our intention all along was to ask the committee to answer the first part of that question, okay, the general indication, and then looking at all of the information that's been presented by the sponsor by our analyses, which may

include in addition to that information collected within the specific indication driven studies, to help us try and make that judgment within this data set, within the overall development program, is there sufficient information to support effectiveness for the treatment of that resistant organism; sort of, again, speaking back to what I said at the outset of the morning.

These are difficult infections to study, and we need to be willing or I think we should be willing to look across all of the information to try and make a judgment. Again, understanding that there are issues related to pooling information, but I think given the situation where in some instances we have infections which are untreatable or may soon be untreatable, we need to think about, again, that risk-benefit ratio that we do as a regulatory agency in trying to certainly insure that drugs are effective for their intended use and they're safe for their intended use, but to also try and get potentially important products to the market as quickly as is prudently possible.

CHAIRMAN RELLER: Dr. O'Fallon and then Dr. Ross.

DR. O'FALLON: Okay. I wanted to point out that the numbers that you guys mentioned are the ones that I was working with, and what I'd like to point out, two little pieces of information that are causing me trouble.

In the second group, hospital acquired pneumonia and you look at that's the one that has the 22 with it, if you take a look at it, there the confidence interval is not -- there the efficacy is not there. The evidence is not good for that. So that's just one cautionary issue. They've been put together with the rest of the pneumonias.

And in the skin infections, the vast bulk of the ones in the VRE are -- the 66 -- are skin and structure infections, and half of -- now, there there's a slight preponderance of favor for the -- you know, when you batch them together, the complicated and the uncomplicated, there's a slight benefit to the new drug, but the problem here is that we don't know what the mixture of the complicated and the

uncomplicated is.

So those are some of the issues.

CHAIRMAN RELLER: Dr. Ross.

DR. ROSS: So in terms of one of the issues is of those patients who carry a label of pneumonia in Study 31, which of those are community acquired and which are hospital acquired, and I think that that's an important point because those are obviously two different entities.

And one point I would make is that the epidemiology of MRSA is such that that's much more likely to be a hospital acquired pathogen. I mean, obviously as we've learned over the last year or so, unfortunately that can be a cause of outbreaks of community acquired infection, but it's much more likely to be a hospital acquired pathogen.

DR. MURPHY: Judith or Dr. O'Fallon, would you go to the next page, to the MIT analysis on 48(a), where we've got the --

DR. O'FALLON: What page is that?

DR. MURPHY: It's page 18 of the FDA. And this is the MITT analysis. It's R-18 handout.

Just trying to get the issue of severity and MRSA. Does that help you any where we've got the ventilated assisted pneumonia, and then you've got those with MRSA and the MITT? Okay.

CHAIRMAN RELLER: Okay. One final question for Dr. Hafkin, just to make sure that we're clear on the numbers. Of the patients with pneumonia, mostly community acquired with Streptococcus pneumoniae, the 32 out of 169 patients had positive blood cultures. So this was a substantial number and somewhat better than what most people had observed.

In that group of 32 though, there was but one penicillin resistant pneumococcus; is that correct?

DR. HAFKIN: The only protocol that we have -- no, not additional. Those patients with resistant Strep. pneumo. bacteremia were found in the pediatric trial.

CHAIRMAN RELLER: So that from the adults, we have no data on bacteremic pneumococcal pneumonia with less than fully susceptible organisms to penicillin?

DR. HAFKIN: We had two with intermediate, yes. For all practical purposes, yes, yes.

CHAIRMAN RELLER: Right. I know there is not necessarily an answer, but I'd like to ask the question anyway, and that is do you have any explanation? Is it the distribution of where the studies are done?

Why is it so difficult when in many hospitals in the United States 20, 30, 40, 50, 60 in our place percent of strains of S. pneumoniae are less than fully susceptible to penicillin; of why one would have basically zero out of 32, but out of the others there were approximately 20 percent less than fully susceptible, ten percent at high level resistance, 15 percent intermediate?

So that of the same groups of patients, the ones who had an organism in their blood and the ones who had an isolate recoverable differences in how the MICs were distributed to penicillin, what's going on do you think?

DR. HAFKIN: Well, of course, I think about things like that. Why don't you have protocols

that provide patients with resistance? And I think it's unfortunately an artifact of the protocol process.

What happens is we strive so hard to have evaluable patients, and so we put so many barriers between the physicians, identifying patients with pneumonia and making sure that patient is likely to be evaluable. So we say, "Well, if the patient has been on therapy for less than three days and is not a failure, they don't fit. If they've had more than 12 hours or 24 hours of antibiotics, they don't fit."

So many of the patients, if you step back and you think about the epidemiology of multiply drug resistant organisms in general, they're patients with comorbidities who have had multiple courses of antibiotics, and in fact, they are probably empirically treated because they are sick. They're at risk for having terrible outcomes, and so they come to the doctor. They're already on the antibiotic. Whether they get better or not is another story.

If the physicians -- if we had a perfect system to capture the failures, then, indeed, we could

have trials. But the problem is, as you know how clinical trials are done in your institution, we have one or two investigators who have an interest, and it's just there are too many barriers to finding those patients that are highly likely to be evaluable and getting them into our protocol.

So I think it's a protocol process itself.

CHAIRMAN RELLER: There's another reason for asking the question. I think some have observed that patients who have unequivocally documented infection with Streptococcus pneumoniae tend to have more susceptible strains as opposed to patients who are colonized or who have respiratory isolates, that is, respiratory isolates versus isolates from the blood.

And it raises the question of the certainty with which one has the entity in hand, and some of these may be respiratory isolates in patients who unequivocally have pneumonia, but maybe not necessarily that that was the organism that was the etiology even though a pneumococcus was recovered, and that's another possible explanation.

One last comment, and from the committee we'll take additional ones, and then we need to get to the voting. Yes?

DR. ANDERSON: Your question was very interesting. So I appreciate a chance to answer it.

We, in fact, specifically tried to identify patients in Protocol 49 who had had the very experience that Dr. Hafkin pointed out as limiting, and the results were that five of 13, maybe it was 14 isolates, were nonsusceptible or resistant. So there you get your 35 to 40 percent.

Because we were looking for patients who had had previous experience, because we had patients that had refractory exposure to antibiotics, we found them, and that's the rate you'll find in the literature.

CHAIRMAN RELLER: Thank you.

Now, we have a strategic issue for the committee. We're actually a little bit ahead of schedule, but we also have pressing deadlines of airline flights so that we wouldn't have everybody with us at the end.

For the committee members, do we press ahead with the questions or do we take a very brief ten minute break and then press ahead with the questions? What's your wish?

All of those who wish to press on, raise their hand.

(Show of hands.)

CHAIRMAN RELLER: Those who would rather take a break?

Okay. Anyone who needs to take a break, do so quickly on the committee members, but come back before the voting.

We will now address the questions at hand. I will read the question, and then we will entertain any relevant discussion that any member of the committee wants to make, and then we'll take a vote, sequentially one by one.

Community acquired pneumonia. Do the data support the efficacy and safety of linezolid in the treatment of adult patients with community acquired pneumonia?

Any comments before voting on this?

Dr. Christie.

DR. CHRISTIE-SAMUELS: I may have misunderstood, but I have one little thing that I want to have cleared up. The thing is that if we approve this drug for adults, it will be used in children, too, and the pediatric data is not yet in.

I'm not sure if I heard earlier on that somebody said that the clinical course in pneumococcal pneumonia is similar to that in adults, and I wondered if maybe there's somebody on your team who could tell us, maybe Dr. Kaplan, if that is, indeed, true.

DR. KAPLAN: I'm Shelly Kaplan from Baylor College of Medicine in Houston. I'm a consultant for Pharmacia and Upjohn.

I would say that pneumococcal pneumonia in children, especially if it's bacteremic, is a very serious infection, and I would not expect the child to get better easily without antibiotics. I can tell you that in the pediatric pneumonia trial with linezolid that in the six children who had bacteremic pneumococcal pneumonia, including two children with empyema, that the agent looked very, very effective,

if that answers your question.

CHAIRMAN RELLER: Dr. Murray.

DR. MURRAY: If you look at the charts from I think the Mandell textbook, the mortality in bacteremic pneumococcal disease for those less than two, after that age it goes down and it goes back up again. I think the less than two is equal to about the over 65 or 70 in terms of mortality, whereas the older child and the younger adult are quite equivalent also.

DR. CHRISTIE-SAMUELS: That's what I thought.

CHAIRMAN RELLER: In considering all of these questions, before the voting I think that, you know, an important consideration in trying to give precise, specific recommendations to the agency on the sense of the committee on these issues, that for the resistant organisms there are a couple of ways to approach it, and considering the data both by indication, as well as the pooled information, that a recommendation for a recognition of safety and efficacy for susceptible strains doesn't necessarily

preclude the treatment of resistant strains, given that some of these organisms -- there aren't other in vitro susceptible strains at the outset.

So that there are lots of ways of being able to handle the questions, and I think it's important as we vote to take them one by one and our best judgment on the specific question asked, and at the conclusion if there be additional studies or things that the committee thinks would be very important in the continued development and deployment of this agent, since we're talking about it today, but it would apply to other things that we address in the future, is that we can make those recommendations as well, but we want to answer these questions as they are written.

The voting. We will start on the right-hand side for those who are voting, and I think from the outset we delineated who were voting members. In addition to the current members of the committee, Drs. Norden and Leggett will be voting this afternoon.

Dr. Soper.

DR. SOPER: Yes.

DR. CHESNEY: We are answering 1(a); is that correct?

CHAIRMAN RELLER: We are answering 1(a) and only 1(a).

DR. CHESNEY: Yes.

CHAIRMAN RELLER: Yes.

DR. NORDEN: Yes.

DR. DANNER: Yes.

DR. RODVOLD: Yes.

DR. CHRISTIE-SAMUELS: Yes.

DR. LOWY: Yes.

DR. MURRAY: Yes.

DR. O'FALLON: Yes.

CHAIRMAN RELLER: Section 1(b). Given that we unanimously believe that this agent has been shown to be effective and safe for the treatment of adults with community acquired pneumonia, do the data support the inclusion of a specific wording to the effect that there are sufficient data to support safety and efficacy in the treatment of methicillin resistant Staph. aureus as an etiology of community acquired pneumonia in adults?

And we'll take these individually. So we're talking now 1(b)(I).

Dr. Soper.

DR. SOPER: No.

DR. CHESNEY: No.

CHAIRMAN RELLER: No.

DR. NORDEN: Yes.

DR. DANNER: Yes.

DR. RODVOLD: Yes.

DR. CHRISTIE-SAMUELS: Yes, based on AGP data.

DR. LOWY: No.

DR. MURRAY: Yes, based on the aggregate data in other sites and in hospital acquired pneumonia.

DR. O'FALLON: No.

CHAIRMAN RELLER: We have a split decision of five-five.

(Laughter.)

CHAIRMAN RELLER: One (b)(2).

DR. SOPER: No.

DR. CHESNEY: No.

CHAIRMAN RELLER: No.

DR. NORDEN: Yes.

DR. DANNER: Yes.

DR. RODVOLD: Yes.

DR. CHRISTIE-SAMUELS: No.

DR. LOWY: No.

DR. MURRAY: No.

DR. O'FALLON: I vote no, but this one had more data than the other one did.

(Laughter.)

DR. MURRAY: But less data for resistant organisms.

CHAIRMAN RELLER: All right. Having completed that question, since the vote here is three yeses and seven noes, would anyone like to amplify for the agency, you know, post voting discussion? Because Dr. O'Fallon has pointed out that the numbers -- and I think it has to do with the inclusion of ancillary data from the specific pathogen studies that were incorporated into the decision.

Dr. Murray, comment?

DR. MURRAY: For the penicillin resistant

pneumococcus, I thought there was, despite the sponsor's efforts, just not enough cases overall of penicillin resistant disease, although biologically there is no earthly reason to think that a penicillin resistant pneumococcus is going to respond any different from a penicillin susceptible pneumococcus. We've had that discussion before with the floroquinalones.

So biologically I think there is no reason to expect a difference. However, we have had a -- we have, in essence, set a standard and asked for very rigorous data for that labeling and gotten it. My contrary vote on the methicillin resistant Staph. aureus relates to the what I viewed as efficacy and hospital acquired pneumonia with the organism and have even less reason then to think that the community acquired pneumonia with an MRSA would be any different.

CHAIRMAN RELLER: Dr. Chesney.

DR. CHESNEY: After lunch, Dr. Hafkin gave us numbers of 23 of 27 penicillin nonsusceptible pneumococci responded, which is a good number, but if

this is approved, then that's what people will use first, and I think those numbers are just too small, and that's why I voted against it, even if we take everything that's available.

CHAIRMAN RELLER: Dr. Norden.

DR. NORDEN: I voted yes because I think in the aggregate -- I'm not sure I know what the right number is, but I remember, and we talked about this at lunchtime, we did approve levoquin for PRSP, PRSP, yeah, something like that, and I don't think the numbers were much greater, and I have no reason to doubt that this data is good.

So it seems to me that I agree with Barbara. It should work, and therefore, I'm not clear why we would vote not to recommend it for pneumococcal pneumonia.

CHAIRMAN RELLER: Dr. Leggett.

DR. LEGGETT: I was not here for the levofloxiquin vote, but I can say that since it's now being used for everything, we are seeing a markedly increased rate of floroquinalone resistance, and the timing is pretty much the same.

CHAIRMAN RELLER: Dr. Rodvold, do you have any comment you want to make?

DR. RODVOLD: The other comment is that this question is a little bit different, I think, than in some of the levoquin discussions, that we're dealing with just the penicillin resistant pathogen, and we didn't get into so much of the bacteremia issue, which I think we dealt a little bit more with levoquin, and I think we got more information.

I think from a post marketing point, okay, or from what the agency maybe should require after whatever you approve is that it would be very helpful to have experience in CAP with bacteremia, with penicillin resistant isolates for everyone, particularly as they're going to proceed on to try to get a pediatric indication because I think that will be even more important up there.

So I voted yes a little bit just based off of a pathogen issue, but I'm not -- if you had said, "And bacteremic," you'd have changed my vote instantly back out to a no.

So I am staying only pathogen, without

going into -- going past the lung, so to speak, and I think it would be very helpful for everyone in multiple of these other indications that they seek those type of patients later on.

CHAIRMAN RELLER: Actually, Dr. Rodvold touched on one of my concerns, and in the discussion earlier, it was noted that many of these patients had multiple organisms isolated, and with all due -- I mean, doing clinical research is an exceedingly difficult task, and getting a precise etiology is also tough, and it's getting tougher, given the microbiological support that is available to some investigators, you know, at the front lines.

But I, frankly, am a bit concerned about Staphylococcus aureus, be it methicillin resistant or susceptible. I think the numbers of patients with pneumonia who have the organism isolated versus the number who have pneumonia caused by the organism may be considerably different, especially in hospital acquired pneumonia.

We need to move on to question number two.

Two (a), do the data support the efficacy

and safety of linezolid in the treatment of adult patients with hospital acquired pneumonia?

Dr. Sober.

DR. SOPER: Yes.

DR. CHESNEY: Yes.

CHAIRMAN RELLER: Yes.

DR. NORDEN: Yes.

DR. DANNER: Yes.

DR. RODVOLD: Yes.

DR. CHRISTIE-SAMUELS: Yes.

DR. LOWY: Yes.

DR. MURRAY: Yes.

DR. O'FALLON: No, and the reason I'm saying that is because the confidence intervals on this are getting down into the dangerous area. That's why I'm saying no.

CHAIRMAN RELLER: Thank you, Dr. O'Fallon.

I think we have nine-one supporting safety and efficacy for HAP.

Two (b), are there sufficient data to support the claim for efficacy with hospital acquired pneumonia owning specifically to MRSA?

Dr. Sober?

DR. SOPER: Yes.

DR. CHESNEY: Yes.

CHAIRMAN RELLER: Yes.

DR. NORDEN: Yes.

DR. DANNER: Yes.

DR. RODVOLD: Yes.

DR. CHRISTIE-SAMUELS: Yes.

DR. LOWY: Yes.

DR. MURRAY: Yes.

DR. O'FALLON: Mixed message. I'll go with yes.

(Laughter.)

CHAIRMAN RELLER: Two (b)(2), penicillin resistant Streptococcus pneumoniae.

Soper?

DR. SOPER: No.

DR. CHESNEY: No.

CHAIRMAN RELLER: No.

DR. NORDEN: Yes.

DR. DANNER: Yes.

DR. RODVOLD: No.

DR. CHRISTIE-SAMUELS: No.

DR. LOWY: No.

DR. MURRAY: No.

DR. O'FALLON: No.

CHAIRMAN RELLER: Eight to two not thinking that that supports that specific claim.

Dr. Chikami, do you want to make a comment?

DR. CHIKAMI: I guess as you discuss this issue also with the community acquired pneumonia, if the committee had any other comments or reasons for their, in particular, for their no votes, with additional information. For example, Dr. Rodvold suggested, for example, more experience in patients with bacteremia. Is that sort of a similar concern in this case?

CHAIRMAN RELLER: I think I could probably speak for the committee. I mean, the reality is that we have 32 patients who unequivocally have pneumonia caused by Streptococcus pneumoniae, and most of them are as appropriate in the community. We know that people can acquire pneumococcal pneumonia in the

hospital. It can be transmitted in the hospital, but the numbers are simply not there with resistant strains.

I don't think anyone has concerns that a linezolid susceptible organism would respond appropriately to treatment, but that's a different issue from having the data in hand for a specific indication for that organism. It doesn't in any way preclude using it for strains that are less than fully susceptible to any other antimicrobial if they're susceptible in that institution to linezolid.

Question three, uncomplicated skin and skin structure infections. Are the data there to support safety and efficacy of linezolid for this indication in adults?

Dr. Soper.

DR. SOPER: Yes.

DR. CHESNEY: Yes.

CHAIRMAN RELLER: Yes.

DR. NORDEN: Yes.

DR. DANNER: Yes.

DR. RODVOLD: Yes.

DR. CHRISTIE-SAMUELS: Yes.

DR. LOWY: Yes.

DR. MURPHY: Yes.

DR. O'FALLON: Yes.

CHAIRMAN RELLER: Are the data there to support a specific subsidiary recommendation for skin and skin structure infections with methicillin resistant Staph. aureus?

DR. SOPER: No.

DR. CHESNEY: No.

CHAIRMAN RELLER: No.

DR. NORDEN: No.

DR. DANNER: Yes.

DR. RODVOLD: No.

DR. CHRISTIE-SAMUELS: No.

DR. LOWY: No.

DR. MURRAY: Yes.

DR. O'FALLON: No.

CHAIRMAN RELLER: Eight to two thinking that there are not sufficient data at present.

Question 4(a) -- comments, sure.

DR. MURRAY: My commentary on the positive

side is based on the overall gestalt and with the other supporting data across pathogen site. If it's going to work in community in nosocomial pneumonia, I think that with supporting data it will work in complicated skin and soft tissue infections.

So I let the across the site organism drive me even with the small numbers for this particular site pathogen.

DR. SOPER: And what I suggest that we do to try to remedy this at the end of the day is add question number six about MRSA.

DR. RODVOLD: I brought up a point earlier and the company answered it, is that in the uncomplicated trial, they actually used 400 milligram dosages. So if you are going to give an MRSA indication, they themselves said that 600 was what they felt comfortable with. So to me if you do come around to an indication, I think you've got to deal with a dosage recommendation here.

And your MICs had a tendency and a means and some of the global data raised a little bit. So I think you may have a labeling dosage issue as well

to sort out or it needs to be at least discussed.

DR. CHIKAMI: May I ask other members of the committee if, in fact, that was an issue that they took into consideration?

Because, as Dr. Rodvold pointed out, if -- that can certainly be handled in labeling, given the fact that the preponderance of the evidence for -- excuse me -- preponderance for data for MRSA comes from Study 31, which a 600 milligram BID dose was used, so, in fact, that, in fact, could be linked to that particular -- treatment of that particular organism in any of the skin indications.

So I just sort of wanted to get the committee's read on that.

CHAIRMAN RELLER: Comments for Dr. Chikami?

DR. NORDEN: Yeah, I agree with Dr. Rodvold on that.

CHAIRMAN RELLER: It influenced my consideration that, you know if there is any singling out of this organism, that it would be important to have the higher dose until we had sufficient data that

the other dose was comparable effective for this particular pathogen.

The other concern that I had was you're exactly right that most of the data that would support this, since there was only one patient with MRSA in the uncomplicated category from the trials is the supplemental data was important and useful, but I'm not absolutely clear.

We saw the depiction of the categories of those patients. Many of them were surgical wound infections, and what role, removing the sutures, draining the stitch abscess, all of those things had, and admittedly those patients were very sick, but I got the sense that they were very sick not necessarily because of the Staphylococcal infection, but because they were very sick patients who had a staphylococcal infection. So I think it's -- you know, I'm not exactly sure of the comparability, not that it isn't important information, but that it's to me a bit different from an enrollment specifically for a skin and skin structure infection.

DR. LOWY: And that was the major reason

for my no, because I'm not sure that the complicated skin and cell tissue people were really that complicated. It sounds like you could just open up the wound, and you didn't really need antibiotics, and we are then going to launch this into diabetic feet, osteo that's not recognized, a whole can of worms that has not even been studied, and the MICs are near the floor level, which is with a bacteriostatic drug makes me very worried.

CHAIRMAN RELLER: Dr. Chesney.

DR. CHESNEY: I just wanted to endorse Dr. Soper's comment that we vote -- make number six be basically study number 30 -- 31.

CHAIRMAN RELLER: We'll get there after five.

Dr. Soreth.

DR. SORETH: Two comments. With regard to complicated skin and skin structure infections with some notation as to how many patients require surgical adjunctive intervention at baseline, that's actually part of the division's guidance document for the definition of complicated skin and skin structure

infections.

So we ask that sponsors study patients in complicated skin and skin structure infections for whom it is assumed and shown that a certain proportion of them require surgical intervention. That's what helps us to deduce that those patients are, indeed, complicated in addition to having co-morbid conditions, perhaps immunodeficiency, and so forth.

A second comment unrelated to that, but related to this proposed sixth question has to do with the way the division grants indications, and this application is no different in that respect. We typically grant indications for a site specific infection, pneumonia or hospital acquired pneumonia, interabdominal infections, urinary tract, and so forth.

VRE represents an exception,a nd I think to date the only exception. We have not granted a methicillin resistant staph. infection indication at all body sites. The sponsor has not requested it, and in developing and co-developing this program of drug development, we thought that the approach of having

this catch-all Protocol 31 that would develop and enrich four methicillin resistant staph. infections would then, in fact, support, give numbers to the site specific indications, knowing from hard experience for however many reasons there are that we don't get large numbers of such resistant organisms within that site specific indication.

So that's why we have not drafted that sixth question, because we don't grant the indication that way.

CHAIRMAN RELLER: I understand.

Question 4(a), do the data support efficacy and safety of linezolid in the treatment of adult patients with complicated skin and skin structure infections?

DR. SOPER: Yes.

DR. CHESNEY: No.

CHAIRMAN RELLER: Yes.

DR. NORDEN: Yes.

DR. DANNER: Yes.

DR. RODVOLD: Yes.

DR. CHRISTIE-SAMUELS: Yes.

DR. LOWY: Yes.

DR. MURRAY: Yes.

DR. O'FALLON: Yes.

CHAIRMAN RELLER: Are there sufficient data to support efficacy and safety of linezolid for the treatment of complicated SSSI caused by methicillin resistant Staph. aureus?

DR. SOPER: No.

DR. CHESNEY: No.

CHAIRMAN RELLER: No.

DR. NORDEN: Yes.

DR. DANNER: Yes.

DR. RODVOLD: Yes.

DR. CHRISTIE-SAMUELS: No.

DR. LOWY: No.

DR. MURRAY: Yes.

DR. O'FALLON: This is crazy. You have in this -- in this study there are 66 in this area that have, you know, information on this, and it's a 70 -- what is it nine versus 73 percent in favor? So there's more evidence here, but I don't know whether it's complicated or uncomplicated. It's just the skin

structures are just stuck together. So I would say there's evidence of some efficacy. Yes.

(Laughter.)

CHAIRMAN RELLER: Yes.

DR. STEVENS: Dr. Reller, it seems like there's some confusion about what a complicated soft tissue infection is.

My name is Dennis Stevens. I have had a major interest in soft tissue infections for a number of years. I participated in a number of the linezolid clinical trials, including the complicated and uncomplicated soft tissue infections.

These patients were very sick patients. They were not folks that just had a simple surgical wound infection that may be manipulating the wound a little bit out, taking a suture out, would go away.

I could give you an example of the type of patient that we admitted into the complicated skin infection. A 65 year old diabetic patient with a huge staph. and Group A strep. abscess on his back that had bacteremia, had a huge debridement, area about this big, and had a necrotizing superficial infection, the

skin and the fat, but not the fascia because that was an exclusion criteria.

I think these were very ill patients. They weren't minor at all, and I think that's kind of been a misconception around the room.

CHAIRMAN RELLER: Thank you, Dr. Stevens.

Any other post vote commentary on question four?

Question number five, do the data support the efficacy and safety of linezolid in the treatment of adult patients with infections caused by vancomycin resistant enterococci?

DR. SOPER: Yes.

DR. CHESNEY: Yes.

CHAIRMAN RELLER: Yes.

DR. NORDEN: Yes.

DR. DANNER: Yes.

DR. RODVOLD: Yes.

DR. CHRISTIE-SAMUELS: Yes.

DR. LOWY: Yes, with a caveat that we continue to look for data to firm up whether it really works.

DR. MURRAY: I ditto those comments exactly. Yes.

DR. O'FALLON: I'm just going to reinforce Dr. Wittes' concern. These data could be biased, and we don't have any way of knowing, and so the results we have look like it's effective, but we aren't sure what kind of data we have here.

CHAIRMAN RELLER: Is that a no, Dr. O'Fallon?

DR. O'FALLON: Make it a no.

(Laughter.)

CHAIRMAN RELLER: For the record.

Now, 5(b) is a very important question because it gives us the opportunity to tell the agency what we would ideally like to see in this whole arena of treating these emerging, increasing infections, but that take place in patients who are so critically ill that sorting out efficacy becomes exceedingly difficult.

Recommended additional studies? Dr. Soper, Dr. Chesney?

We're contemplating.

Dr. Norden.

DR. NORDEN: No, I don't have anything to add.

DR. DANNER: I'm not sure this is exactly part of five, but I would like to see more information on the metabolism of this drug. The fact that it's broken down by oxidants yet to be elucidated, I'm not sure I know what that means, and it makes me concerned that there might be interactions we don't know about with drugs that have oxidant or anti-oxidant activity, and whether there might be interactions with things like inhaled nitric oxide; that, you know, can things like that potentially attack these rings and break down the drug so that if you have somebody in the ICU on inhaled nitric oxide and this drug, they're essentially not really getting the drug.

I don't know if you know the answer to that, but I think it's knowing more about how it's metabolized and potentially interacts with things that affect oxidant pathways, might help us, you know, know how to use the drug in those unusual settings.

DR. RODVOLD: Well, the other things that

you're asking about, one of those things Dr. Murray brought up before about absorption in the ICU. I mean, VRE people are going to be -- a lot of them are going to be in the intensive care unit, and it would be good to know whether or not you can dump this down an NG tube, you know, enteral feedings, et cetera, et cetera, all these other issues about viability and sorting out are these the patients with the low concentrations on the end or not.

And so there's almost a little bit of need of more population pharmacokinetics and/or some interaction studies, and I was a little surprised there was no drug interaction study that's ever been done with antacids, either out-patient or in-patient. At least that's the impression I got. So I mean, that's in all these indications.

The other issue though is that this is VRE, and it doesn't split out whether or not this is faecalis versus faecium, and they had to really grasp the faecalis data and pull it out as we asked for that, and it makes me a little bit -- you know, the numbers are pretty low on the faecalis side here.

And so I think at minimum you need some more post marketing faecalis data in this, and secondly, it would be helpful for the prescriber to have some of that put in the labeling either in the back of the studies or something so that they actually know how many isolates of faecalis have been treating and what the comfortability factor is on that because otherwise you're blanketing this across VRE.

CHAIRMAN RELLER: Dr. Chesney.

DR. CHESNEY: I think maybe it would be helpful to break out the bacteremia data because we kind of had to find it and it was in 31 where we found the staph. bacteremia data, and I think that's always the most convincing for something new.

So I think somehow to present that up front or make that as a separate entity.

CHAIRMAN RELLER: Other recommendations from the committee members? Dr. Murray?

Oh, one is not compelled to have recommendations, but there be any, we want to hear them. Dr. Christie.

DR. CHRISTIE-SAMUELS: Thank you.

I just felt we should collect as much data as possible using compassionate use protocols, gathering data through historical controls, although this is very difficult.

In the pediatric population, I think in newborns we can collect a lot of information, and in the transplant population and in those who are bacteremic.

And I don't know if it's possible to look at a comparator trials with synercid and other agents as they become available.

CHAIRMAN RELLER: Dr. Lowy?

DR. LOWY: I guess I still worry about the hospital acquired pneumonias and the MRSAs and whether there was a way of getting cleaner data on MRSA pneumonias.

DR. LEGGETT: I guess back to the point I made earlier in the day. This is a drug that is going to be used in the hospitals for nosocomial infections, and yet I am not sure I was convinced about the severity of the cases that were presented dealing with a static drug when we may be dealing with line

infections and endocarditis that is not recognized, and I would like to see more data and more serious patients, discitis (phonetic), osteomyelitis, that kind of stuff.

DR. MURRAY: Just to point out that our question asked for VR enterococci, whereas on page 6 in the sponsor's document they were separated out E. faecalis, E. faecium, and I don't think in my opinion that the data were sufficient for VRE faecalis. So I don't know if you wanted any comment on whether we would split them out or not.

And the other thing I would encourage the sponsor to do again relates to the wide diversity of levels that can be obtained because there may be some patients out there whereas in a population they're responding, but as an individual might fail because they are one of those that ends up with a lower blood level. So I would encourage some sort of follow-up study on that because it may benefit that one patient out of -- I don't know -- 20 or 50 that would perhaps benefit from a higher drug level.

And then to go back to points we made

about earlier about metabolism, I assume there will be follow-up studies on, again, looking more at patients who are building up metabolites for their potential clinical adverse events.

CHAIRMAN RELLER: Dr. O'Fallon, any comments?

DR. O'FALLON: I do like the idea of having the so-called enrichment studies. I think that's a very good idea. I just think that for any future studies it would be helpful to break out that data by the indications that we're being asked to evaluate. That would have saved a lot of problems on my part anyway.

In terms of did anyone ever look at the efficacy related to -- are they looking at -- I was interested in the fact that some of them were spiked and some of them were the long, sloping curve, area under the curve. Has anyone looked at the efficacy, you know, by max. level as versus the area under the curve?

That was just thrown out there, but I wondered if it made a difference.

CHAIRMAN RELLER: When the clinical studies were initiated for linezolid, there was not a comparator available, and hence the clinical trial with 200 versus 600 milligrams to show a difference.

I would very much like to see as part of the plans for this compound in what the agency does in its final assessment is to see future data with comparative trials with the options that are now available.

The numbers of patients with vancomycin resistant enterococci, albeit predominantly but not exclusively faecium, are increasing, and they're substantial, and it looks like even with the trials that were done, the numbers are almost as many as with less than fully susceptible pneumococci.

So this is, I think, an important issue to really get comparative clinical trials prospectively, you know, underway so that down the line we'll know.

And given the difference that looked like it was there with 600 versus 200, even the possibility of having a comparator and 200 and 600 to show that 200 might be like the comparator, but the 600 is

better than either or them if the numbers were larger, that's a study that I'd very much like to see.

The difficulty with a straight comparison of this agent versus another is always the nagging suspicion that what would it be if you didn't do anything, but if you can demonstrate 600 versus 200 and the 200 looks more like a comparator, that would be very telling information for the future, I think, especially with patients with positive blood cultures, and with the caveats that Dr. Leggett pointed out.

Now, we probably have a little more discussion that people would like to have. Whether it's in the form of a specific question or simply the kinds of additional information or studies that the committee members would like to see if there were for this or any other agent to have specific indications for methicillin resistant staphylococci.

Dr. Soper? Chesney?

I'd like to see some additional clinical trials. I mean I think everybody on this committee, all the clinicians on the committee have a sense that vancomycin is a tolerable drug for methicillin

staphylococci because we heretofore didn't have anything else really to use, but that it's not necessarily a very good drug for methicillin resistant or staphylococci, period, if you have another alternative and would prefer, as many have pointed out, to use, for example, naphcillin for susceptible strain.

So that comparative clinical trials with the options for serious Staphylococcal infections, both staph. susceptible and the increasing proportion that's more than 50 percent in many hospitals, to really put this and other agents to the test prospectively, all at the same time in randomized trial, for example, three currently available agents and do a blinded prospective trial would be exceedingly good to know.

Dr. Norden.

DR. NORDEN: Yeah, I would like to see this drug tested in osteomyelitis. I think it's in many ways an interesting agent. It's been given for 28 days already, and with the only caveat being the platelet count, which you'd have to watch, but it's

available orally.

For MRSA vancomycin is not a great drug osteomyelitis at all. We don't know anything about synercid for osteomyelitis. So I think this would be an inappropriate indication for the company to consider trials in.

CHAIRMAN RELLER: Any other comments? Dr. O'Fallon.

DR. O'FALLON: In looking at this data, we don't know exactly. Have you ever considered measuring the time to failure, say, of these drugs as opposed to just -- what would you call it? -- cure, yes/no?

Well, that's fine, but have they ever looked at time to cure or time to failure in these as a measurement of the efficacy of these drugs comparing drugs?

DR. CHIKAMI: In the usual studies that we see, that we have reviewed for drug approval, we've not seen those sorts of design, but I think you raise a good point, particularly for and speaking generally for those infections in which the real impact of

antimicrobial therapy is to shorten the course of disease.

Then, in fact, a relevant measure may be time to resolution or cure. Now, of course, that adds a technical complexity to the trials. One needs to then define appropriately what that event is, what cure is, and then design the trial so that you capture the information in a relevant way so that, in fact, you can make reasonable comparisons in regard to the time to event sort of analyses.

But, I mean, I think it's a reasonable suggestion.

I think in those diseases where there's a substantial mortality, for example, one could still make those measurements, but I think ultimately the relevant impact we want to have on those sorts of diseases is the overall impact on mortality, for example, in sepsis trials where the primary thing we're looking at there is the 28 day, all cause mortality.

Well, for example, serious and life threatening infections, such as meningitis, where we

not only look at survival and resolution of the infection, but also the incidence of serious neurologic sequelae at six months, for example.

CHAIRMAN RELLER: Dr. Drusano.

DR. DRUSANO: Just as a commentary to Dr. O'Fallon, I'm currently involved in advising a particular sponsor looking at bacteremia, getting blood cultures every day and looking at the time to clearance of the blood culture and then looking at covariates like measure of drug exposure relative to the MIC, AUC-MIC, peak to MIC, time above MIC as covariates in a Cox proportional hazards analysis.

We've also done this and published this in the journal AIDS. There was an analysis that was requested by the FDA for the time to progression of CMV retinitis with the drug phoscarnate.

So this is a very powerful way of being able to get more information about how well a drug actually does its job, and it's much more sensitive than using Lodgets (phonetic) or just any other kind of yes/no kind of analysis.

CHAIRMAN RELLER: We've just heard from

Dr. George Drusano who's a professor of pharmacology and infectious disease clinician in Albany Medical College.

Are there other comments or questions?

Dr. Chikami, have we done our job and is there any other thing that you want to ask of us?

DR. CHIKAMI: No.

(Laughter.)

DR. MURPHY: Barth, but we do want to say thank you.

(Laughter.)

DR. MURPHY: And that we do think we are moving this field forward as we develop these products. It has been a very difficult row to hoe here with not having standards as comparators and having to do standards of cares, dose response type of studies, and we think that we are continuing to move.

Some of the suggestions were very helpful, and we do thank you for your input.

CHAIRMAN RELLER: In closing, I'd like to thank all of the presenters, especially Pharmacia/Upjohn for their collegial addressing all of

the questions posed and then some into those from the FDA in their presentations to try to do justice to the importance of the topic at hand.

Thank you and have a safe journey home.

(Whereupon, at 4:01 p.m., the meeting was concluded.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE 68TH MEETING

Before: FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: MARCH 24, 2000

Place: GAITHERSBURG, MARYLAND

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.

Rebecca Davis