We talked about it more, and we finally decided that the study had been ongoing for long enough. We needed to know and fully understand the nuances of the study and its performance.

So we closed the study, and we felt at that time, well, that's it. We've closed it. We're going to look at it.

Then we got encouraging words from some investigators that they were really wanting to continue the study, the same general design. The protocol was modified somewhat, but it was continued in many of the same sites, but we consider the, if you will, this 54 study to be a separate protocol.

The protocol modifications included some improvements that our investigators felt might suddenly improve their ability to recruit patients, but we see them as separate protocols.

DR. WITTES: So what's the interim analysis in 54?

DR. OLIPHANT: Dr. Wittes, the results you've seen presented for Study 54, the 82 patients out of the 186, those results were presented at the

request of the agency to see results that we had available at the time.

We presented those results, but did not do any statistical testing or any calculation of confidence intervals or anything of that nature. So you did not see any of those results in our presentation of results for those 82 patients.

CHAIRMAN RELLER: Yes, Dr. Chesney.

DR. CHESNEY: Just two points of clarification. The 12 patients that had the resistant pneumococci, I probably misheard. Those don't include the five children who had resistant pneumococci. They do?

DR. TARPLEY: They do.

DR. CHESNEY: And the children had what infection? They had the community acquired pneumonia also?

DR. TARPLEY: Dr. Anderson can respond best to that question

DR. ANDERSON: Right. Those included the studies reported in Protocol 45 and 49. There were three bacteremic Strep. pneumoniae isolate from

Protocol 45, all these from cures. There were five overall Strep. pneumonia microbiologically evaluable in Protocol 45. They were all cures, but these were always based on blood culture because there is no other way we can get microbiologic evaluability.

Two cures came from Protocol 49. That included two PRSP.

There were other isolates that were intermediately susceptible, but in fact, those that I've indicated as PRSP were clearly resistant.

DR. CHESNEY: Just one more clarification. All of the complicated skin and soft tissue infections in which methicillin resistant Staph. were a problem are in our handbooks, which is, I think, two, three, two successes; is that correct, on page 60?

DR. TARPLEY: Could you repeat the page, please?

DR. CHESNEY: Page 60, the top of page --

DR. TARPLEY: Six, zero?

DR. CHESNEY: Six, zero, yeah, of what we got before.

DR. TARPLEY: Thank you.

DR. CHESNEY: Right. I think it's three patients with methicillin resistant strains. Two were successful.

DR. HAFKIN: Indeed, that is the results of our Protocol 55, which is the straightforward, traditional, complicated skin and soft tissue trial. The reason we performed Protocol 31, the MRSA trial, was just so we could augment that number.

Speaking to MRSA, we had 15 patients with bacteremia due to MRSA, and we had four recurrent MRSA bacteremias. Each one of those recurrent MRSA bacteremias were associated with short term therapy, except for one patient that had osteomyelitis and received 20 days of therapy. Diagnosis of osteomyelitis was made, and they had recurrent Staphylococcal infection.

So we have substantial experience with MRSA because of this additional clinical study.

CHAIRMAN RELLER: Dr. Leggett.

DR. LEGGETT: On the Slide 53, you showed in Protocol 31 that most of your MRSAs had skin and soft tissue infections, which seems rather less

challenging than the 50 cases of bacteremia.

Could you describe the causes of those 50 cases of bacteremia due to MRSA and specifically how many cases of right side endocarditis, which I believe you mentioned in several different cases.

DR. HAFKIN: Yes, there was only one patient with right side endocarditis recruited, Protocol 31, that they were recruited to vancomycin. Indeed, they failed.

DR. LEGGETT: Do you recall bacteremia? You list it?

DR. HAFKIN: I already shared with you the 15 cases of microbiological evaluable MRSA infection with bacteremia. The others that had bacteremia may have had bacteremia, but they were not evaluable because they didn't take medicine or they were randomized to vancomycin.

CHAIRMAN RELLER: We are a little over the time for our break. We'll have ample time to come back to these questions.

Before breaking, however, for the benefit of the sponsor, some of the things that I think we

will be wanting to address subsequently, to give you time to pull together either out of a composite of what's there or if it's already packaged are some of the following.

The questions will include for adult indications, but yet we've heard that some of the data presented on resistant organisms include pediatric data. So I think we need to see what information we have on those organisms from adults alone. The pediatric data are supportive and interesting, but we have to deal with what we have today.

So specifically, we know that there's a high concordance of macrolide resistance and penicillin resistance among Strep. pneumoniae, despite totally different mechanisms of resistance. It would be of interest if you have those data available what the profile on the resistant organisms included in your patients were for macrolides, as well as penicillin, and what the response rates were.

What proportion of patients with pneumonia owning to Streptococcus pneumoniae, ideally by category of resistance, in fact, did have positive

blood cultures?

And do we have any resistant organisms with bacteremia that responded to the compound?

And I think the same issues apply for infections with methicillin resistant Staphylococci, and ideally showing, including those with bacteremia, those with bacteremia with methicillin susceptible and resistance, and if there are any response differences, to see what those numbers end up being.

So it's delving into more specific detail having to do with the critical issues of resistant organisms, confirmed with positive blood cultures and without positive blood cultures in adults, and then what supplemental information there may be from pediatrics, but so that we see what there is currently with the adult indications.

At this time we'll take a 15 minute break and begin promptly at five minutes of 11 to hear the FDA's presentation.

(Whereupon, the foregoing matter went off the record at 10:40 a.m. and went back on the record at 10:58 a.m.)

CHAIRMAN RELLER: We'd like to begin the session this morning, complete the session this morning.

For those who are recording this session, if any of the questions are not clear or the mechanics of things are not working, if you would raise your hand, I'll take a special effort to get the question or answer both repeated to capture the proceedings.

We now have Dr. David Ross, who will step to the podium and present the FDA's considerations on linezolid.

David.

DR. ROSS: Thank you, Dr. Reller.

I'm going to ask the obligatory first question, which is: can everybody hear me? And I guess the microphone is on. So the answer is yes.

I'm a medical reviewer in the Division of Anti-infective Drug Products, and I'll be presenting the agency's analysis of a new drug application for linezolid.

Could I have the next slide, please?

What I'm going to do is briefly review

some issues related to the clinical pharmacology of linezolid, discuss the agency's clinical and statistical analyses of efficacy data in this NDA, our analyses of safety data in this NDA, and then discuss development of resistance to linezolid.

Could I have the next slide, please?

Just to review, after IV administration of linezolid, peak plasma concentrations are reached in about half an hour, in about an hour after oral administration. Maximum concentration after IV administration is 15 micrograms per mL, 21 after oral administration, and these refer to 600 milligram doses given BID.

Trough concentrations are 3.7 micrograms per mL for IV dosing, 6.2 for oral, and the half-life is about five hours for both IV and PO.

I'd just like to remind you that the key pharmacodynamic parameter for linezolid is time above MIC in that as you've heard in the mouse thigh model, the time above MIC is the most important parameter with concentrations needing to be above the MIC for about 40 percent of dosing interval for efficacy

against Streptococcus pneumoniae.

Okay. The next slide.

With 600 milligram oral BID dosing, there's considerable variation in the exposure to linezolid with AUCs ranging from 68 to 209. This variability remains after you normalize for body weight, with the exposure after normalization ranging from 11.2 to about 24.

Next slide.

As you've heard, linezolid has two major metabolites. The toxicity of these metabolites has not been studied separately from the parent compound in animal or human studies. The drug is excreted in urine and feces. About 35 percent in the urine is parent drug; 50 percent in urine is metabolites; and ten percent in the feces is metabolites.

And, again, as you've heard and seen in the briefing package, these metabolites accumulate in patients with renal impairment with the degree of accumulation increasing with patients with more severe renal impairment.

Next slide.

Let me move on to analyses of efficacy data by the agency.

Next slide.

The clinical studies that I'm going to discuss are those for community acquired pneumonia. One study of community acquired pneumonia in in-patients, one in out-patients. Hospital acquired pneumonia for which a single study was submitted in the NDA. Skin and skin structure infections, and here there were two studies for uncomplicated skin and skin structure and one for complicated skin and skin structure.

A supporting study of methicillin resistant Staphylococcal species infections, and a study of VRE infection, and these are Studies 54(a) and supportive data from Study 54.

Next slide.

What I'd like to do before discussing the individual studies is highlight some differences in the FDA's method for assessing outcomes versus the sponsor's.

For patients who did not have a post

baseline efficacy assessment, the sponsor considered such patients to be failures, whereas the FDA considered such patients to be missing unless they met certain prespecified conditions for failure, such as receiving another antibiotic for lack of efficacy.

Deaths were considered by the FDA to represent failure regardless of the cause in the ITT analysis. The sponsor did not directly consider death in assessing outcome. Such patients were generally considered missing, again, unless they met certain prespecified criteria for being considered failures.

Finally, with respect to patients who were discontinued from study for lack of efficacy, these patients were generally, although not invariably, considered to be failures in the sponsor's analysis. Such patients were considered by definition failures in the FDA's analysis.

Next slide.

With respect to the analytic populations studied in the FDA analysis, the all randomized patient population was used to define the ITT all treated patient population. A modified intent to

treat population was identified, which consisted of all ITT patients who had a pathogen isolated.

The ITT patient population was also used to define valuable protocol populations. These included clinically evaluable patients who met baseline and post baseline criteria.

A microbiologically evaluable patient population was also defined as those clinically evaluable patients who had a susceptible pathogen isolated within the baseline visit window. Usually this represented 48 hours within -- patients who had pathogen isolated within 48 hours of study entry.

For specific studies that I will discuss later, particularly complicated skin and skin structure and VRE, the FDA analysis included examination of specific ITT patient populations that were predicated on important baseline characteristics.

Next slide.

Let me move to a discussion of specific studies. For community acquired pneumonia, as I've said, the sponsor conducted two studies.

Next slide.

The first one that I'm going to discuss is Study 33. This study enrolled and treated 747 in-patients with community acquired pneumonia. This was a multi-center, multi-national, randomized, open label trial. The trial was initiated as an evaluated blind study, and then was changed to open label during the course of the study.

Patients were randomized to linezolid or to ceftriaxone given for seven to 14 days. At the discretion of the investigator could be switched to oral therapy, oral linezolid in the case of the linezolid arm, cephpodoxime in the case of the ceftriaxone arm.

Concomitant as aztreonam was allowed for Gram negative infections.

The primary endpoint in this study was microbiologic outcome.

Next slide.

This slide shows a summary of the demographics for patients enrolled in the study. As you can see, the arms were balanced with respect to age, gender, and race.

Next slide, please.

Seven hundred and forty-seven patients were enrolled and treated. Of these, 254 had a pathogen isolated. There were 559 clinically evaluable patients. One hundred and ninety-one of these had a susceptible pathogen isolated at baseline.

Next slide.

Response rates in the FDA analysis are shown here for the various populations: ITT, MITT, clinically evaluable, and microbiologically evaluable.

Sizes of the populations are shown here. These numbers exclude patients with missing outcomes, that is, those patients for whom there was no follow-up efficacy data.

As I indicated, patients who died before the test of cure assessment were considered failures in the ITT and MITT analyses. Such patients were excluded from the clinically evaluable and microbiologically evaluable analyses unless they were assessed as having died of their initial infection.

As you can see, although the response rates vary, the analyses are similar across the

various populations analyzed.

Next slide.

This slide shows the confidence interval around the difference in response rates in the FDA analysis and the corresponding confidence interval for the sponsor's analysis.

The dashed line indicates a difference of zero so that values to the left favor comparator. Values to the right favor linezolid. The hashed marks indicate the point estimate of the difference in response rates.

And as you can see, the confidence intervals for the FDA and the sponsor and similar for the various analytic populations.

Next slide.

With respect to results by pathogen, and here we are discussing the microbiologically evaluable patient population, let me just focus on one line here. For patients with pneumococcal bacteremia, with 30 patients in the ME patient population, the linezolid arm, 24 in the ceftriaxone arm, with response rates of 90 percent and 63 percent.

Next slide.

This analysis shows clinically relevant subgroups for the clinically evaluable patient population for a number of factors that are predictors of poor outcome, such as bacteremia, age greater than 50 years, and so on, and the response rates are as shown.

For patients with tachypnea at baseline, which has been identified in prospective studies as a risk factor for poor outcome, the response rates were 79 percent for linezolid, 31 -- I'm sorry -- 74 percent for ceftriaxone.

It's important to remember that, in general, these are small numbers for these subgroups, and these were not respectively specified subgroup analyses.

Next slide, please.

Now, the results that I showed you before for efficacy rates exclude patients with missing outcomes. To examine the effect of this missing data, we did one type of sensitivity analysis, which is to consider such patients to be failures, although it's

important to remember that we don't really know the outcome since we don't have complete follow-up information on these patients.

And the results are shown here. This represents the patient population analyzed by excluding such missing patients, and this represents the patient population including such patients as failures.

As you can see, the response rates fall as you would expect by including such patients as failures, but the pattern between the treatment arms is similar to that of the primary ITT analyses.

Next slide.

Let me move on to Study 51. This was a study of linezolid in the out-patient treatment of community acquired pneumonia. This study enrolled and treated 540 patients with community acquired pneumonia.

This is a multi-center, multi-national, randomized, evaluated blind trial. Patients were randomized to linezolid or cefpodoxime; were given for ten to 14 days. The primary endpoint was clinical

outcome.

Could I have the next slide, please?

Demographics are shown here. As you can see the treatment arms were balanced for age, gender, and race.

Next slide.

Five hundred and forty patients were enrolled and treated. One hundred and 20 of these had a pathogen isolated. There were 421 clinically evaluable patients. Of these, 98 had a susceptible pathogen isolated at the baseline.

Next slide.

Response rates are shown here. Again, sizes of population are shown below. The response rates are comparable across the various analytic populations. In contrast to Study 33, linezolid had higher response rates. Lower response rates were seen in the ITT clinically evaluable and microbiologically evaluate analyses. I'm sorry. Just the ITT and CE.

Next slide.

Confidence intervals are shown here. In general the FDA's and sponsor's confidence intervals

were comparable with the exception of the clinically evaluable patient population.

Next slide.

With respect to results by pathogen, for pneumococcal pneumonia, response rates were 93 percent for linezolid, 91 percent for cefpodoxime. There were a few bacteremic patients in the pneumococcal pneumonia group. Three out of three were cured in the linezolid arm and three out of six in the cefpodoxime arm.

Next slide.

With respect to subgroup analyses, and again, this is a clinically evaluable patient population this time, and these were not respectively specified in the protocol. The results for predictors of core outcome are shown.

Next slide.

We again examined the effectiveness in data. The sizes of the relevant patient populations are shown below. Again, as one would expect response rates fall, but are similar to the primary ITT analysis.

Next slide.

Let me move on to hospital acquired pneumonia. In this study the sponsor enrolled and treated 396 patients with hospital acquired pneumonia. This was a multi-center, multi-national randomized comparative double blind trial. Patients were randomized to linezolid or to vancomycin. They could receive concomitant aztreonam.

The primary endpoints were clinical and microbiologic outcome.

Next slide.

Demographics are shown here. The treatment arms were balanced with respect to age, gender, and race. In addition, APACHE II scores at baseline were similar between the treatment arms.

Next slide.

Three hundred and ninety-six patients were enrolled and treated. One hundred and seventy-seven of these had a pathogen isolated. There were 225 clinically evaluable patients. Of these, 95 had a susceptible pathogen isolated at baseline.

The Applicant also identified a

subpopulation of microbiologically evaluable patients who had a susceptible pathogen isolated through invasive respiratory procedures using quantitative criteria. This constituted 42 patients.

Next slide.

Response rates for the various populations are shown on this slide. As you would expect, these vary from ITT to the per protocol patient populations. In general, there were higher response rates for linezolid over vancomycin in these analyses.

I think it's important to recognize for the microbiologically evaluable patient populations these are relatively small numbers.

Next slide.

Ninety-five percent confidence intervals are shown here. The width of the confidence interval to the microbiologically and clinically evaluable patient populations reflect the sizes, the decreased sample sizes, relative to the ITT analyses.

Next slide.

With respect to results by pathogen, and again, this is for the microbiologically evaluable

patient population, these are as shown. For Staph. aureus the response rates were 61 percent in both arms.

For MRSA, and these are small numbers, 59 percent for linezolid versus 70 percent for vancomycin.

Next slide.

We also examined subgroups of interest, of clinical interest. With respect to ventilator associated pneumonia, and this was defined here as patients who went on the ventilator at baseline, the ME patient population, the response rates were 61 percent for linezolid, 41 percent for vancomycin.

If we did an analysis stratifying by APACHE II score, for patients with the highest severity of illness at baseline, and these are very small numbers here, the response rates were 62 percent versus 25 percent.

If we look at the same analysis in the MITT patient population -- could I have the next slide, please? -- because this analysis includes patients who died before test of cure and considered

such patients to be failures, and there were a substantial number of deaths in this study, response rates are lower. For ventilator associated pneumonia, the response rates were 54 percent for linezolid, 30 percent for vancomycin, and for patients who were most ill at baseline, 46 percent for linezolid, 17 percent for vancomycin.

Again, these are small numbers in these groups.

Next slide.

Again, to examine the effectiveness in data, we considered such patients to be failures. The results are shown here.

Could I have the next slide, please?

And finally, let me discuss mortality rates. Again, let me just remind you this was one issue where the FDA's analysis or analytic plan differed from the sponsors, and the deaths were directly considered by the FDA as to be failures. In the sponsor's analysis these were not directly considered in terms of assessment of cure failure.

And for studies with a substantial amount

of deaths, this study and the MRSA study, which I will discuss in a little bit, this could lead to a discrepancy between the FDA's analysis, analytic results, and the sponsor's.

But at any rate, with respect to mortality rates, for all cause mortality the rates were 18 percent in the linezolid arm and 25 percent in the vancomycin arm. For patients whose death was assessed by the reviewer as being due to their initial infection, the mortality rates were five percent and nine percent.

Next slide, please.

Let me move on to uncomplicated skin and skin structure infections.

Next slide.

The sponsor conducted essentially two studies of this, 39(a) and 39. Thirty-nine (a) enrolled 753 North American patients. Study 39 enrolled 332 non-North American patients. This was essentially one study that was divided into two.

This was multi-center, randomized, comparative double blind trials. Patients were

randomized to linezolid at a dose of either 400 milligrams -- I'm sorry -- at a dose of 400 milligrams or they were randomized to clarithromycin at a dose of 250 milligrams.

Patients were treated for seven to 14 days. The primary endpoints were clinical and microbiologic outcome.

Next slide.

Demographic characteristics are shown on this slide. As you can see, the treatment arms are balanced with respect to age, race and gender.

Next slide.

In Study 39(a), there were 753 patients enrolled and treated. Six hundred and twenty-seven of these were clinically evaluable. Of these, 210 had a susceptible pathogen isolated at baseline.

Next slide.

Response rates in the FDA analysis are shown here for the ITT, CE and ME patient populations. The percentages here differ from those in the briefing package. This only reflects patients who had Staph. aureus or Group A Strep.

Next slide.

And the confidence intervals are shown here. As you can see, the FDA's and the sponsor's analyses of confidence intervals are similar.

Next slide.

With respect to specific pathogens, the majority of isolates were Staph. aureus. There were no MRSA in this study.

Response rates were 86 percent for linezolid, 85 percent for clarithromycin.

Next slide.

This shows the effect of missing data. Again, if you consider patients with missing outcomes to be failures, response rates fall, but are similar, in general, to the primary ITT analysis.

Next slide.

Study 39, which had, as I've mentioned, essentially the same design as 39(a), but were non-North American patients. The treatment arms were balanced with respect to age, gender and race.

Next slide.

Three hundred and thirty-two patients were

enrolled. Two hundred and fifty four of these were clinically evaluable. One hundred and one had a susceptible pathogen isolated.

Next slide.

Clinical efficacy results are shown here. Again, the ME patient population numbers are different from those in your briefing package because here only patients with Group A Strep. or Staph. aureus are considered.

Next slide.

And confidence intervals are shown here. The ME patient population, and this is true for 39(a), for the FDA is different than that for the sponsor. It's a smaller population because we only consider Group A Strep. and Staph. aureus, leading to wider confidence interval.

Next slide.

With respect to results by pathogen for Staph. aureus, 97 percent versus 96 percent for clarithromycin. There were a few MRSA isolates with the results as shown.

And this -- I'm sorry. This is my chin on

the slide. This is the microbiologically evaluable patient population.

Next slide.

Let me move on to complicated skin and skin structure infections. The Applicant studied this in Study 55 in which 819 patients with complicated skin and skin structure infections were enrolled and treated. This was a multi-center, multi-national, randomized, comparative, double blind trial. Patients were randomized to linezolid or to oxacillin. They could be switched to oral therapy with linezolid or dicloxacillin, depending on which arm they had been randomized to.

The primary endpoints were clinical and microbiologic outcome.

Next slide.

The treatment arms were generally balanced with respect to age, race, and gender.

Next slide.

There were 819 patients enrolled and treated. The FDA analysis focused on those ITT patients who met inclusion criteria for complicated

skin and skin structure infections at baseline. This population is referred to here as the ITT prime patient population. There were 629 patients in this population.

Of these, 487 were clinically evaluable. So these are patients who met baseline inclusion criteria. These are patients who met baseline inclusion criteria and post baseline criteria, such as length of therapy.

Finally, there were 209 microbiologically evaluable patients who had a susceptible pathogen isolated at baseline.

Next slide.

Response rates are as shown for the ITT, ITT prime, clinically evaluable and microevaluable patient populations.

In general response rates for linezolid were higher than those for oxacillin in all analyses.

Next slide.

The confidence intervals are shown here. The sponsor did not define an ITT prime population. So only the FDA confidence interval is shown.

As with the other studies, this is a different ME population than the sponsor's. It does not include many of the coagulase negative Staph. species. It really just includes Staph. epidermidis. Therefore, it's a smaller sample with a wider confidence interval.

Next slide.

For specific pathogens, the rates were as shown. For Staph. aureus, 88 percent for linezolid versus 86 percent for oxacillin. There were two out of three patients with MRSA in the linezolid arm who were cured.

For Group A Strep. the response rates were 69 percent versus 75 percent for oxacillin.

For the Enterococcus faecalis and faecium, I should mention that none of these isolates were vancomycin resistant.

Next slide.

With respect to subgroups of clinical interest, for patients 65 or older, the response rates were 87 percent versus 82 percent; for diabetic patients, 79 percent versus 68 percent; and for the

patients who were identified as having peripheral vascular disease in the reviewer's analysis, 60 percent versus 44 percent.

Next slide.

And, again, we examined the effect of missing data through one type of sensitivity analysis by considering such patients to be failures. The response rates are as shown.

Next slide.

Let me move on to methicillin resistant staphylococcal species infections, and this was a supportive study, the idea being to garner data on effectiveness of linezolid in the treatment of MRSA infections at defined body sites, infections at defined body sites. So this is a pathogen driven study, but in the context of specific infections.

There were 460 patients with known or suspected methicillin resistant staphylococcal species infections, with pneumonia, skin and skin structure, urinary tract infection, bacteremia of unknown origin.

This was a multi-center, multi-national, randomized, comparative, open label trial. Patients

were randomized to linezolid or to vancomycin for seven to 28 days.

As you heard from Dr. Hafkin, linezolid could also be at the discretion of the investigator -- could be given PO after the IV course of therapy. Patients could receive concomitant aztreonam or gentamicin, and the primary endpoints were clinical and microbiologic outcome.

I should just mention that the criteria used to define pneumonia and skin and skin structure infections were consistent with those used for the indication specific studies that I've already discussed.

Next slide.

Characteristics of the patients are shown on this slide. As you can see, the mean age for both groups was 64 in the linezolid arm, 60 in the -- 64 years of age in the linezolid arm and 60 in the vancomycin arm. The groups were balanced overall in terms of demographic characteristics.

Next slide.

Four hundred and sixty patients were

enrolled and treated. Three hundred and one of these had a pathogen isolated. There were 241 clinically evaluable patients. Of these, 126 had a susceptible pathogen isolated at baseline.

Next slide.

Response rates are shown for the various patient populations. We focused on the MITT and the ME patient populations since this was a pathogen driven study. The response rates for MITT were 59 percent versus 66 percent, whereas for the ME patient population, the response rates were 76 percent versus 72 percent.

One thing I want to remind you is that in the FDA analysis, patients who died before test of cure were considered failures in this analysis. Those patients were excluded from this analysis unless they died from their initial infection.

Next slide.

The confidence intervals in the FDA's analysis and the sponsor's analysis are shown here. let me just mention two things about the FDA analysis. In the MITT analysis, as you've seen, the point

estimate of the difference in response rates is negative. For the ME analysis it's positive.

A similar shift is seen for ITT to CE.

Next slide.

With respect to results by pathogen, the vast majority of the isolates were methicillin resistant Staph. aureus. The response rates in the microbiologically evaluable patient population were 78 percent for linezolid versus 72 percent for vancomycin.

Could I have the next slide?

In the MITT analysis, the response rates were 56 percent for linezolid versus 66 percent for vancomycin. So the ME analysis response rates were higher for linezolid for MRSA patients. In the MITT analysis they were lower.

Next slide.

When outcomes were broken down by site of infection, pneumonia, skin and skin structure with their primary diagnoses, and this is the ME analysis, response rates for pneumonia were -- and these are small numbers -- 90 percent versus 71 percent; for

skin and skin structure 79 percent versus 73 percent.

Could I have the next slide?

In the MITT analysis for pneumonia the response rate for linezolid was 43 percent versus 54 percent in vancomycin; for skin and skin structure 69 percent versus 77 percent.

So, again, in the ME analysis response rates were higher for linezolid by site of infection for the two major categories of infection. In the MITT analysis, they were lower.

Next slide.

The effect of missing data is shown here. Again, response rates fall as one considers patients with missing outcomes to be failures.

Next slide.

Let me move on to studies involving vancomycin resistant enterococcal infections.

Next slide.

As you've heard, the sponsor had as its pivotal study Study 54(a) which enrolled and treated 145 adult patients with known or suspected VRE infection, which was defined in the context of

infection at specific body sites. This was a multi-center, randomized, dose comparison trial which was double blind, and unlike the equivalence trials that I've described before, this was a superiority trial.

Patients were randomized to receive linezolid 600 milligrams IV or to receive linezolid 200 milligrams IV, and the study hypothesis was that the high dose arm was superior to the low dose arm.

Patients could receive concomitant aztreonam or aminoglycosides, and the primary endpoint was clinical outcome.

Next slide.

This shows the demographics of the patients who were enrolled and treated. As you can see, the demographics were similar. The Applicant also obtained data on severity of illness at baseline using an MPM II score. The arms were balanced with respect to this characteristic.

Next slide.

The primary patient population analyzed by the FDA were those intent to treat patients who had VRE at baseline, which is referred to here as the

MITT-VRE patient population. So this excluded those ITT patients who did not have VRE at baseline.

We also focused on the patients who had VRE bacteremia at baseline. There were 117 in the MITT-VRE patient population. Thirty-four of these had VRE bacteremia baseline.

Next slide.

Response rates are shown here. In the MITT-VRE patient population, and these exclude patients with missing outcomes, the response rates were 67 percent versus 52 percent. The P value for the difference was .16.

For the bacteremic patient population, the sizes of the population are shown here, 59 percent versus 29 percent, with a P value of .15.

Next slide.

With respect to results by pathogen, as you would expect, most of the pathogens isolated were E. faecium. There were a handful of patients with E. faecalis. A few patients had both pathogens. Response rates in the high dose arms were 67 percent for E. faecium and the low dose arm 53 percent.

For faecalis, three out of four patients in the high dose arm were cured; zero out of two in the low dose arm.

Next slide.

With respect to outcome by site of infection, the response rates in these obviously are small numbers. Five out of ten for bacteremia of unknown origin were cured in the high dose arm; two out of seven in the low dose arm.

Skin structure infections, skin and skin structure infections, 69.2 percent versus 100 percent.

Urinary tract infection, 63 percent versus 60 percent.

Pneumonia, two out of three high dose patients were cured versus zero out of one.

And for a category of other, which was almost entirely complicated interabdominal infections, the response rates were as shown.

Next slide.

Covariate analyses were performed. It's important to recognize that these were not prespecified in the protocol. The multivariate

analysis performed by the FDA incorporated risk of mortality at baseline, primary diagnosis in terms of site of infection, age, sex, weight, and presence of bacteremia at baseline, and the bottom line was that the adjusted and unadjusted analyses were consistent.

Next slide.

With respect to the effect of missing data, again, if one puts in patients with missing outcomes as failures, response rates fall, as shown here for the MITT-VRE and VRE bacteremia patients.

Next slide.

With respect to mortality in this study, all cause mortality in the MITT-VRE patient population is as shown. In the bacteremic population, four out of 18 patients died in the high dose arm. Nine out of 16 in the low dose arm.

Next slide.

We looked at causes of death in the bacteremic patients. These are as shown. In the high dose arm, one patient was felt to have died by the reviewer -- was felt by the reviewer to have died definitively from VRE infection. Two patients died

from sepsis. The possibility that VRE contributed to this cannot be excluded. One patient died from respiratory failure.

For the low dose arm three patients were felt to have died from VRE infection, one from sepsis. FRE cannot be excluded as a cause of death in that patient, with the other causes as shown.

Next slide.

Covariate analysis of mortality in bacteremic patients was performed. Again, this was not prespecified. It incorporated risk of mortality at baseline, age and sex. The adjusted and unadjusted analyses were consistent.

Next slide.

Now, before presenting results from Study 54, let me just recapitulate some of the history of this study. Originally the Applicant planned a study designated as 54 which would enroll 500 patients. In June of 1999, a blinded decision was made to submit patients already enrolled as Study 54(a), which constituted the 145 patients that you've just heard about.

This was submitted as a stand alone study, and all alpha was considered to be spent on this trial.

Study 54 was continued as a support of trial. Data on 82 patients was submitted to the FDA in December of '99. As you heard from Dr. Hafkin, there was a total of 186 patients. So we do not have data on 104 patients.

I think it's important to recognize that there bolstering the nonsignificant results of 54(a) with these results from Study 54 could correspond to multiple looks at the data without appropriate, that is, prespecified statistical adjustment.

Next slide.

With that in mind, the efficacy results are as follows. For the MITT-VRE patient population, there were a total of 71 patients. For patients with non-missing outcomes, there were 28 in the high dose arm, 35 in the low dose arm. Response rates were 64 percent and 49 percent. These are the response rates if you add back in those patients with missing outcomes as failures.

Next slide.

All right. Let me change gears a little bit here, a lot, I guess, and move on to safety. I'm going to be discussing clinical adverse events, laboratory adverse events, and potential drug-drug interactions.

Next slide. Next slide.

Adverse event rates for the various Phase III comparator controlled studies. So I'm not going to show you any data from the dose comparison studies; just the comparator controlled studies are shown here.

As you can see, there were significant adverse event rates in both treatment arms across all studies.

For all studies combined, the adverse events rates were 56 percent versus 50 percent for linezolid versus comparator.

Next slide.

If one looks at drug related adverse events, in a number of the studies there were a higher rate of drug related adverse events in linezolid arm than in the comparator arm, although this was not

invariably true. For example, in HAP there was a lower rate.

Overall the rate of drug related adverse events was 22 percent for linezolid, 16 percent for comparator.

Next slide.

With respect to discontinuations related to adverse events, the rates are as shown. These varied across studies for linezolid from three to ten percent. Overall six percent of linezolid treated patients were discontinued for an adverse event; five percent of comparator treated patients.

Next slide.

If one looks at discontinuations due to drug related adverse events, for some studies, particularly the pneumonia studies, the rate of discontinuation due to drug related adverse event was higher in the linezolid arm, although, again, this was not invariably true for HAP. The rate was higher for the comparator arm.

For all studies combined, 2.4 percent of linezolid treated patients discontinued for a drug

related AE versus 1.9 percent of comparator treated patients.

Next slide.

This shows discontinuations according to specific adverse events, and one thing I want to be very clear about is the percentages shown are relative to the number of patients discontinued for any adverse event, not the entire patient population.

So nine percent of linezolid treated patients who discontinued for any adverse event did so for nausea versus four percent for the comparator. The second most common cause was pneumonia for linezolid. The third most common was headache.

Other causes included diarrhea, dyspnea and vomiting, and again, these are just all adverse events whether drug related or not.

Next slide.

If one now looks at drug related adverse events, and again, this refers to patients who discontinued for any drug related adverse event, not the entire patient population, 22 percent of linezolid treated patients who discontinued for a drug related

adverse event did so for nausea versus eight percent for comparator.

For headache, the figures were 16 percent versus three percent; vomiting, 12 percent versus eight percent; diarrhea, 12 percent versus 11 percent; thrombocytopenia, six percent versus zero percent.

Next slide.

Let me move on to a consideration of laboratory findings, and then I'm going to focus on thrombocytopenia.

Next slide.

This shows the development of thrombocytopenia in different studies in patients who had normal platelet counts at baseline. We do not consider in this analysis those patients who have abnormal platelet counts at baseline, and the sponsor has looked at this issue.

So the rate varies with studies for linezolid ranging from two percent in the skin and skin structure infection studies to 11 percent in the MRSA studies.

It's important to recognize that the MRSA

study involved sicker patients with a longer duration of therapy.

Next slide.

If one looks at the degree of thrombocytopenia and uses, for example, the NCI common toxicity criteria, when we look at Grade III thrombocytopenia, which was the most severe grade that developed, so we're looking at patients who develop a platelet count of less than 50,000 during study. The rates for linezolid range from zero percent to 2.5 percent. Again, the most common -- this was most common in the MRSS study, Study 31.

Next slide.

If one looks at the effect of linezolid dose on the development of thrombocytopenia, there appears to be an effective dose. If one looks at the dose comparison study, the rates were 13 percent for the high dose arm versus 11 percent for the low dose arm.

For all Phase III studies, and here we're describing high dose as greater than a gram a day; low dose is less than a gram a day of linezolid; five

percent versus three percent.

For Study 11, this was a Phase II study of linezolid in bacteremic patients. This only used the high dose. So there was no low dose arm for comparison here, but the incidence of thrombocytopenia in patients with normal platelet counts at baseline was six percent.

For all Phase II studies, three percent versus two percent; and for all Phase II and III studies combined, five percent versus three percent.

Next slide.

We also looked at the issue of resolution of thrombocytopenia, and I just want to mention that this entire analysis for laboratory findings, and as I'll show you in a little bit for drug-drug interactions, was done with the assistance of Dr. Ana Scharffman, as well as Dr. Joyce Korvic, and I really want to thank them for their assistance with this, which allowed us to look at a variety of issues.

I also want to thank the Applicant for reorganizing the data sets to allow this analysis to be done.

But at any rate, this is linezolid. This is comparator, and this is just for Study 31, which as you remember is the study in which the most pronounced effect on thrombocytopenia was seen.

Each red line or green star represents a patient with thrombocytopenia. The minimum value is at the left. The maximum value is at the right or -- I'm sorry -- value at follow-up is at the right.

If the line continues off the graph, that patient showed complete resolution of thrombocytopenia. So for the majority of patients in the linezolid arm who had thrombocytopenia, thrombocytopenia resolved or it was going in the right direction.

For these patients we do not have laboratory follow-up on these patients. However, there were no clinical adverse events that were identified in relation to thrombocytopenia, such as gastrointestinal hemorrhage for these patients or a requirement for platelet transfusions.

Next slide.

So let me try and summarize this. The

incidence of thrombocytopenia in the studies was one percent of 13 percent; for Grade III, zero to 2.5 percent, depending on the patient population. Higher doses appeared to be associated with an increased incidence.

Thrombocytopenia appeared to resolve in linezolid treated patients who had laboratory follow-up.

There were no related adverse events identified, and finally, I'll just mention that looking at other cell lines, no parent effect was identified.

Next slide.

Let me move to drug-drug interactions.

Next slide.

Let me just step back for a minute, and you've seen some data before from the Applicant about the relative MAO inhibition activity of linezolid. These are two classic MAO inhibitors, clorgyline and selegiline. I want to focus on the inhibitory constants, the KIs.

For MAO A, and that's the activity that's

associated with adrenergic hypertensive type crises, as well as MAO B, which is associated with serotonin syndromes.

As you can see, the KI for linezolid is considerably higher than for a drug such as selegiline. However, I think it's important to recognize the peak plasma concentrations of linezolid that are achieved are in the neighborhood of the KI.

Next slide.

The sponsor was aware of this issue and has examined this in their Phase I studies by conducting a number of drug interaction studies, and I'll just mention one here, and you've seen this data in another form. They looked at both interactions with sympathomimetic agents and serotonergic agents just to look at the sympathomimetic amine interactions.

A study was performed in which patients -- and these are -- I'm sorry -- not patients, but normal volunteers -- received placebo, phenylpropanolamine, linezolid plus placebo or linezolid plus phenylpropanolamine.

The maximum change in systolic blood pressure from baseline is shown here.

Next slide.

As you've heard, patients received a number of concomitant medications during the course of the study. One of the outcomes of the Phase I studies was that the sponsor incorporated this issue into the study design both with respect to cautioning physicians and investigators about patients receiving concomitant medications, as well as capturing data on the frequency with which these medications were administered.

These are some of the agents that we've looked at. As you can see, in general, for concomitant medications the proportion of patients receiving these were similar between treatment arms, generally five percent or less, except for some pathomimetic bronchodilators where it was 18 to 20 percent in the two arms.

Next slide.

We examined the database in the NDA for potential MAO inhibitor associated drug-drug

interaction events. There were only small numbers of events found in patients who had received concomitant medications.

There was no clear association between adverse events examined and the use of concomitant medications, and classic MAO inhibitor associated events were not seen. There were no hypertensive crises identified and no cases of serotonin syndrome.

Next slide.

Let me move on to linezolid resistance. This has been induced in the laboratory. The mechanism appears to be a GDU transversion on the 23S ribosomal RNA. The sponsor has found that the frequency is less than one to ten to the ninth. It may result in cross-resistance to lenclosomides (phonetic) and chlorinfenacol.

Next slide.

With respect to development of resistance in linezolid in clinical trials, as you've heard, this has only been seen with enterococcal species. There were 15 cases in the NDA database, nine in the compassionate use study, six in the dose comparison

studies.

Mean duration of therapy in these patients was 32 days. Almost all of the cases involved enterococcus faecium. There was only one that involved faecalis.

The increase in the MIC was to eight micrograms per mL for six isolates; 16 micrograms per mL for eight isolates; and 32 micrograms per mL for one isolate, which was the Enterococcus faecalis isolate.

Next slide.

In the compassionate use trial, there were nine cases of resistance developed. Eight of these were faecium. One was Enterococcus faecalis. Six of these patients were considered therapeutic failures. Three were considered cures.

Next slide.

In the dose comparison trials, there were six cases of resistance development. All of these were Enterococcus faecium. There were two in the low dose group. I'm sorry. Four in the low dose group. Three of these four were considered failures. There

were two in the high dose group. One of these patients was considered a failure.

So can I have the next slide?

This concludes the FDA's analysis. I just would like the committee and the audience to be aware that this analysis was the result of a lot of hard work by a group of scientists of the agency who are shown here. I want to thank all of them.

I'd also like to thank the Applicant for provision of data for this NDA.

Thank you. I'll be happy to answer any questions.

CHAIRMAN RELLER: Thank you, Dr. Ross.

Questions?

Barbara.

DR. MURRAY: Dr. Ross, do you or perhaps the sponsor over the lunch break would pull out in the MRSA group, you mentioned some got aminoglycosides, and I would be curious to know how many. Were those documented MRSA and what was the susceptibility of the MRSA to getimicin if it was an MRSA that patients that got that.

DR. ROSS: What I can tell you, and let me just give you some numbers from the MITT analysis, and this is not just MRSA. This is just the entire MITT patient population. So it does include some MRSE and it does include a handful, actually very few methicillin susceptible.

But for those patients who received aminoglycosides, we identified -- let me just look at these numbers here -- in the MITT patient population there were 14 out of 30 cures in the linezolid arm. So that's 47 percent, versus 15 out of 27 in the vancomycin arm. That's 56 percent.

We do not -- I don't have data for you on susceptibility.

If you look at patients who did not receive aminoglycosides, there was a larger patient population. That was 61 out of 98 in the linezolid arm. So that was 62 percent, versus 59 out of 85 in the vancomycin arm, which is 69 percent.

I have the corresponding figures for the microbiological evaluable patient population if you need those.

CHAIRMAN RELLER: Other questions?

Yes, Dr. Danner.

DR. DANNER: Yeah, I have two questions actually related to potential toxicity and one related to a question on metabolites.

In terms of potential toxicity, earlier in the day I think the numbers were that there were 13 of 632 patients had episodes of hypertension, and these were patients on potentially interacting drug. Of those patients, there were 13 of 632 had episodes of hypertension as an adverse effect, but only one of those were thought by the clinician on the scene to be related to linezolid.

What was the incidence of hypertension as an adverse event in subjects not on potentially interacting drug? Anybody know the answer?

DR. HAFKIN: If I could show I-98, please.

CHAIRMAN RELLER: Dr. Hafkin is answering this question.

DR. HAFKIN: Now, it turns out that for the great majority of both linezolid treated patients and the comparator treated agents, the blood pressure

elevation was actually at baseline or was after the end of therapy analysis.

If you actually look at linezolid, of the patients we have up there, the 13 with an interacting med., actually six patients had adverse event of hypertension reported at a time after the patient got linezolid and the comparator. So it was actually within the -- made pharmacokinetic sense that he could have had a hypertensive response.

Only one of those patients was thought by the investigator to have been related.

Now, it's important to understand the details of that one patient. It was a 92 year old man who was hypertensive in his history, had acute pneumonia, was admitted to the hospital, and was treated simultaneously with salbutamol and linezolid.

The investigator became frightened, stopped the treatment. So we had no opportunity to rechallenge the patient.

DR. DANNER: My other question with regards to potential toxicity is regarding the effect on the bone marrow effects and effects on platelets.

From the earlier presentation, it sounded to me like perhaps Pharmacia/Upjohn found the problem might be more of a problem with people who start out with lower platelet counts, and that raises a question, is if you have patients who have bone marrow insufficiency like somebody who has had a bone marrow transplant or has a hematologic malignancy or who has been heavily pretreated with myelosuppressive chemotherapy, is it conceivable that this problem with platelets, in fact, might be a bigger problem in that population?

Were there any patients like that in the compassionate use?

DR. HAFKIN: I don't have slides prepared for the compassionate use trial, but what I can tell you is that patients with terribly severe underlying illness have taken linezolid for up to three months, and even in that circumstance, our hematologic adverse event rate is around three percent.

If you have a minute, perhaps looking at the worst case, which is the platelet count, we could go through a couple of those slides that I showed you. Would that be appropriate at this point? Because we

actually go straight to the data.

Let's start out with the hazard function curve, which is on screen. L51 would be fine. This is the analysis we did to detect the problem, and I might note I think that you see no difference until 16 days, and then you start seeing a divergence of the curve. That divergence of the curve represents one percent of the population.

As I said, there are 16 patients that that increase in slope between 16 and 18 days represents.

Let's go to the next slide, which is the scattergram for the -- this is the distribution for the whole patient population. I'd like the abnormal patient population, which should be the very next one. Yes, this is exactly what I want, 54.

If you'll note here, about half -- you can't see them carefully. It turns out that if you look at the relative risk, having a low platelet count at baseline drives you to having a greater risk of reduction of platelets at any time during the treatment period.

But note that for those people that are

down here or below this blue dotted line, which is normal limits, the change in platelets count over time is very minimal, and it's our view that there's no increased risk for this patient population. There is an increased risk for them to stay down here, but there's no increased risk to get down lower.

There is that one example where we have this one patient who starts out at something like 75,000 and then goes to about 19,000. Those numbers might be off a little bit, but they're based on my memory of the case, but even that worst case analysis where you saw the slow decrease in platelet count, because of the platelet count, suppression is the patient's underlying illness. This patient had malignancy and was on chemotherapy -- had a malignancy and was on chemotherapy.

DR. DANNER: Did the metabolites have an effect on this?

DR. HAFKIN: When we look at those people, remember again we've got two lines of evidence. We've got 34 patients in the compassionate use trial who have received linezolid for up to 60 days. When we

look at hematologic changes in that group, they are not different from the main group of patients that are treated with their dreadful underlying illnesses. These are very sick people, often transplants, immunosuppressed.

Perhaps a shift table would help you see the extent of change. Would you like to see a shift table that's --

DR. DANNER: Okay.

DR. HAFKIN: Yes?

CHAIRMAN RELLER: Dr. Hafkin, let's see the shift table. Dr. Hafkin was addressing the platelet --

DR. HAFKIN: This is the worst -- another way of showing you the worst of the worst, and what I would point out to you is that the shift in platelet count is typically one box. There isn't anybody that goes from this to this point, and here we've defined the platelet number, and this is linezolid treatment and this is comparator treatment.

So you'll see if you look at the shift tables the typical response if there's going to be one

will be from this box to that box or that box to that box.

CHAIRMAN RELLER: Dr. Rodvold.

DR. RODVOLD: Maybe we could just follow up with this because I've done some platelet studies in cats.

Did you look at percentage? I mean you're trying to explain that to us, but if you look at percentage drop from the baseline sometimes it gives the clinician a better handle a little bit than if you start at 100,000 and then drop by 50 percent, if at first I start at 300,000 and I only drop it 25 percent. Did you look at that?

DR. HAFKIN: We only at one cut. That initial table where we detected a signal in 2.4 percent of patients in the linezolid group versus 1.5 percent in the comparator group, we used a 75 percent reduction for that first cut. We found that to be the most sensitive percent reduction.

DR. RODVOLD: The other question I have on the platelet count goes back to metabolites, but did you look at -- you said you had a group of people that

had impaired renal function of platelets greater than four.

DR. HAFKIN: Yes.

DR. RODVOLD: Did those patients have a higher incidence of adverse events in the platelet count and maybe even the hepatic test count in regards to the renal impairment which indirectly may be telling you the metabolites contributed to that profile if it was higher?

DR. HAFKIN: Well, if you'll recall the safety data I had to share with you, I only had 17 patients that fall into that area. Let me pull up a slide that I showed. It was S-194, and we'll actually go from this.

We're looking at the number of deaths of these patients with serum creatinines greater than four, the number of patients that died. No difference there. The number of patients with an adverse event leading to discontinuation. Well, we've got one patient on the linezolid.

If I could go to the next slide in this series, you'll see the reasons for or the adverse

events that are reported in the study for the small number of patients, linezolid here, comparator here. You'll find anemia here.

Let's go to the next slide.

So there is no mention of thrombocytopenia or anything that we can logically connect to hematologic toxicity except for that anemia.

DR. RODVOLD: But did you look at percentage changes in the --

DR. HAFKIN: When we look at -- I can tell you what we've done. The average anilide result, whether you are talking about hemoglobin, hematocrit, white count, platelet count is terrible for both of these groups, and it's really terrible throughout the period of treatment. These are super sick people.

CHAIRMAN RELLER: Dr. Ross, in your analysis of patients with uncomplicated skin and skin structure infections, one of 39 had infection owning to methicillin Staph. aureus, and in the complicated category of SSSI, three of 83 patients were infected with methicillin resistant Staph. aureus, and yet for the studies where there was an enrichment for

methicillin resistant strains, we had 33 MRSA out of 51, 33 patients out of the 51 with MRSA had skin and skin structure infection as the site involved.

Do we know of those patients -- so now we have the 33 with MRSA with SSSI -- how they broke down in terms of uncomplicated and complicated infection?

DR. ROSS: Actually I'm going to once again refer you to the Applicant to see if they can provide that information.

CHAIRMAN RELLER: Seeking to see what our numbers are having to do with the issue of MRSA in SSSI uncomplicated and complicated in adults.

DR. HAFKIN: Yes. If you use -- it depends on our definition. The number of people that had in hospital infections, were severe enough in terms of comorbidity to require hospitalization, all of them, if you were to use that global diagnosis of an adverse event that was severe enough to keep you in the hospital, virtually everybody in Protocol 31 -- I mean the number of people who got to leave the hospital in that protocol with oral therapy was small because we had such a severely ill population of

patients.

For those people that had the traditional indicator of severity requiring surgery debridement over the period of therapy, about one-third of patients in Protocol 31 required at least one surgical intervention at baseline.

Let me go to Slide E-32 or ER-32, which breaks down the data a bit more by diagnosis. This still doesn't get to what you're trying to get to, which is the severity of illness, but at least this gives you specific diagnoses and outcome. This is the clinical care of the sponsor's group. This is linezolid. This is vancomycin. You'll see very comparable outcomes for each diagnosis.

As I say about a third of this group, maybe as high as 38 percent of this group actually required for both linezolid and vancomycin repeated surgical debridement because their infection was so extensive.

Perhaps after lunch, if there is more information that could be shared with us, whether these were infections that were complications of other

things going on and not the primary reason for hospitalization, whether any of them were community acquired versus hospital acquired being complications of surgical procedures, that sort of information, to get a better feel for how this compound works in patients with documented MRSA infections involving skin and skin structure, and if we got bacteremia information on those patients, in what setting it occurred.

Dr. Rodvold, do you have any further questions? Dr. Lowy.

DR. LOWY: Regarding the hospital acquired pneumonia, in the original study design was there any consideration for switching patients to oxacillin, the isolate of methicillin susceptible rather than vancomycin?

CHAIRMAN RELLER: So the question is those patients who ended up having methicillin susceptible strains; was there a revision or reversion to oxacillin even though they may have been treated initially with vancomycin?

DR. HAFKIN: For Protocol 31, that patient

would not have been valuable if they had -- if they had a baseline isolate that -- perhaps I don't understand your question, sir.

DR. LOWY: I'm just wondering in terms of the original design of the study if it would be possible rather than continuing on vancomycin for an individual who has a methicillin susceptible Staph., whether that individual after initiation of therapy could have been switched to oxacillin, which might have been a preferable regimen.

DR. HAFKIN: There were several patients who had methicillin resistant Staph. by the local lab, but when we got that isolate to our central lab, they were found to be methicillin susceptible.

The physicians, of course, were always capable of doing anything they wanted to do. They always do, if you've ever participated in a study, on the one hand.

On the other hand, under the criteria of the study, you had to be evaluable microbiologically for this study. You had to have a methicillin Staph. at baseline.

DR. LOWY: Not for the hospital acquired pneumonias.

DR. HAFKIN: No, no, that's true. The complex skin and soft tissue trial 55, that patient population did get oxacillin. The comparator population did get oxacillin.

DR. LOWY: Let me ask another question then. Don't the individuals who had Staphylococcal infections that were hospital acquired pneumonia cases -- how many of them were actually mixed infections with other organisms. A great many of them.

In fact, at baseline virtually every investigator used concomitant medications because they were -- we actually have specific information that we could show you about Gram stain results, culture results for that patient population.

CHAIRMAN RELLER: Could we have that after lunch as part of the follow-up to questions posed earlier?

The final question before lunch goes to Dr. Leggett. You had a question?

DR. LEGGETT: In a follow-up to this one

in terms of trying to look at comparator arms, I think he was alluding to vancomycin as a lousy drug perhaps. Maybe we're going to use a better one. So my question is in terms of the comparator arms, both with the oxacillin two grams Q6 and the clarithromycin, 250 milligrams BID, did you do any calculations either before or during your studies about what the anticipated population time above MIC for your pathogens would be to make it similar to the time greater than above the MIC at 40 percent for the linezolid?

DR. HAFKIN: In Protocol 55, we felt that we had -- at two grams every six hours, we felt we were well above the MIC of our target pathogens throughout the dosing interval.

In terms of clarithromycin, the pharmacokinetics of the drug are quite interesting. It's well distributed, as you know. We didn't try to look at the activity of that drug from that perspective because of its penetration into inflammatory cells.

CHAIRMAN RELLER: The sponsor has been

working on the questions that were posed before the break, and they will be handled when we resume at 1:30 this afternoon. At the moment we have no individual schedule for the open public hearing, but we will ask for three minute queries from the floor at that time.

There's a table reserved for members in the restaurant, and we will resume for follow-up of the questions addressed this morning promptly at 1:30, and then address the questions posed by the agency.

One, thirty reconvene.

(Whereupon, at 12:17 p.m., the meeting was recessed for lunch, to reconvene at 1:30 p.m., the same day.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:31 p.m.)

CHAIRMAN RELLER: Good afternoon. We have a new audio system for the members around the table. I'd like to demonstrate it.

There's an on/off button. When it's on, the red light shows. When it's off, the mic goes off and you don't hear me. Simple as that.

(Applause.)

CHAIRMAN RELLER: I'd like to call the meeting to order. It is now time for the open public hearing. Are there any who would like to make comments about the topics under discussion from the public?

No response.)

CHAIRMAN RELLER: See and hearing none, the open public hearing is closed.

There were several questions that remained at the close of this morning's session. Pharmacia/Upjohn has organized responses to those questions, and I'd now like to ask Dr. Tarpley to introduce the presentation of that responses, and this

does not mean that there can't be additional question. Quite the contrary, but this is an organized forum from which to proceed to more detailed questions, anything that the committee wishes to discuss that would help us then vote on the questions asked of us by the FDA.

And when it comes time to voting, we will have lots of discussion, but when the votes come, it will be yes or no so that we have crisp replies, and then any additional recommendations over and above the questions asked we can forward on to the agency, but we will answer those questions yes or no at the end of the discussion.

Dr. Tarpley.

DR. TARPLEY: Yes, thank you, Dr. Reller.

There were a number of questions that were asked of us this morning. What we'd like to do is I will introduce Dr. Hafkin who will provide the responses, and in order to organize those questions, we've agreed. We've decided that we would repeat the question so that everybody can remember what the particular question was, and then we would provide the

response, and there are four or five of these that we will proceed in that order.

DR. HAFKIN: Well, thank you.

I heard several related questions, and so I would propose that we try to answer questions about Strep. pneumoniae together. I think that there was one very firm question about activity of linezolid against Strep. pneumoniae taking the pediatric data out, the activity of linezolid in Strep. pneumoniae resistant penicillin, Strep. species, and then activity of linezolid in bacteremia.

And so let me go first to all of our Phase III adult clinical trials, EB-1, and on this slide we have -- it's a course slide that comes out of our integrated summary of efficacy, but as you'll see, we have the pathogen to the left, the treatment the patient group received, the clinical outcome, and the microbiologic outcome, and then finally the pathogen outcome.

And you'll see that for Strep. pneumoniae we have about 90 percent, you know, pathogen outcome cure. If you look at Strep. pneumoniae that is

resistant, you see essentially the same number. The number of Strep. pneumo. species resistant to penicillin in adults is only eight.

Now, if I can go to the next slide, this is that slide that I showed you just a few minutes ago with linezolid Phase III and linezolid Phase II with the pediatric data removed.

And here you have for all patients with Strep. pneumo. -- we have a 92.7 percent cure rate, for intermediate Strep. pneumo. and for resistant Strep. pneumo. This is bringing in all of our Phase II pneumonia trials.

So we have ten resistant Strep. pneumo. here. We have 17 intermediate there, and we have 164 patients with Strep. pneumo. across all of our protocols.

Now, if I can go to the next slide, now looking at our bacteremia and our success rate, the most fertile source of this data is in our in-patient community acquired pneumonia trial. We identified 29 patients with Strep. pneumo. with bacteremia, and we have a 93.1 percent cure, and when you look at the

comparator, roseferin, you see a lower cure rate.

And go to the next slide, please.

We did have just a couple of people in our out-patient pneumonia trial with Strep. pneumo., and we had good cure rates with both agents.

Now, if I can go to one more slide to give you a little bit more feeling for the patients that failed their treatment with bacteremia, only one patient, and this is the 71 year old with chronic lymphocytic leukemia, profound immunosuppression and radiation. That patient was treated for seven days with linezolid, was doing very, very well, went home, didn't complete his prescription, of course, went home, came back to the hospital in septic shock.

On reculturing his blood stream a couple of weeks post discharge, he still had Strep. pneumo., and this is the patient I told you just a little bit about. We never got the second isolate to show definitively that they are the same bug. We don't know whether this is a recurrence of the original Strep. pneumo. infection or whether this is a new infection.

So in conclusion, we have a solid database with Streptococcus pneumoniae. When we put the pediatric experience together with the adult experience, I think we have an excellent cure rate. In the pediatric pneumonia trials, we had five patients with Strep. pneumonia resistant to penicillin. Two were bacteremic, and those in all the patients, whether they were bacteremic or not, were clinical cures.

The other point I'd make is that the biology and the natural history of pneumonia in children is equivalent to adults. I mean obviously they have special issues, pharmacokinetic issues that are critical, but we feel that the natural history of pneumonia in children is quite similar to adults and that you should consider the data that we're providing from the pediatric program and the adult program as well.

DR. MURRAY: Would you show that first slide again?

DR. HAFKIN: Yes, if we could go to the first Strep. pneumoniae, yes, EB-1.

CHAIRMAN RELLER: Dr. Hafkin, are any of the 32 patients with bacteremic pneumococcal pneumonia -- were any of those with resistant isolates, intermediate or highly resistant to penicillin?

DR. HAFKIN: There was no adult with resistant Strep. pneumo. bacteremia. There were two children that had excellent -- I mean they were cured. We have two pediatric cures with resistant Strep. pneumo.

And to answer the question you asked us earlier, both the children with bacteremia had Strep. pneumo. resistant to penicillin and erythromycin in both cases.

CHAIRMAN RELLER: Thank you.

Other questions related to Streptococcus pneumoniae in community and hospital acquired pneumonia?

DR. KUEHNERT: I just had --

CHAIRMAN RELLER: Dr. Kuehnert.

DR. KUEHNERT: -- just a question, really a clarification about your definition of hospital acquired pneumonia versus community acquired

pneumonia, and just so that it has some bearing because I saw that you had Strep. pneumo. as being a common pathogen, and I don't really see that very often as a cause of hospital acquired pneumonia.

So if it was nursing homes that were involved in that or hospitals?

DR. HAFKIN: It was a global study, and we were quite surprised as well. There were several patients that came from an Eastern European site that had very good evidence of Streptococcal pneumonia two days after they had been in the hospital, three days after they had been in the hospital for other diagnoses. So it was interesting, and it's the first time I had seen that, as well.

Should I go on to the Staphylococcal questions you asked?

CHAIRMAN RELLER: If there be no other questions for Streptococcus pneumoniae now, please go ahead.

DR. HAFKIN: Again, these slides weren't prepared for this presentation. So they're a little hard to read. If we could go to EB-6, this has all of

our Staph. aureus that we identified and treated in skin and soft tissue trials, all adult trials, and here we have linezolid treatment outcomes across the top. We have oxacillin outcomes there, and we have vancomycin outcomes across the bottom.

Recall that the patients who were randomized in the vancomycin arms were patients that were fundamentally sicker than those patients identified and treated in our oxacillin treatment arm.

Then if we look at methicillin resistant Staph. aureus, you see a subset. This group is a subset of this group. You'll see the outcomes here, the clinical outcomes, the micro outcomes, the pathogen outcomes, and you'll have vancomycin down along the bottom.

Obviously we did identify two patients with MRSA randomized oxacillin, and one patient was a cure, at least clinically.

Now, if I could go after you've had a chance to study to the next slide, which is the analogous slide in pneumonias, if you look at Staph. aureus treated with linezolid in our pneumonias, this

is all protocols, the MRSA protocol, the nosocomial pneumonia protocol. We have the clinical outcomes here for all three agents. Here we have the microbiologic outcome, and here we have the pathogen outcome.

Please, again, recall that the vancomycin studies recruited much sicker patients. So if we look at linezolid versus vancomycin, here's their outcome.

Now, if we could see the next slide, when we look at Staphylococcal bacteremia, Staph. that came from these trials, we did not identify very many people with MRSA bacteremia. We actually have an additional story to share with you because there are in total, taking this patient and putting them into our entire database, we have 15 patients with MRSA bacteremia, but the Staph. aureus sensitive to oxacillin are listed up here, and you can see very comparable results for linezolid and oxacillin.

Now, if we consider the MRSA bacteremia that we identified across all of our protocols, we found 15 patients with MRSA bacteremia either due to pneumonia or skin and soft tissue.

If I could have the next slide, this is the slide that gives you a flavor of each of the patients who failed. A 56 year old diabetic with an infected line, never removed, on steroids, looked great after 15 days of therapy, had recurrent bacteremia 43 days later.

It was a bacteremia with Staph. aureus. We don't know what the relationship of that recurrent bacteremia to the original infection was.

A 69 year old, profoundly immunosuppressed, bacteremic. They treated the patient only nine days or, rather, they only treated the patient for five days, and shortly after therapy, nine days after therapy, the patient had recurrent bacteremia. Why they treated this patient for only five days is beyond me.

A 69 year old with diabetes, media stinitis, post CABG, was profoundly ill. This patient had, it turns out later on subsequent questioning, external osteomyelitis. They treated the patient for 24 days, and the patient had recurrent bacteremia, and this is, I think, a real failure, but the patient had

a diagnosis that made them ineligible for the study.

Then this last one, an 81 year old treated for six days. He had an abscessed kidney, Staphylococcal abscess because of the obstructive uropathy. The patient was treated for six days and then had recurrent bacteremia.

So these are our failures associated with MRSA that had recurrent Staphylococcal bacteremia post therapy.

Now, if I could go on to deal with another question if there are no questions following this.

CHAIRMAN RELLER: Dr. Lowy.

DR. LOWY: Regarding the information you just provided and also the recommendations that you have on page 6 for length of therapy for complicated skin and soft tissue infections, the recommendation is ten to 14 days. Many clinicians would be concerned about treating bacteremic Staphylococcal infections, particularly if the bacteremia was prolonged for 14 days alone because of the high risk of either recurrence or metastatic seeding.

I was wondering whether you had had any

additional considerations about that.

DR. HAFKIN: The data that we have suggests the failures -- in fact, all the failures whether we look at Strep. pneumo. or Staph. aureus or MRSA or even -- well, we don't have any Streptococcal bacteremias that failed, but all those failures seem to be associated with failures of treatment less than seven or eight days.

So I can't answer the question. We've all seen failures with the beta lactams under those circumstances, and we don't for a minute believe that we're better than oxacillin or naphcillin against a sensitive Staphylococcal species. We think we're equivalent to the beta lactams against beta lactam sensitive organisms.

CHAIRMAN RELLER: Dr. Norden.

DR. NORDEN: Yeah, Hafkin, I'm a little confused by numbers at this point, and I think this is me, but the last slide you showed showed four failures.

DR. HAFKIN: Yes.

DR. NORDEN: The slide before that I

thought I saw only one MRSA.

DR. HAFKIN: That's true because it was a different protocol. Let's go to the slide.

DR. NORDEN: I see.

DR. HAFKIN: If we can bring this slide up, I thought I had made that point. Perhaps I -- this is one of the 15 MRSA patients that I told you about. I stole the patient off this slide and put it into that group of 15. When I told you 15, I mean 15 patients with MRSA bacteremia from any kind of diagnosis, any treatment anyplace.

DR. NORDEN: In both the pneumonia and the skin and soft tissue.

DR. HAFKIN: Skin and soft tissue, yes.

DR. NORDEN: Thank you.

DR. HAFKIN: Next I'd like to deal with the amino glycoside questions, and I believe ER-30 is the slide I believe I want. Yes. If I could have this slide.

We looked because a few patients as we told you in our MRSA program, Protocol 33, looking for resistant Staph. We allowed patients who needed to

have an amino glycoside to have it, and so we looked at outcomes of patients who got amino glycoside and linezolid, and those patients that got no amino glycoside.

And so here's linezolid outcomes, and here's the vancomycin outcomes. This is the success of patients that got linezolid and amino glycoside. Here is the percentage of patients that got vancomycin and amino glycoside.

It certainly didn't have any effect on linezolid, didn't seem to improve a thing, but the numbers are small, as you can see. We only -- in the entire protocol only identified these handful of patients that were clinically evaluable.

CHAIRMAN RELLER: Any further questions about this component of the Staphylococcal infection group?

DR. HAFKIN: Now, you asked a very important question, I thought, about the relationship of linezolid sensitivity to Strep. pneumonia that might be resistant, rather, to penicillin and erythromycin, and although we don't have -- we didn't

have enough in the way of isolates in our clinical trial, we did have -- we've taken the opportunity to look at that in the Sentry database isolates, and we could share that information that Dr. Zurenko has done if you're interested in seeing the relationship of linezolid sensitivity to these organisms.

CHAIRMAN RELLER: Anyone not want to see it?

(Laughter.)

CHAIRMAN RELLER: Please.

DR. HAFKIN: Well, then I'd like to call Gary Zurenko to the podium to show his work.

DR. ZURENKO: Thank you for the vote of confidence.

(Laughter.)

DR. ZURENKO: Slide Y-129, please.

I'm Gary Zurenko from Discovery Research.

And early in our evaluations of linezolid we were very interested in, of course, the erm genes, which are shown here for the MLS B phenotype. This is a study using isogeneic strains in most cases, some transconjugants, some transconductants, and as you can

see, for ermA, ermC, ermB, ermTR, most specific interest here is the ermA. The MIC of linezolid was unaffected by these resistance genes.

Y-130, please. Slide up.

Also looking at macrolide efflux specifically here in estimoniae, the MEF E gene (phonetic), we saw virtually no difference in MIC. Therefore, the data predicted that we would not have, in effect, by the common erythromycin resistance genes on linezolid activity, which is compatible with the mechanism of action being distinct.

Looking at the overall century database, we did several correlations, one with erythromycin versus linezolid, Y-270. Slide up, please. This is just an X-Y scattergram of linezolid on this axis versus erythromycin across the bottom, MIC versus MIC with virtually no correlation.

So hopefully that would convince all of us that based on at least laboratory evaluations, we would not expect any cross resistance to occur with erythromycin.

CHAIRMAN RELLER: Thanks, Gary.

Do you have, Dr. Tarpley, additional information for us about the place of acquisition and severity of skin and skin structure infections with the methicillin resistant Staphylococci?

And then secondly, further information about the species of enterococci in the vancomycin resistent enterococcus protocol 54 and 54(a)?

DR. HAFKIN: We're pulling that slide up.

No, no, the complex skin soft tissue in 31.

What we're going to show is -- actually I didn't identify the slide very well. Yes, please, if you'd bring ER-32 up, this is the clinical outcome for 31, and these are the sickest of the patients.

Recall that we identified in the 31 trial 230 patients with skin and soft tissue infection, and then what we did in this analysis is we looked at everyone for evidence of fever and high white count, and then we said who of those patients had a significant comorbidity, and you'll have that patient observation here.

So you see that in linezolid we were able

to identify 33 patients out of the 115, and then in the vancomycin, we had about 30. So these are the sickest of our MRSA protocols by diagnosis.

Most of these patients had very extreme illness, but as you can see, many of them did have infected surgical incisions in both arms.

This infected wound cellulitis, these could have been associated, of course, with central lines. If you look at the kind of illness that you collect in MRSA trials, looking at skin and soft tissue, it is quite often associated with an implanted device, but certain abscesses, cellulitis are rarely.

Now, this is the tip of the iceberg. These are the sickest of the patients we have. The rest of the 230 patients -- I guess it would be about 180 patients or something like that -- the rest of those patients will have had less severity of their MRSA illness.

Let's go to the next slide, which shows you a slightly different cut of the data. The other was the ITT. This is the clinical evaluable patients, and we fall then into only 28 patients here and 27

patients in vancomycin.

But, again, give you the sense that no matter what cut of the data we have, we have that same assurance of comparable outcomes.

CHAIRMAN RELLER: You had a total of 15 patients with methicillin resistant Staph. aureus bacteremia. Were most of them out of these patients?

DR. HAFKIN: They came primarily from Protocol 31, and they came primarily from the patients you're seeing here, yes.

CHAIRMAN RELLER: Dr. Chesney.

DR. CHESNEY: I wanted to go back to Group A strep. if I could, and looking at the information that the FDA presented this morning, on page 22, there were five uncomplicated strep. infections treated, 100 percent cure.

On page 25, again, uncomplicated, there were seven with an 85 percent cure rate, and then on page 29, there were 26 complicated skin and soft tissue with only a 69 percent cure rate, and I guess my instincts would have said that they should have been 100 percent across the board, and I'm wondering

why 69 percent, why not 100 percent across the board.

DR. HAFKIN: Yes, yes. As you'll recall, our numbers are similar, but because the FDA uses slightly different rules for evaluability, their numbers -- you know, they're very consistent.

We've tried to understand what happened in these Group A strep. infections, and unfortunately the physicians that called these patients failures did not give us enough information about the clinical basis of their failure.

They were not microbiologic failures in general. In other words, they had Group A strep. at baseline. So they had the bug there, and it was the pathogen that was important. Unfortunately, because there were so few, we have only one with a positive culture at follow-up, and that patient was clinically cured, but was a microbiologic failure.

So we really don't know what's happening. Did we pick up a group of patients that failed clinically whose Group A strep. was cured? I'm afraid that we're only talking about a handful of observations, and I can't -- you know, I don't

understand it. You know, I can't tell you a story that somehow puts it in perspective.

DR. CHESNEY: Well, obviously if this were to be approved for skin and soft tissue, people would assume that it was effective for Group A strep, and this is a little unnerving to --

DR. HAFKIN: Well, we have a substantial animal model database, and if you'd like us to go into that.

DR. CHESNEY: Thank you. That would be good.

DR. HAFKIN: Before we go too far, would you like me to give you the enterococcal data? Because it involves another group of people.

CHAIRMAN RELLER: Let's finish with the Group A Streptococcal question so that then we can keep these in categories, and then we'll come back to the enterococci.

DR. HAFKIN: Great. I'll call one of my preclinical colleagues.

CHAIRMAN RELLER: Gary Zurenko will be presenting this data.

DR. ZURENKO: Yes. Thank you.

CHAIRMAN RELLER: These data.

DR. ZURENKO: The in vivo activity of linezolid was evaluated in the Myan Acrusis (phonetic) model by Dennis Stephens, and in this model of necrotizing fascitis mice were infected. Mice were infected as shown. Treatment with antibiotics was initiated four hours after the challenge and then continued every 12 hours BID for six doses.

Next slide.

Linezolid was administered in three doses, ten, 20, and 40 milligrams per kilo. Clindamycin was administered at 86 milligrams per kilo and penicillin G at 98.

The animals were followed as described here, and the endpoints were considered as shown.

Next slide.

Let's go to -- let's jump right to the end. Y-198 please. Slide up.

In this figure we show that percent survival post treatment at 12 days with the antibiotic dose across the bottom, as you can see, very good

survival in these treatment groups. This is a group treated with ten to the seventh, ten to the eighth, and ten to the ninth cells. Obviously there's very severe challenge as is shown here. The drug is not as effective as with the other two challenges, which are, in fact, still quite large.

The conclusion of the investigator was that the activity was quite similar to that seen with clindamycin, which is a very effective agent in this model, but that he felt that a longer term of dosing might be required to handle these very severe challenges.

CHAIRMAN RELLER: Dr. Murray.

DR. MURRAY: What's the half-life of the drug in mice?

DR. TARPLEY: One moment please.

DR. LOWY: I think it was between a half hour and an hour when I read this over before, as opposed to penicillin in 15 minutes and clindamycin about 20 minutes in mice.

DR. TARPLEY: It's about an hour.

CHAIRMAN RELLER: Thank you.

Dr. Rodvold.

DR. RODVOLD: I was wondering if you could maybe clarify something with me for the methicillin resistant Staph. aureus. It seems in your protocol for uncomplicated skin and skin structure there wasn't that many isolates, if any, for MRSA, and then the other isolate you've tied in from both your complicated studies as well as just the MRSA directed pathogen study.

My question gets to be that in uncomplicated you studied a 400 milligram dose and in complicated you studied a 600 milligram dose, but you want indication for MRSA in both. Is the 400 milligram dose in an MRSA adequate enough to treat it?

DR. HAFKIN: We agree that patients with MRSA, known MRSA infection should have 600 milligrams of linezolid twice daily. We agree with you.

CHAIRMAN RELLER: I think we're ready for the enterococcal discussion.

DR. HAFKIN: You know, you make a wonderful slide and you don't bring it with you. So we're going to have to live through a less than

perfect collection. If I could have ER-63 up, this is not the complete database unfortunately, this is just that initial database.

ER-63, please.

What I'm going to try and share with you is the efficacy of linezolid against VRE by species. If I could have this slide up, please.

Unfortunately this does not include our compassionate use and our 54 isolates, but this gives you a sense of that first 145 patients where we have E. faecium, E. faecalis, and E. avium, rather, faecalis and faecium.

And we have the microbiologic response here and the microbiologic response here, this being the 200 milligram, this being the 600.

We've just found the other slides, but let me go through one more of these, and then we'll find the real slide.

Let me see it now and see if we have it. Yes, this is a great bottom line slide. M-93, please.

Now, this is -- what we've done here is I've taken the 600 milligrams twice daily dose results

for Study 54(a) and the results in our compassionate use trial. Recall that most of these patients have interabdominal abscess. More than 90 percent of those patients have interabdominal abscess. This is the E. faecalis result for the two.

And then our conclusion, of course, is that the drug is quite effective in the management of vancomycin resistant enterococcus whether it's faecium or faecalis.

CHAIRMAN RELLER: Just so that we're perfectly clear, the number of vancomycin resistant faecalis isolates treated was two?

DR. HAFKIN: Well, two, and this is half, you know; this is half of our 50 -- the two represents half of the experience I'm sharing with you. This comes from the 54(a), and this is from compassionate use. These are patients that are microbiologically evaluable. So we have nine from compassionate use, and we have two from our Study 54A.

CHAIRMAN RELLER: So a total of 11 patients with vancomycin resistant E. faecalis?

DR. HAFKIN: Yes.

CHAIRMAN RELLER: Dr. Murray.

DR. MURRAY: Just along those lines, it's kind of interesting since there probably would have been a comparator unless these were allergic patients for the vancomycin resistent E. faecalis. I'm kind of surprised it was included in this protocol.

Is that maybe they didn't know what it was when they first started therapy?

DR. HAFKIN: Actually in Protocol 25, 70 percent of the patients roughly came to the protocol because there was no option in terms of therapeutic choices. The patient had no other antibiotic that would work, but the rest -- it is interesting -- came because of intolerance, allergy to beta lactams, allergy to vancomycin. So these few were allergic patients. They couldn't take something else.

CHAIRMAN RELLER: Are there additional questions for the sponsor?

Dr. Murray.

DR. MURRAY: A couple of questions sort of going back to early clinical data, and one relates to just partly curiosity, but it would, I'm sure,