FOOD AND DRUG ADMINISTRATION

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CENTER FOR DRUG EVALUATION AND RESEARCH

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ANTI-INFECTIVE DRUGS ADVISORY COMMITTE

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68TH MEETING

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FRIDAY,
MARCH 24, 2000

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The meeting was held at 8:30 a.m. in the Marriott Washingtonian Hotel, 9751 Washingtonian Blvd, Gaithersburg, Maryland, Dr. Barth Reller, Acting Chairman, presiding.

PRESENT:

L. BARTH RELLER, M.D.,	Acting Chairman
P. JOAN CHESNEY, M.D.,	Member
CELIA CHRISTIE-SAMUELS, M.D., M.P.H.,	Member
ROBERT L. DANNER, M.D.,	Member
JAMES LEGGETT, JR., M.D.,	Temporary Voting Member
BARBARA E. MURRAY, M.D.	Member
CARL W. NORDEN, M.D.,	Temporary Voting Member
JUDITH R. O'FALLON, Ph.D,	Member
KEITH RODVOLD, Pharm.D,	Member
DAVID E. SOPER, M.D.,	Member
JOYCE DRAYTON, M.D.,	Guest Expert
MATTHEW J. KUEHNERT, M.D.,	Guest Expert
FRANKLIN DAVID LOWY, M.D.,	Guest Expert
JANET WITTES, Ph.D.,	Guest Expert
KIMBERLY TOPPER,	Executive Secretary

I-N-D-E-X

P-R-O-C-E-E-D-I-N-G-S

(8:30 a.m.)

CHAIRMAN RELLER: Good morning. Good morning if everyone could take their seats, like an airplane the doors are closing for an on time departure.

Good morning again. I'm Barth Reller, Acting Chairman for this meeting of the Anti-Infective Advisory Committee of the FDA. I'd like to welcome everyone to today's meeting and we'll begin with a reading of the conflict of interest statement by Kimberly Topper, our Executive Secretary for today's meeting. Kimberly.

MS. TOPPER: The following the announcement addresses the issue of conflict of interest with regard to this meeting and is made part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda and information provided by the participants the Agency is determined that all recorded interests and firms regulated by the Center for Drug Evaluation and Research present no potential for conflict of interest

at this meeting with the following exceptions:

In accordance with 18 U.S.C. 208 (b), a full waiver has been granted to Dr. Keith Rodvold. A copy of this waiver statement may be obtained by submitting a written request to FDA's Freedom of Information Office located in room 12A-30, located in the Parklawn Building.

In addition one of our committee members has had a past interest relating to Zyvox, that we believe should be disclosed. The FDA believes that it is important to acknowledge this involvement so that his participant may be objectively evaluated.

Dr. James Leggett was listed as an investigator on the study for Zyvox, while Dr. Leggett was listed an investigator on this study he did not enroll patients and was not otherwise directly involved.

I would like to remind the committe members to please speak directly into the microphone this is being recorded.

Thank you.

DR. CHESNEY: Joan Chesney, the

University of Tennessee in Memphis.

DR. SOPER: David Soper, Medical University of South Carolina.

DR. KUEHNERT: Matt Kuehnert, Center for Disease Control.

DR. WITTES: Janet Wittes.

CHAIRMAN RELLER: Dr. Wittes could you introduce yourself again. I don't think the mike was working properly.

DR. KUEHNERT: Matt Kuehnert. Center for Disease Control and Prevention.

DR. WITTES: Janet Wittes. Statistics Collaborative.

DR. SORETH: Janice Soreth, I'm a Medical Officer in the Division of Anti-Infectives.

DR. CHIKAMI: I'm Gary Chikami.

CHAIRMAN RELLER: We need a little help with the audio portion.

DR. MURPHY: Diane Murphy.

CHAIRMAN RELLER: Let's go to the other side of the table and we can pick up when we get power. Dr. O'Fallon.

DR. O'FALLON: Judith O'Fallon. Mayo Clinic, Cancer Center for Statistics.

DR. MURRAY: Barbara Murray, University of Texas, Medical School at Houston, Infectious Diseases.

DR. LEGGETT: Jim Leggett, Medical Center, Oregon Health Sciences University.

DR. DRAYTON: Joyce Drayton, Morehouse School of Medicine, Division of Infectious Disease.

DR. LOWY: Frank Lowy, Columbia University, College of Physicians and Surgeons. Infectious Diseases.

DR. CHRISTIE: Celia Christie, University Hospital of the West Indies, Pediatrics, Infectious Diseases.

DR. RODVOLD: Keith Rodvold. College of Pharmacy and Medicine, University of Illinois, Chicago.

DR. DANNER: Bob Danner. Critical Care Medicine Department of NIH.

DR. NORDEN: Carl Norden. Infectious Diseases at University of New Jersey. School of Medicine and Dentistry.

CHAIRMAN RELLER: Back to Dr. Murphy.

DR. MURPHY: Mine is working. Dr. Diane Murphy, Office Director of ODE-4, which has anti-infectives, anti-viral, and special pathogens in it at FDA. Thank you.

DR. CHIKAMI: And I'm Gary Chikami. I'm the Director of Division of Anti-Infective Drug Products, FDA.

CHAIRMAN RELLER: For today's meeting we're especially pleased to have with us, Dr. Carl Norden, Dr. Leggett who will be voting members for today's session. And a special welcome also to our guest experts who will be participating, but not voting on the questions that we'll address later. And those individuals are Drs. Joyce Drayton, Matthew Kuehnert, Frank Lowy, and Dr. Wittes.

Next we'll have opening remarks for today's meeting by Dr. Gary Chikami, who's the Director of the Division of Anti-Infective Drug Products of the Office of Drug Evaluation for the FDA.

Gary.

DR. CHIKAMI: Thank you Dr. Reller. And

just a few organizational comments. I'd like to welcome --

CHAIRMAN RELLER: While Gary's doing that I realized that I didn't introduce myself, fully.

I'm in the Division of Infectious Diseases in Direct Clinical Microbiology Laboratory at the Duke University Medical Center. And as noted earlier, will be the Acting Chairman for today's meeting. Now Dr. Chikami.

DR. CHIKAMI: Thank you Dr. Reller. I'd like to first of all, welcome Dr. Reller as the new chair of the committee. He's -- because of the paperwork, he will be acting as chair, but in future meetings he will be the permanent chair of our committee.

In addition, I'd like to welcome Dr. Leggett who also is joining the committee as a new member.

Today's meeting we'll be hearing the presentation of the new drug application for Zyvox or linezolid from Pharmacia and Upjohn. And I would also like to extend my welcome to the applicant this

morning, and also members in the audience who will be here for what I think will be an important discussion of this new drug product.

We're having a little technical glitch with the slides. I just have a few general comments that I want to make.

This meeting today will discuss an application for a new drug product being developed for a number of indications, but particularly for the treatment of resistant gram positive infections. Over the past several years there have been -- this committee has met to discuss both specific and general issues related to development of products in this area.

In July of 1998 and October of 1998 there were two general meetings that -- one with industry members of academia, the second in October, specifically with this committee, to discuss some issues related specifically to development of drug products in this area. In March of '98 -- and there had been two product specific meetings. One for Synocin (ph) in March of '98, the second most recently

in November of '99 to discuss supplemental application for Levaquin for the treatment of penicillin-resistant strep pneumo.

Now I think during the course of these meetings a number of issues were raised and in two broad areas. One is what sort of evidence do we need to gather in the course of drug development to support the -- to support granting indications for resistant organisms?

And I think the second area that I think relates to the specific issues today is what are specific trials designs that one: may increase the experience available for the treatment of resistant organisms. Because as is often the case, in the course of the usual clinical trial, it's difficult to gather sufficient evidence on infections with specific resistant organisms.

And the second, if you're developing products in an area where there is no approved comparator, what sorts of designs would be acceptable or provide us with control clinical trial information?

In regard to the first area I think some

general issues or principles have come from the four meetings that I've talked about. One is that one would like to see a drug product being studied in a number of areas to provide both in vitro evidence of activity against both susceptible and resistant isolates.

One would like to also develop other preclinical sources of information such as animal model data, which would speak to activity again, not only against suspectable strains of the organism but resistant strains. And finally the important underpinning of clinical information coming from controlled clinical trials.

And then with regard to specifics -- how would one apply those principles. For example, if one is developing a product for resistant infections in pneumonia. It's important to understand how a product works, not only for that side of infection that is treatment of pneumonia in general, but treatment of pneumonia for susceptible strains. For example, susceptible strains strep pneumo and finally gathering whatever information is available for treatment of

pneumonia due to PRSP.

I think one can step through a development program and look for those themes in regard to the information that's gathered.

In regard to the second issue that -- specific designs which would one, gather information or enrich clinical trial information for experience with resistant organisms. People have suggested a number of approaches and one of them, I think, which is exhibited in the application that will be discussed today is to study or design pathogen driven studies as opposed to the indication driven studies that we are used to seeing in the course of anti-infective applications.

And that is to look at design specific trials for particular resistant organisms. We've seen this in applications in the past for VRE vancomycin-resistant enterococci and we will see it today it that setting and also in the setting of methicillin-resistant staph aureus.

How one integrates that information collected from those sorts of trials into the overall

portfolio, I think, is important in our consideration of how we determine whether or not a product has been demonstrated to be a safe and effective for the treatment of a resistant infection.

Finally, I will touch briefly on the issue of the comparator. There are clearly certain areas as we address the important needs of treatment of infections for resistant organisms, where there may be either no approved comparator agent or an acknowledged standard of care. This raises particular challenges in an area where we are used to seeing active control trials and moreover where the ethical imperative is that one cannot run placebo control trials or -- there is that real issue.

And I think people have looked at various approaches. One approach may be to do a historical controls or look for historical controls. That is problematic, particularly in areas where patients have multiple core morbidities. And the second approach that has been discussed in several meetings that we've had with this committee is to think about alternative designs, such as a dose comparison.

And I think we'll see an example of that in today's development, the development program that Pharmacia and Upjohn has designed for linezolid.

So I think, as you consider the application before you -- a number of these themes are evident in the development of this product and we certainly look forward to the committee's discussion on the issues that relate to the development of this product and certainly, the important indications for which this sponsor is requesting approval.

Thank you very much.

CHAIRMAN RELLER: Thank you Dr. Chikami. I'd like to next invite Dr. Gary Tarpley to step forward and initiate the presentation by sponsor for linezolid.

DR. TARPLEY: Good morning. I'm Gary Tarpley from Discovery Research at Pharmacia and Upjohn. And it's my privilege to begin our presentations today on linezolid. Linezolid is a new anti-bacterial from a an entirely new structure of class. The oxazolynons.

We are here today seeking approval of

linezolid for the following indications: nosocomial pneumonia, community acquired pneumonia, complicated and uncomplicated skin and skin structure infections, and vancomycin-resistant enterococcus faecalis and e. faecium infections.

In our presentations today we will present substantial data that linezolid is effective and well tolerated in treating these gram positive bacterial infections. I will begin with an introduction to linezolid and a summary of its microbiology and Dr. Hafkin will present linezolid's clinical pharmacology, pharmacokinetics, and the results of our clinical program. Next Dr. Anderson will provided a brief presentation summarizing our early experiences treating children with linezolid. And then to conclude I will make a few final remarks.

I'd like to begin today by reminding us of the serious clinical challenge we face treating gram positive pathogens. As you know the five pathogens listed here are very commonly isolated and the top three of these are gram positive bacteria. And these bacteria are an increasingly common cause of serious

infections. Infections such as pneumonias, skin and soft tissue infections, and bacteremias.

Now one striking example of the increased prevalence of these bacterias in U.S. hospitals come from the SCOPE Project. And in SCOPE surveillance for blood stream infections was monitored at 49 U.S. hospitals over a three year period. And greater than 10,000 infection were detected and as shown here the gram positive staphylococci and enterococci species were found to have count for almost 60 percent of those infections.

Now not only are these serious hospital acquired infections increasing in frequency, but they are frequently caused by drug resistant pathogens. The percentages of drug-resistance in the U.S. are already very significant for many of the gram positive bacteria. And many of the drugs historically used to treat these pathogens are losing their efficacy.

Drugs such as methicillin for staph-epidermidis or staph aureus, penicillins for strep pneumo, or vancomycin for the enterococcus. And in 1997 we had the first the reports of

glycopeptide intermediate resistant staph aureus. Perhaps signaling the future loss of vancomycin for treating s. aureus infections.

So clearly the human and economic burden associated with these infections are very significant and new antibiotics are required. We need new drugs not only to help us preserve the efficacy of our current agents, but we also need to address some of the limitations of these drugs. Limitations such as tolerability, limited formulations or routes of administrations, as well as drug resistant issues.

We need new anti-bacterials that have new mechanisms of action and thus have broad bacterial coverages that are well tolerated and flexibly dosed by both the I.V. as well at the oral routes.

Linezolid provides one important solution toward meeting these goals and was discovered at Pharmacia and Upjohn as a result of a massive medicinal chemistry effort that has thoroughly investigated the structure activity relationship of the phenyl substituted oxazolynon ring by designing, synthesizing and evaluating literally thousands of

individuals compounds.

Linezolid is an entirely synthetic molecule from the oxazolynon class. Of course, a class that's not previously been found in nature. It has a very broad gram positive anti-bacterial spectrum, which includes coverage of both drug sensitive bacteria as well as bacteria resistant to any other drug class.

Linezolid is an inhibitor of bacterial protein synthesis, that blocks synthesis at immediate site of action. And of course an important consequence of this novel mechanism of action, is that there is no pre-existing cross resistance between linezolid and any other marketed antibiotic.

Now specifically, linezolid disrupts bacterial protein synthesis by blocking the formation of the essential initiation complex. This slide is a schematic of the ribosome cycle in bacterial protein synthesis and as you know, in this process a variety of ribosomal nucleic acids complexed with multiple protein factors to form a functional 70-S ribosome.

And this the site of peptide bond

formation. Linezolid disrupts the initiation of this process by binding principally to the 50-S ribosome and thereby interfering with the ribosome binding of the essential fMET transfer of RNA. And as a consequence of these binding interactions disrupts the initiation of peptide bond synthesis and actually prevents the formation of the first peptide bond.

Now, of course, you are very familiar with a variety of other antibiotics that are clinically useful and also protein synthesis inhibitors. Drug such as the aminoglycosides, the macrolides, or the streptogramins. All of these drugs also inhibit bacterial protein synthesis, but they do so much later in the cycle by blocking the elongation step.

These drugs have no inhibitory activity disrupting initiation. And in contrast to these drugs, our experience have determined that linezolid has no effect on blocking proteins synthesis elongation, but rather all of its inhibitory is a consequence of blocking the initiation of this process.

Linezolid has an excellent pharmacokinetic

profile, which includes a 100 percent oral bioavailability in multiple dosage forms. We have studied three forms. An isotonic solution for I.V. infusion, tablets, and suspension for oral administration. All of these dosage forms are equivalent, meaning that equal drug exposures are obtained after equal doses independent of the formulation or the route of administration.

Now this property of linezolid will be clinically very useful, allowing a switch from an I.V. to an oral form without the burden of a dose adjustment. Thereby, potentially minimizing the length of I.V. therapy and thus, for some patients will offer the benefit of a more rapid hospital discharge.

We have extensively studied linezolid in a variety of gram positive bacteria infections.

In a few moments Dr. Hafkin will review the results of seven phase III studies in adults. The protocol numbers are illustrated here as well as the types as infections that we have studied. In all seven of these phase III studies, linezolid has been

demonstrated to be effective and well tolerated in this patient population.

I'd now like to change topics and talk about linezolid's microbiology. Of course, focused on the key gram positive strains that are relevant to the indications.

The entire in vitro susceptibility database for linezolid submitted in the NDA, consisted of three major parts.

There were numerous pre-clinical studies that studied a variety of different isolates that were conducted by both Pharmacia and Upjohn, as well as multiple outside laboratories. Isolates were collected and surveyed as part as the Sentry Surveillance Study collected in 1998, from over 30 medical centers.

And of course, we've also obtained and studied a variety different isolates as part of our phase III program.

Taken together the entire susceptibility database consists of more than 4,000 isolates of streptococci, greater than 12,000 isolates of

staphylococci, and nearly 4,000 isolates of enterococci.

The next several slides will summarize linezolid's MICs versus the particular gram positive strains, as well as focused on the key resistance issues within each group. Against the streptococci, linezolid was deeply active against penicillin-sensitive, intermediate resistant, and resistant strep pneumo isolates. With MIC 50s and 90 values that are about two-fold different from one another, and MIC 90 values that are consistently between one and two micrograms per mil. Against a group A and B strep. Strep pyogenes and agalactiae, there were similar levels of activity with MIC 90 values of about two micrograms per mil.

Comparisons of the MIC population distributions of the strep pneumo isolates that we've studied in our phase III program compared with those isolates collected in the Sentry Program, shown here in gray, reveal a very similar population distribution. These data allow us to conclude that the strep pneumo isolates that we've studied in our

phase III program were a very relevant collection and very representative of isolates obtained very broadly as part of the Sentry Surveillance Program.

Against the staphylococci, linezolid was equally active against methicillin-sensitive and resistant staph aureus and staph epidermidis with MIC 90 values between two and four micrograms per mil.

We've also had the opportunity to evaluate a limited a number of glycopeptide intermediate staph aureus and staph epidermidis and again linezolid was equally active against these bacteria. Perhaps not surprising for an agent that has a very different mechanism of action compared to the glycopeptides.

Comparison of the MIC populations distributions of the staph aureus isolates studied in phase III, with the isolates obtained from the Sentry Surveillance Program, again reveals a very similar population distribution. Allowing us to conclude that the staph isolates studied in our clinical program were a very relevant clinical population.

And similarly for the enterococci, linezolid had equal activity against vancomycin-

sensitive and vancomycin-resistant enterococcus faecalis and e. faecium. With MIC 90 values between two and four micrograms per mil. And as we've seen with the other gram positive bacteria the distribution of isolates that we've studied of the enterococcus species that we've studied in our phase III program were very representative of isolates very broadly as part of the Sentry Program.

Now we've generally described the in vitro antibacterial activity of linezolid as generally bacteriocidal versus the streptococci and bacteriostatic versus staphylococci and enterococci.

Now, of course, we have been very interested in studying the potential for linezolid resistance and we have investigated this thoroughly in the laboratory. First, it's important to note that we were unable to select for linezolid resistant bacteria via spontaneous mutation and thus at the limits of our detection of this experiment were able to conclude that resistance development via spontaneous mutation is very rare.

We estimate a frequency less than one in

ten to the minus ninth.

We were similarly unable to derive resistant mutants by standard chemical mutagenesis or serial passage experiments through two-fold direct concentrations. These are methods that we and others have used in the field routinely to isolate bacteria resistant through a variety of other antibiotic classes. Because these procedures were unsuccessful, we relied on a much more rigorous selection process, which involves a spiral-gradient serial passage method.

This is a method that allows you to capture very subtle changes in antibiotic susceptibilities that result from prolonged selected, drug pressure. In using this more rigorous selected method we were able to isolate two strains of resistant bacteria. A strain of aureus and on of e. faecalis for our mechanistic work.

We determined that the linezolid resistance determinance resided within the 50-S ribosome. And genomic sequencing of the 23-S ribosomal RNA genes revealed the presence of new

mutations that had not been previously been described for any other antibiotic class.

These mutations correlate with the changes of MICs with linezolid and result in the presence of verticular transversions within Domain 5 of the 23-S ribosomal RNAs, a domain known to be very centrally involved in peptide bond formation.

Now very interestingly, it's known that the gram positive bacterias contain five to six copies of the 23-S ribosomol RNA genes. And we determined that the linezolid MICs correlated with the ratio of wild-typed mutant genes and then in fact, a significant increase in MIC required mutations in at least two of the six genes.

So over all, the results of our laboratory work on linezolid resistance indicated that it occurred only after prolonged selected drug pressure and significant changes in MICs were not the result of a single point mutation, but rather required multiple mutations and a multi-gene copy family.

Now we have investigated the in vivo

antibacterial activity of linezolid thoroughly and the animal models that are most relevant to the indications today are shown here. Linezolid is very effective in mirroring models of systemic infection with the gram positive bacteria administered by a variety of different routes.

It's also very active in mouse models of soft tissue infection. Active in a localized group A streptylcoccal myonecrosis model and a model of severe pneumococcal pneumonia.

Linezolid was also evaluated in the mouse thigh infection model, which indicated that a key correlate of it's efficacy would be drug concentrations exceeding the MICs for approximately 40 percent of the dosing interval. So in summary our data demonstrate that linezolid is a new antibacterial that has a very broad gram positive coverage, because of the novel mechanism action of this agent there is a lack of inherent cross resistance with other marketed antibiotics.

We expect that linezolid therapy will be initiated principally in a hospital or the

institutional care setting. And the multiple dosage forms, coupled with the equivalent I.V. oral dosing will provided treatment flexibility needed to manage these serious infections.

Thank you and now I would like to turn the podium over to Dr. Hafkin.

DR. HAFKIN: Thank you. It's a pleasure to be here this morning. I'd like to speak first about the pharmacokinetic profile of linezolid and because it's oral bioavailibility is the most remarkable part of the story.

Let's start with the time concentration curve that we see with linezolid at steady state at 600 mgs, twice a day.

Within about an hour the concentration maximum is reached typically. Peak concentrations are on the average about 18 micagrams per ml, and at twelve hours when at the nader of the dosing interval, our average concentrations are still right at the MIC 90 for staph aureus. Note the enterococcus and strep species, in this case, strep pneumonia, MIC 90s are noted by the dotted lines.

When we compare the oral and IV preparations, we have in the orange color the I.V. preparation, you see a brief peak, but within a couple hours the concentrations, on average, are equal to the oral preparation and it troughed twelve hours, these really looked very much alike. The yellow preparation is noted here, the oral linezolid is there, as you can see the AUCs are virtually identical with time.

So drug exposure is equal whether the drug is given intravenously or orally. This is not an example of a typical step down therapy that we have used to in medicine.

Looking at the clinical pharmacology, as I've already told you, bioavailbility is a 100 percent by AUC, there is very little food effect. With the Cmax decreasing slightly, 18 percent, but the AUC being equivalent whether the drug is given with food or without food. The volume of distribution of 15 liters is about the volume of water in the body. Protein binding at 31 percent is low, and the half life is five to seven hours.

The drug is a weak reversible inhibitor of

monoamine oxidase.

Now linezolid is not a substrate or an inhibitor or an inducer of p450 enzymes. It is metabolized by oxidation and there are two primary metabolites of linezolid in that. The drug is eliminated primarily through the urinary tract. Thirty-five percent of the drug is eliminated through the urine unchanged, 50 percent of the drug is eliminated through the urine as the primary metabolites, and ten percent of the drug is eliminated through the feces.

There is virtually no active drug in the gut. It's very well absorbed and there's very little detectable intact drug in the feces.

Now what we know now is that primary metabolites can accumulate in patients with severe renal insufficiency. Creatinine clearance of less than 30 mls per minute. Both linezolid and the metabolites are dialyzable.

In summary then, what we know is that there will be no dose adjust recommended for -- dose or route of administration so that -- whether the

patient were to take the oral suspension, the tablet or the intravenous preparation, the pharmacokinetics are virtually identical. There is no need to change the relationship of food and meals.

Indeed, gender and age doesn't effect AUC or exposure to the drug because the concentration of the active drug doesn't really change whether the patient has severe or minimal or no renal insufficiency, we can't recommend a reduction in the dose of linezolid.

And because the drug is almost eliminated through the urinary tract, our studies have shown that there is no change in AUC with hepatic insufficiency.

I'd like next to talk about the efficacy that we've seen in our phase III trials. I'm going to use this road map as a way to aggregate the studies and actually to remind where I am.

The first study I'm going to discus is Protocol 55, which is a complex skin and soft tissue trial.

In this trial we compared in a double-blind, randomized, equivalence trial, linezolid 600

mgs to oxacillin, two grams every six hours. The study was set up the patient would be randomized to one of the two treatments. They were treated initially in hospital with I.V. medication. When the physician felt it was clinically appropriate they switched to oral therapy.

If the physician felt that gram negative coverage was necessary aztreonam would be added. Very few patients had aztreonam, because this was a hospital based protocol, these patients had fairly deep infection associated with wounds and abscesses. Some severe cellulitis was recruited to the trial. There was some post-operative wound infections as well.

Typical treatment was ten to twelve days, although by protocol physicians could choose bewteen a ten to 21 day period of therapy. A test of cure was two to three weeks after antibiotics were stopped, in follow-up and the population that we recruited to this protocol, 819 patients.

Now I have here a series of histograms for clinical cure. ITT population represents that group

of patients that got at least one does of medication.

Clinically evaluable population meant that the patients got at least five days of antibiotics and were called a clinical cure, or at least two days of antibiotics and then they could be an evaluable failure.

The microvaluable population was based on the clinically evaluable population. You had to have a baseline and a be clinically evaluable to be microbiologically evaluable in our analysis. Clinical cure for linezolid in the orange and in the gray was the oxacillin group.

Note that here is the confidence interval. And in each case we are equivalent or better to the comparator. The missing and indeterminate number for each of the patient population is noted here. So that we have about equal missing and indeterminate patients for each of the arms of the trial.

I'm going to use this design to report the results of all of our trials. When we look at pathogen eradication rates, whether we are talking about staph aureus or the strep species you see very

comparable results in terms of eradication in these patients with complex skin and soft tissue infections.

I'd next like to tell you about our out patient study called, Protocol 39. This study was carried out in North America. We compared linezolid 400 mgs to clarithromycin, 250 mgs, twice daily.

The treatment duration was a week to two. The test of cure was seven to 14 days and the population was 753 patients.

Again, the same cure histograms and for each of these populations, whether we consider the ITT or the clinical evaluable or the microevaluable, we are equivalent to the comparator. Again, these are the missing patients and are indeterminate in each of the arms.

When we look at the pathogen eradication rates in this study you see the same percentage of eradication very comparable outcomes.

In conclusion, we feel that we have demonstrated that linezolid is quite effective at both complicated and uncomplicated skin and soft tissue infection. The drug is quite effective in treatment

of staphylococcal Group A strep, and Group B strep skin infections.

I'd like next to turn to pneumonia. The first trial I'm going to describe to you is a trial that was designed to recruit patients with community acquired pneumonia, but in a patient population sick enough to require hospitalization.

The patients were randomized either to linezolid, and if necessary concomitant aztreonam, or they were randomized to receive ceftriaxone.

When the patients were stabilized and the physicians felt appropriate they could switch to oral therapy in both of these arms. Treatment duration was seven to 14 days, typically patients got eleven days of therapy for both drugs. The test of cure again, was two to three weeks after the end of therapy and we recruited 747 patients into this trial.

Again using the same clinical cure histograms you see the same pattern of equivalence for every other populations, every population up here. Again we've got the missing and indeterminate listed below. When we look at the pathogen eradication rates

for this trial, again, you see the same comparability of eradication for staph and strep species.

Turning to an outpatient pneumonia trial, where we recruited patients and randomized half to linezolid 600 mgs twice daily and half to cefpodoxime to 200 mgs twice daily. These patients got ten to 14 days of therapy. The test of cure was the same as the one we've discussed, two to three weeks after the end of therapy. And we recruited 540 patients and treated them as out patients in this trial.

When we look at all of the three populations and again, we see the same consistent sense of equivalence, if you'll note the confidence intervals are here and the missing and indeterminate patients are there.

So we have an equivalence again in this trial when we look at the pathogen eradication rates, the same patients were randomized to 600 mgs of linezolid twice daily or to vancomycin one gram, BID.

Patients were given concomitant aztreonam most of the time. Very few patients did not receive something for gram negative coverage. Treatment

duration was seven to 21 days, test of cure was the same two to three weeks. We recruited 396 patients. More than half were on ventilators at baseline, when they were recruited to the study.

And again looking at the cure histograms, we have the same confidence of equivalent performance of these drugs for each of the populations. When we look at the pathogen eradication rate, you see the same comparable results for both strep pneumo and staph aureus.

In conclusion, we feel that we've shown quite conclusively that the drug works well for community acquired pneumonia and nosocomial pneumonia due to strepto pneumonia and staph aureus.

Now I would like to turn to our resistant pathogen studies and the first study I would like to discus is MRSA.

To come into this study the patient had to have the strong epidemiologic clinical story that suggested a gram positive infection that was resistant to routine battle actems. The patients were admitted empirically into this trial, randomized either to

linezolid 600 mgs, twice daily, or vancomycin one gram, BID, on the basis of gram stain or a positive culture that had MRSA in it.

Concomitant aztreonam was allowed. Treatment duration was seven to 28 days. We recruited 460 patients into this trial. You could be admitted into this trial if you had MRSA in any part of you body. This wasn't a site-specific, but it was a bug-specific protocol.

As you know primary source of infections are listed here and about half of the patients that we recruited, 230, had skin and soft tissue infection. About 99 patients had pneumonia as the diagnosis and other diagnosis realized in this protocol are listed there.

The clinical cures for this group of patients, whether we consider ITT or clinically evaluable or microevaluable populations are the same throughout. Missing and indeterminate are here.

I should mention one other point, a few patients who were found after admission to the study to be infected concomitantly with resistant gram

negative pathogens and could not be managed with aztreonam did get aminogylcoside, but the number is small.

Clinical cure of the patients for skin and soft tissue infection are shown here, and again you have the same comparable outcome, no matter which of the three patient populations we consider. When we look at pneumonia, again you have the same pattern of equivalence or similarity.

Here are the pathogen eradication rates for those patients at the end of the day, proven to have MRSA, due to skin and soft tissue infection, very comparable outcomes. And again for those patients with hospital pneumonia -- hospital acquired pneumonia or nosocomial pneumonia, have the same comparable outcomes.

If you take all of the patients with MRSA, treated with linezolid and vancomycin you have the same comparability. Now the VRE study was similar in many ways. The requirement was that you would have to have VRE in some site in the body.

You could have pneumonia, skin and soft

tissue, urinary tract infection, intra-abdominal abscess, what-have-you. But we had no comparator at that time, when we started this study there was no widely held effective study for VRE infection, there was no consistent choice of our investigators.

It was very difficult to try and come up with a comparator that our community, the infectious disease community felt comfortable with.

As a result of that we compared what we felt to be the best dose, 600 mgs of linezolid, twice daily to the lowest dose of linezolid based on our animal model work and our in vitro model would work. When we give 200 mgs linezolid twice daily we're above the MIC 90 for 50 percent of the time in the typical patient population. So we chose to compare 600 mgs of linezolid to 200 mgs of linezolid.

It's important to know that we felt that 200 mgs of linezolid would have efficacy, we thought that we would be able to find better clinical outcomes and maybe faster clinical outcomes. So this was a randomized, double-blind superiority trial and we recruited patients to the either 600 or 200 mgs of

linezolid, concomitant antibiotics were allowed.

Treatment duration was seven to 28 days. And I'm going to report to you about two populations here.

We have a completed study that we call 54A. We recruited after more than a year, and a hundred sites, 145 patients with VRE infection. We closed that study and did a full analysis and then started a supportive study that we call 54. It had very similar designs. Eighty-two of the 186 patients recruited into that trial are available for us to discuss today.

Now for both of these protocols, about 20 percent of our patients had bacteremia, about 20 percent had intra-abdominal infection. Primarily those patients were post-liver transplant. Urinary tract infection was common and we had a surprising number of skin and soft tissue infections in this protocol. A few pneumonia.

I'm going to report on the data in several fashions. When you look at all patients with VRE infection, no matter what their site of infection is,

and look at the ITT, the clinical evaluable and microevaluable population. The study is underpowered and did not reach statistical significance, but we have a consistent pattern of improved performance with 600 versus 200.

When we look at the interim result for the smaller protocol of 82 patients, you have the same pattern in the ITT and the clinical evaluable population. But we have very few microbiological evaluable patients recruited into this small interim group.

When we looked at clinical cure by site of infection. If you look at intra-abdominal infection and typically these people had peritonitis, liver abscess, they had infections in the wounds that were persistent and recurrent, they were fairly sick people and in fact most of them had bacteremia with VRE. And then we had the bacteremia of unknown origin. Urinary tract infection, and of course, as I told you skin and soft tissue infection. But the point of this slide is that we had that same pattern of generally better outcomes with 600 over 200.

And this is the data for our interims analysis of 82 patients, again in a way you see a pattern of better outcomes with the high dose versus the low dose. If you look at patients from microbiologic outcome perspective and you compare linezolid 600 to linezolid 200 mgs, you'll see that this is a statistically significant difference with this p value associated with this comparison.

So you did have a better microbiologic outcome in our study of 145 patients if you were randomized to 600 mgs versus 200 mgs. Now in support of the observations we have here, you may have heard about our Compassionate Use Program which did not recruit patients, but physicians who had patients for which there was not practical therapy would call PNU and patients could be treated with linezolid, 600 mgs, twice daily for up to three months.

The patients that I'm going to report to you today on -- will be 230 patients that we collected in this Compassionate Use experience by June of 1999. To date we have more than 750 patients in the Compassionate Use Program.

When you look at Compassionate Use patients you won't be surprised that many of them were not culture positive or baseline, didn't have follow-up cultures, weren't worked up very completely, so the number of wholly evaluable patients we actually have is small. But if you look at the patients with intra-abdominal infections like peritonitis, liver abscess, the cure rate is noted here.

Patients with bacteremia are noted here, the patients with complicated skin and soft tissue here, and in general good outcomes with all of the patients that were clinical evaluable had received at least ten days of therapy and had microbiologically proven VRE infection.

So in conclusion, we feel that linezolid 600 mgs, twice daily is effective in the treatment of vancomycin resistant enterococcus. And we feel that out two comparative trials, which by the way are the largest comparative trials of VRE infection to date.

We did see a persistent and consistent improved outcome in patients randomized to 600 versus 200 mgs. And we think our Compassionate Use Study

supports the results of the dose comparative study very well.

Now in terms of efficacy, we've shown efficacy in community acquired pneumonia and in nosocomial pneumonia. We've shown good efficacy in skin and soft tissue, both complicated and uncomplicated and we've shown efficacy in MRSA infection and VRE infection. I'd like to turn to resistance surveillance.

The clinical trials the we've performed were organized in a fairly traditional fashion. All organisms isolated at baseline were sent to a central lab, every failure that resulted in a positive culture at follow-up was sent to that central lab.

So we've had very good data concerning MIC creep, resistance of development to linezolid in our clinical trials. We've treated more than 3,000 patients in the past few years with linezolid at full therapeutic doses and we've identified no staph species, whether we're talking about a coagulase positive or coagulase negative staph that has become resistant to linezolid. There has been no four-fold

change in MIC in any isolate.

We've identified 15 patients who had isolates with the four-fold elevation of MIC at follow-up out of 832 patients of enterococcal infection.

Where did the patients the patients come from? Well, we identified one patient in our first study of a 145 patients and in the second study, of a 186 patients with VRE infection, we identified five isolates enterococci that became more resistant, four-fold resistant at the end of therapy. And in Protocol 25 our Compassionate Use Program, 501 patients had been exposed and treated with linezolid for their enterococcal infection and nine resistant isolates were found.

When we looked at all of the cases we had three stories that kept coming again, and again, and again.

Number one. Patients had in-dwelling prosthetic devices. Left ventricular assist device, in-dwelling catheter that couldn't be removed, intra-abdominal devices that couldn't be removed. Or we had

undrained abscesses. We had intra-abdominal abscesses, we had abscess that could not be removed because of the surrounding dwelling device, or we had also a fair number of patients randomized to this 200 mgs of linezolid twice daily.

Now I would like to turn to the safety information that we have been able to collect in our phase III trial. Could I go back one slide? Okay, thank you. I must have changes my lecture over night. Next. Go forward please.

The safety data that I'm going to be discussing is based on three ideas. Number one. That it -- when we went into development, when we started this program, we knew from our preclinical work that the drug was a mild reversible inhibitor of monoamine oxidase.

We also knew that when we pushed the dose of linezolid high enough we could get transaminase abnormalities, when we push the dose of linezolid high enough we could get trans-hematopoietic suppression.

In every experiment when we did that, we found rapid reversal of the abnormality when the drug

was stopped. So we went through our phase III program specifically looking for the signals that we saw in these early studies.

What is a monoamine oxidase? How do you look for it? Well there are two classical syndromes associated with potent irreversible MAOI drugs, like the classic anti-depressants, Nardil. It's been associated with side-effects when a serotonergic agent is given. A serotonergic agent would be a common cough suppressant like dextromethorphan.

When these drugs are given together you can get fever, confusion, hyperthermia, with flushing, you can get hypertension. You can get tachycardia. And that's called the serotonin syndrome.

There's another classical syndrome that's called the adrenergic syndrome, or the tyramine syndrome. Where you get hypertension and you can get very accelerated hypertension. We've shown in the experiments that follow that linezolid is a weak, is not irreversible, very revisable MAOI inhibitor.

So let me share with you some of the phase I trials that we did. We used the classic

dextromethorphan as a serotonergic agent drug. We treated patients with linezolid and dextromethorphan, 20 mgs, every four hours. We found no change in temperature, blood pressure, no cognitive difference. It was a negative study.

In another phase I trial we treated patients with linezolid in tyramine. And we found that that it required more than a 100 mgs of tyramine to get a detectable blood pressure increase. Now to give you some reference, the typical glass of wine will have one mg of tyramine. The typical serving of blue cheese might have two milligrams of tyramine, the typical elaborate blood sausage might have ten mgs of tyramine.

So we feel that no diet would give you a 100 mgs of tyramine and feel that no food restriction would be necessary when using linezolid.

Next we turn to another study of concomitant medication where we treated patients with linezolid and phenylpropanolamine, or pseudo-ephedra. And what we found in these studies is that we could show detectable increases of blood pressure when used

these two drugs concomitantly. When we took our patients in the phase I unit and treated them with placebo, we could increase their blood pressure on the average of eight mm of mercury and we might have a range of seven mm of mercury. And when we treated them with linezolid we had essentially the same response that we got with placebo.

When we gave patients phenylpropanolamine, again we got an increase in response, it was just a little bit more than the placebo. When we used phenylpropanolamine and linezolid we had a detectable change from the placebo. Note that this range of blood pressures is still the range of blood pressures that you get in daily living. I would assume that my blood pressure is at least that high at the present time.

(Laughter.)

DR. HAFKIN: So -- it's not outside the normal daily experience when you do get concomitant phenylpropanolamine and linezolid.

Now what happened in our trials? When our phase II trials -- we were cautious, we warned our

physicians participating in the phase II trials to watch for the possibility of an interaction between MAOI potentiator and MAOI drugs, and linezolid.

So what did we find? We found that our investigators recruited 247 patients out of the 867 patients that were actually recruited to our trials that had some exposure to these -- either potentiator of MAOI effect, at least sometime during the treatment interval and they -- the investigators were trained to look for trends of hypertension, arrhythmia, what-have-you.

When we looked at the data we found that there were no adverse events attributable to linezolid in the phase II trial. Food restrictions were lifted by us in our phase III trials as result of learning that. We had been terribly harsh in our phase II trial, warning people against people against American cheese. Warning them against the most elaborate sort of diet, I mean you had to stay on peanut butter and white bread initially.

And when we realized that the protocol had recruited 247 patients that had potentially

interacting drugs and we had seen nothing, we were very relieved.

So in our subsequent phase III trials, all though we warned the physicians that the potential could exist, if somebody drank a full bottle of soy sauce.

(Laughter.)

DR. HAFKIN: The reality is that the patients any problems in our phase II trials, so we lifted those restrictions. There were no restrictions. And we lifted the restriction about MAOI, we said that if you have a patient that needs the therapy, you have to watch them. So there was a warning not only in the protocol, but in the consent form for the patient.

Well, what was our experience in phase III? We identified 632 patients that had linezolid and concomitant MAOI potentiator. Something that could potentiate the effect of the MAOI drug. And these are the drug classes realized in our trials.

Well, what did we find after we sliced and diced the data? We found, that well -- we had found

the 632 patients. We looked for adverse events such as hypertension, hypothermia, things like that.

We found 13 patients that have hypertension as an adverse event. Twelve of the 13 patients who have hypertension as an adverse event were felt by the investigators to have nothing to do with linezolid. One investigator felt his episode of hypertension was related to linezolid.

There was another experiment embedded in our phase III trial. We asked in Protocol 55 and 48 for investigators who were going to use MAOI drugs or potentiator of MAOI effect to take blood pressure before that drug was given and after that drug was given. And that follow-up vital sign was supposed to be within two, two and half hours.

Now it's a limited experiment, because most of our phase III investigators really didn't do that. But we have observations on about 100 patients here.

When you look at the baseline blood pressure for those patients who got linezolid, compared to the comparator, look at the post-treatment

with concomitant medicine blood pressure or the potentiator and the comparator. You see there is no difference in the pre and post-blood pressure results.

Here is the range of blood pressures noted in the experiment, here's the range of the comparator blood pressure. That's for systolic and the same is true for diastolic blood pressure. Again it was a small study. It was limited, but it was out there in the field and I was just going to say almost 100 patients were recruited into the trial and the data was collected in this fashion.

Now what are our conclusions in terms of mono amine oxidase inhibition? Well, we've proven in our preclinical and in our phase I unit that we do have a weak and reversible MAOI effect and in phase II and phase III we had 879 patients exposed to linezolid and a potentiator of MAOI effect.

We found one patient in whom blood pressure was attributed to the combination of drugs. We feel that the risk of MAOI effect is small enough that benefit/risk relationship for linezolid in clinical use is not effected.

Next I would like to turn to the traditional safety analysis that we do and for that I'm using every phase III comparative trial observation that I have, so we're including Protocol 55, the complicated skin and soft tissue trial, 39A, which is the large North American skin and soft tissue trial as an out patient, and then there is a smaller study that was carried out in Europe, Latin America, and Asia.

Where we used the same dose, the same protocol as the 39A along with our pneumonia trial and our comparator trial for MRSA. So all in all I'm taking 2,046 patients randomized and treated with linezolid and comparing them to 2,000 patients treated with comparator.

On this slide, this is one of two slides that I have, every AE that was reported in our trials with or without attribution to drug. And if you look at the most frequent adverse events reported they are typical for antibiotic trials. The typical nausea, vomiting, and diarrhea. The results are comparable for both of the populations.

Here's the continuation of the greater than two percent. AE presentation, we have essentially the same rates for both of the populations, linezolid and the comparator group.

When we look at drug related adverse events, these are adverse events attributed by the physician to be due to the drug being used. You see the same pattern of diarrhea, nausea, and headache for both linezolid and the comparators. Taste alterations, malaises are seen in comparable numbers, please note that this abnormal LFT is slightly lopsided with an increased number associated with linezolid. I'm going to share an analysis of more quantitative data in just a moment.

Looking at the common serious adverse events, these events are associated with the patients underlying illness. The infection that's being treated, not drug related in any of these cases. Turning to the laboratory assessment.

What did we do with the safety labs that we collected on these patients? Well, as always we did the mean standard deviation and there are no

difference between the experience linezolid treated patients and the comparator treated patients.

We also used regression analysis to look for differences between these populations and we found that linezolid wasn't any different than the comparator. The deed I'm going to show you is outlier analysis, hazard function analysis, and an extreme outlier analysis to assure you that there are really are no significant differences between the linezolid experience and the comparator experience.

If we look at patients that significant abnormalities in biochemistry, with typical liver function tests and the amylase, lipase, bilirubins, creatine and kinase. These are very comparable numbers, because we had the report of increased ALT in our adverse event profile.

Let me next go to the ALT analysis and show you what we did. This is called a hazard function, at least we call it a hazard function. Where the risk of the abnormal result is here, and the time that that result occurs is here in terms of days. Linezolid in the orange curve, the comparative it the

gray curve and we see no difference between these two hazard function for linezolid treatment over time.

Now this is every patient that developed a significantly abnormal liver function abnormality. And in this case we're talking about ALT, patients treated with linezolid. As you can see the great body of patients have low level ALT abnormalities, many of them fall to normal within the treatment period. This is the extent of ALT abnormality, this the baseline, this is the number of days of therapy, this -- from this point on is greater than 13 days. It's a complicated curve.

This green line is the switch from treatment to post-treatment and this is the follow-up period. As I was saying most every patient will have low level ALT abnormality and it'll fall down within the normal treatment period. A few patients went wildly up high -- up here. And of these patients, all of them have pneumonia and all of them came down shortly after therapy, without adverse events. None of them dropped out of the study. Indeed they all had lower lobe pneumonia, all except for one, who had a

right lower lobe pneumonia. He had a left lower lobe pneumonia and had a history of hepatitis and that's this one right here.

Let's look at the comparator now. It's the same pattern. There is no difference. We have the same story of transient increases in transaminase, wildly high and then resolved. And then these two patients, typically have right lower lobe pneumonia. We have the same dated presentation with baseline -- here. Treatment -- here. The green line demonstrating the post-treatment phase.

Lets's look at the hematologic indices. If we look at the red cell series or the white cell series, it's really no difference between linezolid and the comparator. There may be a difference here in the platelet count, so let's investigate that with more care.

When we look at linezolid treated patients, the orange line and compare it to the gray line, the comparator, you see that there's no difference until you get to 16 days when there seems to be a divergence. This divergence represents almost

one percent of patients. And it represents about 16 patients, so the difference between this line and this line is 16 patients.

What's happening in the patients treated with linezolid? This is a time of analyst result curve, It's a bit complicated and I appreciate that this may be the first time you've seen something quite like this. What we did is, we plotted the patients individuals analyst over time. This is the baseline isolate and these are results of the various platelet counts through time and this is the first post-treatment day.

And you can see, I think, that the drop in platelet count in patients treated wit linezolid is slow. that most of the patients, about 50 percent, although you can't see it in this slide, because of the way we display it. More than 50 percent of the patients that actually had low platelet count on therapy, actually had low platelet count at baseline.

The patients rapidly increase in their platelet count post-therapy and this lowest of the low, this 19,000 platelet count patient had no

bleeding episodes and basically this patient's initial platelet count was here.

So they went from about 50,000 to about 19,000 on therapy. Let's look at the comparator. This is what happens in those patients that have significant platelet count abnormalities with the comparator. It's exactly the same curve. It is qualitatively identical.

So what do we conclude from our analysis of the platelet data? That we've found two risk factors associated with decreased platelet counts. One is that if you have a low baseline value, you don't get better with linezolid therapy. The underlying illness that caused the thrombocytopenia isn't affected by it.

We saw a slight increase in the risk of platelet counts dropping after more than two weeks of therapy, we've found that the decrease in platelet counts were mild, they weren't rapid, they weren't precipitous, and they were reversible. And we had no clinical consequences in any of the patients who had decreased platelets counts in our trial.

And finally, what do we have to say in terms of the safety of linezolid therapy with 600 mgs for up 21 days? Well, the common side effects were the ones you've associated with antibiotics everywhere, diarrhea, nausea, and headache. There is no clear association between adverse events and the use of concomitant medication.

We didn't see a pattern that demonstrated a monoamine oxidase inhibition caused clinical detectable adverse events. Changes in platelet events were mild and transient and frankly we're not sure if it's related to linezolid therapy.

Well, I'd like to ask Dr. Don Anderson to come up and report to you on our early pediatric observations. Thank you.

DR. ANDERSON: Good morning. I'm proud to have the opportunity to speak briefly to you today about the development and our progress in the development of linezolid, specifically for children.

Pharmacia and Upjohn's commitment to the earliest possible development of both oral and intravenous formulations for pediatric use is

certainly justified and for several reasons.

It is self evident to the pediatricians here today. An unmet medical need in children is clearly not less urgent than in adults, historically, that has always been true. Gram positive bacteropathogens are of major importance in children in the emergence and continued emergence of PRSP, MRSA, VRE are of serious concern in the pediatric community.

Currently few safe and effective therapeutic options exist in the setting of infections due to suspected or proven resistant gram positive pathogens. Some cases there are actually no options as reflected by our experience in the Compassionate Use Protocol 25.

We believe that a critical need exists, even now for alternative I.V. and oral agents for management for serious infections in both healthy children in high risk pediatric groups, including neonates.

Linezolid is remarkably well positioned to address these concerns. This is true, not only

because of it's spectrum of anti-microbial activity but in addition to other attributes. Among these include its potent bactericidal activity for pneumococci, an activity for virtually all isolates studied throughout the world.

In addition, opportunities exist here for flexible dosing regimes, such as the I.V. to oral switch. So for these reasons it is appropriate for the committee to consider even for a few minutes our experience and progress in use of linezolid in children by this sponsor. We do not seek specific indications today.

You can bet we'll be back to do that, but we want to assure the advisory committee and the pediatric healthcare community that we will carry out the requisite clinical trials to make linezolid available for children soon after it's registration.

So our pediatrics program to date has included phase I pharmacokinetic studies in patients ages 3 months to 17 years. Planned studies will include pharmacokinetic assessments in all age groups, including neonates, to define optimal dosing

requirements.

Two phase II studies focused on pneumococcal disease have been completed. These included population pk, safety and efficacy assessments in children with community acquired pneumonia and acute middle ear disease. Linezolid use in children in our Compassionate Use Protocol has provided some encouraging experience of systemic VRE infections.

Enrollment in this program, as Dr. Hafkin indicated continues to increase, to allow linezolid treatment in pediatric patients with essentially no other therapeutic options.

Finally, a phase III study has been carefully planned together with the Food and Drug Administration and is very near implementation. Comparative pharmacokinetic data from these pediatric trials has revealed that the clearance of linezolid when adjusted for body weight is inversely proportional to age.

Higher clearance in this inverse relationship is especially apparent in patients less

than five years of age, in which optimal dosage requirements will require further definition.

In children five years of age or older, receiving 10 mgs/kg oral doses, twice a day, the steady state values for clearance, volume for of distribution and elimination half-life are similar to those for adult patients.

Now the designs for two completes phase II studies are shown here. A dose of 10 mgs/kilo given BID was selected for both based on phase I data. These were open label, uncontrolled studies. The primary objectives of which included the accrue of pharmacokinetic and safety data in exposed children.

Populations were selected, however, in an attempt to target pneumococcal infections. These included seriously affected and hospitalized patients with the community acquired pneumonia, this was Protocol 45. In patients with acute otitis media enrolled at investigative sites with a high prevalence of antibiotic resistant pneumococci and with an emphasis on previously treated and refractory disease.

Now since the clinical and microbiological

outcomes of these trials were not compared or controlled and because the results are described in detail in the brochure that you've already reviewed, I will only indicate this morning that we are very encouraged with the over all results especially with the management of severe pneumococcal infections, including those due to PRSP.

The safety analysis in these studies included assessments of adverse events, chemistry, and hematologic safety studies, and vital sign determinations. Overall, both I.V. and oral formulations of linezolid were well tolerated in these pediatric populations. As shown, gastrointestinal symptoms and nonspecific skin eruptions accounted for the most common drug related adverse events reported in these studies.

Overall, however, these were of mild intensity, transient and self limiting. Only four of 143 patients in these two trials were discontinued from the study because of adverse events considered to be drug related by their investigator. All reported serious adverse events are summarized on this slide.

So this is the worst case scenario over the entire safety profile. These included one example each of bronchiolitis, convulsion, neutropenia, pneumothorax, and vomiting.

Among these the occurrence of neutropenia and vomiting was the only basis for discontinuation of linezolid treatment. All serious adverse events were self limiting and only one, the example of neutropenia, was considered to be drug related by the enrolling investigator.

So in summary, the results of our preliminary studies in children are very encouraging to us. They certainly justify our plans to conduct more definitive studies as part of a phase III pediatric program which is near implementation. Completed pharmacokinetic studies to date suggest that a dosing regime of 10 mgs/kg BID in children five years of age or older approximates the pharmacokinetics and exposure in adults receiving 600 mgs BID.

Further, pharmacokinetic studies are underway to define the appropriate dosing regimes

under five years of age including detailed studies in term and pre-term neonates.

In closing that Pharmacia and Upjohn will certainly develop linezolid with the unmet needs of children in mind, we don't have all of the answers, but we will pursue these aggressively because children as well other patient groups deserve the benefits of this unique and very exciting agent. All of us at Pharmacia and Upjohn look forward to working with the FDA and committed pediatric investigators towards the achievement of this goal. Thank you for your attention.

Now I would like to introduce Dr. Gary Tarpley once again, who will make some concluding comments and restate the indications for which we seek approval today.

DR. TARPLEY: Over the past hour you've heard quite a bit about linezolid. In closing I'd like to briefly review a few of the salient facts.

There is an important unmet medical need treating Gram positive bacterial infections, and our current antibiotics have significant limitations.

Linezolid addresses many of these limitations. It has a very broad Gram positive coverage and a unique mechanism of action.

Our clinical results indicate that linezolid is effective in treating Gram positive bacterial infections and that it has important advantages, such as it's favorable PK profile and multiple dosage forms.

Linezolid was also well tolerated in this patient population. Overall linezolid has a very promising safety profile. The extensive clinical results presented today support the use of linezolid in patients with known or suspected Gram positive infections.

As I've indicated, we expect that linezolid therapy will be initiated principally in the hospital or institutional care setting, and that it will provide the needed flexibility and the clinical management of these serious infections.

Our studies have demonstrated significant clinical benefits of linezolid administered at doses of 400 or 600 milligrams twice a day to adult

patients. The data presented today strongly support approval of linezolid for the following indications shown here, and we seek the committee's concurrence that linezolid is effective and safe in the treatment of these infections.

Thank you for your attention. That concludes our presentations, and we'd be happy to answer your questions.

CHAIRMAN RELLER: Thank you, Dr. Tarpley, and I'd also like to say that it's been most helpful to have such a comprehensive, clear, sharply focused and superbly organized presentation from Pharmacia/Upjohn.

The data, the issues presented by Pharmacia/Upjohn are now open for committee questions. Dr. Norden.

DR. NORDEN: I'd also add my compliments on the presentation. I have one concern, and that's the two metabolites that you have. In terms of your recommendation for no addressment of dosage of patients with renal failure, one, what do we know about the toxicity of the two metabolites, and, two,

what do we know about their potential at high levels to interact with MAO inhibitors.

DR. TARPLEY: I'd like Dr. Jungbluth -- is this on? Thank you -- I'd like Dr. Jungbluth to address that question from our clinical pharmacology group and then Dr. Slatter from our toxicology group.

DR. JUNGBLUTH: Gail Jungbluth from Clinical Pharmacology.

First, to address your question on the no dose adjustment, I'd like to go back to the linezolid pharmacokinetics in renal impairment to show why we feel that is necessary.

Could I have this slide on, please?

This graph shows a single dose studies in patients with varying degrees of renal impairment in its linezolid plasma concentration versus time curve, and you can see that regardless of renal function, similar concentrations are achieved of linezolid, and this is why we feel that no dose adjustment is needed in order to maintain parent linezolid concentrations.

And the linezolid metabolites do accumulate in renal impairment. We have found this in

the single dose study. Because of this finding we evaluated the two primary metabolites and have found that in patients in the severe impairment group and the anuric patients do accumulate, and the patients with moderate impairment do not have a significant accumulation of these metabolites.

So we evaluated these in multiple dose setting using patients in our compassionate use study.

The next slide, Dennis.

As I said, our single dose data indicated accumulation of these metabolites, and we then evaluated multiple dose data in patients with severe impairment with serum creatinines of over four or a creatinine clearance estimate of under 30 mLs per minute.

What we have found is that these levels plateau during one week of dosing, and our data up to four weeks of dosing shows no additional accumulation of these, and we have also found that linezolid metabolites are removed by dialysis.

I think another of your questions is what do we know about the linezolid safety and MAOI

potential, and Dr. Greg Slatter will talk about the MAO.

DR. SLATTER: Hello. I'm Greg Slatter from Drug Metabolism Research.

We have investigated the MAO inhibition potential of linezolid and its primary metabolites.

Slide up please.

We've used human MAO A and MAO B in a specific enzyme kinetic assay. Here you see the results for linezolid. The KI for MAO A, which mediates the pharmacokinetic drug interactions of hypertension, et cetera, is 56 micromolardeaths. The KI of the two major human metabolites, first the minor metabolite 20-fold higher at 1.1 millimolar, almost too slow to measure, and this one about threefold higher at 147 or at 1.47 -- 147 nanamolar -- 147,000 nanamolar. My apologies.

So the MAOI potential of these two agents against MAO A are significantly less than the parent drug linezolid, it itself being a mild competitive reversible inhibitor.

DR. HAFKIN: And finally, if you don't

mind, I'll share with you some of the clinical data that we have in patients that receive linezolid. In our Phase III trials, we did not exclude patients that had renal insufficiency. We recruited patients of varying renal insufficiency, and we've taken and put to these tables the most severe, patients that had serum creatinines of four or greater. The greatest serum creatinine in this small subgroup of patients was 12.

Could I have S-194, please?

And if you'll look, we've identified 17 patients in the Phase III clinical database that received linezolid and had very high serum creatinines and 15 comparator agents. As you can see, the typical therapy was about ten days. The ITT population is generally the same size. The numbers of patients with adverse events in either one of these small observational groups are small. I mean, we have, you know, only a small number of patients this sick would not have some adverse event.

If you look at the number with drug related adverse events, we've got comparable numbers.

The number of serious adverse events, they're comparable. If you look at the number of deaths or adverse events leading to discontinuation of the medicine, they're also very comparable.

Go to the next slide in this series.

Looking at -- this will be fine, 197, please -- if you look at the specific medical term for the adverse events, you see there is really, I mean, because the number of patients is so small; they are really very comparable. The adverse events like infection and sepsis are the underlying illness. The other adverse events are rare and not properly related to anything concerning the drug.

Could I have the next slide, please, with an extension of this slide?

Again, the serious adverse events that were seen for the linezolid and comparator are very similar in the sense that there's no pattern. There's no signal.

The only additional line of evidence I have to answer the question how safe is linezolid in this patient population comes from our compassionate

use trial. If we look at the database of the first 230 patients we have reported to the FDA and FDA has had a chance to look at, you'll find 34 patients with very poor renal function, estimated creatinine clearance of less than 30 milliliter per minute.

When you look at those patients and you compare them to patients with renal insufficiency that is mild, there is no different -- or renal insufficiency that is normal, there is no difference in the pattern of serious adverse events for these populations.

And in the compassionate use trial, we have patients that have taken the drug for up to three months who have nothing but an occasional dialysis. So we're not implying that this is an adequate safety database to assure safety, but what we feel confident is that there's no clear signal of increased toxicity.

CHAIRMAN RELLER: Dr. Murray.

DR. MURRAY: Barry, with some of the data from the FDA, it would look like one of the pedalites pedialites -- and with a three times less inhibition of an MAO you still might expect that. So how would

you address that?

DR. HAFKIN: Yes, we agree with you, Dr. Murray, that the way to deal with this is to share with the physician the lack of information that we have and the fact that efficacy safety in this small population group can't be spoken to as clearly as for those of the primary database.

So we agree with you totally that it should be a labeling issue.

CHAIRMAN RELLER: Yes, Dr. Christie had a question. Go ahead.

DR. CHRISTIE-SAMUELS: I think it's more to that, when you have some details regarding antibiotic trials in children to look at.

My question, however, I noticed that in one of your slides you said about 12 to 80 percent of your -- trials have -- cough suppressants but really I wondered, bearing in mind that children -- from taking over-the-counter drugs, cough medicines while being treated for community acquired pneumonias and other respiratory tract infections.

I was wondering about the immune

inhibitory effect, and if this was of value to the prelim trials. If so, what did you find? What were your preliminary findings?

DR. TARPLEY: So your question is the mono amine oxidase inhibitory effects as they pertain to the pediatric trials?

Thank you.

DR. SLATTER: Thank you for the question.

Could I have slide K-21, please?

In fact, many patients in the pediatric trials were on medications with MAOI potential effects and interactions. The answer to your question -- I'm sorry. Can you hear me?

The answer to your question, however, is that you've seen the safety profile. There were no adverse events that would reflect significant clinical consequences of MAOI inhibition. Clearly the pediatricians enrolling were alerted, and of course, discussion in the protocol indicated this potential effect. There were no examples of hypertension, no examples of hyperthermia, no examples that would suggest an adverse event related to an MAOI effect in

the entire study population.

CHAIRMAN RELLER: Dr. Leggett.

DR. LEGGETT: Back to the question about the dialysis of --

DR. TARPLEY: Dr. Jungbluth.

DR. LEGGETT: --

DR. TARPLEY: I'm sorry. I think we got the first question, but we were unable to hear. Maybe we could deal with the first question and you could repeat your second.

The first question, I believe, related to the method of dialysis used in the studies.

Thank you.

DR. JUNGBLUTH: And I think there was an additional part of your question on whether the elimination of the metabolites was similar. From the single dose data that we have in the renal impairment study, the metabolites appear to be reduced to the same extent as linezolid, and that's about 30 percent of the dose.

And we did not have specific information on what dialysis membranes were used in that study.

DR. LEGGETT: And the second question was did you see any more severe hepatic impairment patients in the case of study?

DR. TARPLEY: Again, let me repeat it just to make sure I'm answering your correct question. Did we treat any severe hepatic impairment patients in the compassionate use program?

DR. LEGGETT: Or the entire program?

DR. TARPLEY: Or throughout the entire program.

DR. HAFKIN: Unfortunately we did not have any of those patients recruited into any of our Phase III trials. They weren't specifically excluded.

However, I should say since I think the audiovisual is off, I'll try to yell.

(Laughter.)

DR. HAFKIN: The compassionate use, we had some very, very sick patients who got linezolid for short periods of time. Those people with dreadful hepatic function were typically patients who had very profound infections in their interabdominal cavity, and they were really going down fast. They didn't

even survive five days.

We have no reason to believe they died because of the drug. They had fulminant infection. So there were one or two observations with people who had just interabdominal catastrophes who had no renal -- no hepatic function and no renal function, and they received a couple of days. We had one child, in fact, like that.

But there was no pattern of adverse event that would have suggested a signal.

CHAIRMAN RELLER: Dr. Wittes.

DR. WITTES: I actually have a series of -- can you hear this?

DR. TARPLEY: Yes.

DR. WITTES: A series of questions related to design and statistics. First, it wasn't only just factual. The first is I don't understand. The total number of patients who are listed in the slide for almost every study was considerably larger than the number even in the IIT, and I assume that means that there was a group of people who didn't get any drug. Is that right?

And what was the mechanism by which somebody gets randomized and not in the IIT?

DR. TARPLEY: Dr. Oliphant from our Biostatistics Group will answer the question.

Thank you.

DR. OLIPHANT: Dr. Wittes, Tom Oliphant, PNU biostatistics.

I believe your question is what differentiates the patients randomized from those who were included in the ITT analysis populations.

Slide on, please.

Here we see for the Phase III studies for both linezolid and comparator the number of patients randomized, and those included in the ITT populations, and I believe the numbers, total numbers, range from about zero as you see in Study 54(a), all patients randomized were in the intent to treat population. For a couple of the studies it was as high as ten or 12 patients who were randomized but were not included in ITT.

The ITT population is basically those patients who were randomized and did receive at least

one dose of study medication.

DR. WITTES: Okay. That's very helpful. My calculation showed bigger differences. So that's what I needed to see.

Can I --

CHAIRMAN RELLER: Please continue.

DR. WITTES: Okay. The next one has to do -- the next question really has to do with historical controls. Are there any data that would give a sense of sort of an anchor of what you would expect in an untreated population for cure rates?

And I know it would vary from indication to indication.

DR. HAFKIN: I suspect you're interested in the VRE historical perspective.

DR. WITTES: Well, no, actually I'm more interested in the others.

DR. HAFKIN: Oh, well --

(Laughter.)

DR. HAFKIN: -- in that case, I believe that the performance of the comparator agents in our comparative trials, our control trials are very

similar to the results that other companies have used in their comparator trials. So that if you look at --

DR. WITTES: No, I'm asking actually a different question. In untreated population, that's the question I'm asking.

DR. HAFKIN: Okay. I'm sorry. Untreated controls.

DR. WITTES: Yeah.

DR. HAFKIN: If you go back to the pre-antibiotic era for diseases like skin, soft tissue, and pneumonia, outcomes are really pretty good. It was rare for a calamity to occur after a skin and soft tissue infection, but it did occur.

The difference between the pre-antibiotic era and the antibiotic era is the time at which patients are feeling better, and that's something that the displays that we share with you are not sensitive to.

You get better from very severe skin and soft tissue infection with enough time in the great majority of cases. Osteomyelitis, life threatening sepsis did occur with regularity. You know, we're in

Washington. I believe President Wilson's son died of Staphylococcal bacteremia after stepping on a branch in the White House lawn, but that was a rare event.

And so that the great majority of patients with skin and soft tissue infection would with time and care resolve. The likelihood of a catastrophic complication was very real. It was relatively low. Actually there are people here that are much more learned in this area of the history of medicine than I, and if we might, we can ask one of the real world's experts to come up here and talk about it.

But pneumonia II would with time resolve in the great majority of healthy hosts. It did kill with great regularity elderly patient populations, and if you look at our out-patient study, we have fairly young people there, and so that the great majority of the patients randomized in 51, Protocol 51, would have been expected to get better with a long period of time.

However, if you look at 33 or 48, those patients would have very high mortality rates.

CHAIRMAN RELLER: Dr. Chesney.

DR. CHESNEY: My question has to do with the community acquired pneumonia and the penicillin intermediate and resistant strains, and on the materials we have before we came, on page 45 if I added up right, you have a total of 12 patients who did well with linezolid -- excuse me -- 16 patients, 12 of 16 did well. So four did not, and I was curious to know if this is your total information that is penicillin nonsusceptible information or if you have additional to what we have here.

DR. HAFKIN: Yes. Let me show you Slide 189.

This is an aggregate of all the data that we have, looking at linezolid performance in Phase II and linezolid performance in Phase III, and if you will note here, we have really excellent results with penicillin resistant Strep. pneumo. very comparable to the performance of linezolid in the treatment of typical Strep. pneumo. There really is essentially no difference.

This is the result for Staph. aureus and MRSA. Recall that the patient populations in the

Staph. aureus group are very different than the patient populations in the Strep. pneumo. group.

Slide off.

So we feel that we've got excellent activity, that the limited but real life experience of treatment of resistant pathogens is pretty solid.

DR. CHESNEY: Can I ask one question?

DR. HAFKIN: One other point I had forgotten to mention. There were five PRSP in pediatric age group patients, and they all were cured.

DR. CHESNEY: Why did you choose cefpodoxime as your comparator?

DR. HAFKIN: Well, it's a wonderful drug.

(Laughter.)

DR. HAFKIN: We think it's under appreciated, and we think that we've shown in many studies that it's just a lovely drug. It's just not loved enough.

So in all honesty, it was available easily and quickly for us. We feel that it is equivalent to all the second generation cephalosporins available.

CHAIRMAN RELLER: Please continue the line

of questions and we'll come to the others here, Dr. Chesney.

DR. CHESNEY: This is my last. I don't mean to -- Group A strep., are these the total numbers that you have for Group A strep. infections on page 60? It shows us 23 of 29 for palpitated skin and soft tissue was successful.

DR. HAFKIN: Yes.

DR. CHESNEY: Which is 79 percent.

DR. HAFKIN: That's correct. That is our entire experience.

DR. CHESNEY: Thank you.

CHAIRMAN RELLER: Dr. Rodvold.

DR. RODVOLD: I had a couple of questions. Let me start with the efficacy question on Streptococcus pneumoniae. Can you tell us more about these patients in regards to the severity and/or their pathogethic oral component areas, in particular, the penicillin resistant bacteria?

DR. HAFKIN: The question, I think, is of these patients that we treated with Strep. pneumo. infection, we'll get the right slide. I want to get

that original slide that I showed. I think it was EP-138, was it? The original one where we have Phase II and Phase III together.

We have 32 patients in the linezolid treated group that had pneumococcal bacteremia in all of our trials. Protocol 51, which was the out-patient pneumonia trial, had very few patients. Most of them came from Protocol 33.

Yes, if you could put this slide up, 189.

So when we look at this, the population we have here with more than 150 Strep. pneumo. infections, only 32 of them on the linezolid arm were bacteremic. Every one of the patients treated with linezolid had resolution of the bacteremia. Two recurred. Let me tell you about those patients.

Patient number one was a patient with COL, was on active immunosuppression, and I don't know why that he stopped his therapy on day six. He looked great. He came back in two weeks with recurrent Strep. pneumo. infection. Unfortunately the second isolate never got to our central lab. So we were never able to understand whether it was recurrent

infection, recurrent bacteremia or whether it was a new infection.

The second story is the same story. It was an out-patient pneumonia trial. Protocol 51, a patient with AIDS, with very low CD-4 counts. He took the medicine for five days and he died. We don't know why he died.

So we have in this population 32 blood culture proven Strep. pneumo. infections. Both cases were associated -- both failures associated with short term therapy.

The comparator actually is associated with slightly more failures. Frankly, I haven't looked at them at the same level. I mean I'm one of those people that believes that you learn a lot from studying failures. The failures for the cephalosporin groups are actually slightly greater in number, number one; same number of bacteremias, about 30. They tended to be more complicated. The patients that failed with cephalosporins tended to be more associated with either short-term therapy as well, but also very resistant Gram negatives. So that these

patients at baseline would have Strep. pneumo. in the blood and then they would die with enterobacter or pseudomonas.

So there was one patient with recurrent bacteremia with Strep. pneumo., but so we don't have a clear picture of this. At least I don't have a clear picture of the cephalosporin failures.

DR. RODVOLD: But are the 12 isolates that are penicillin resistant for those patients?

DR. HAFKIN: We had no recurrent bacteremia.

DR. RODVOLD: And how many were bacteremia and how many of those were considered severe infections?

DR. HAFKIN: Well, yes. Five of them were kids. The additional population were all in elderly or very sick people. None of them came from our out-patient trial at all in adults. They all came from 33. These were all people who had to be in the hospital because their infection was severe.

I honestly don't think we did a cut of the analysis to see how many were bacteremic. I would

assume that we're talking about two or three.

CHAIRMAN RELLER: Please.

DR. MURRAY: I'd like to make a clarification because I'm a little confused. The sponsor has not presented us with data in a form or in a written indication that they're looking for an indication for resistant organisms.

On the other hand, FDA has given us that in their question. Do we think they're efficacious in each of these settings?

So I'm a little caught. It does not appear that the sponsor is asking for specific labeling for resistant pneumococcus or MRSA, and yet FDA is asking us to evaluate that. So I'd like clarification. We're not asking for that specific labeling.

DR. RODVOLD: Actually that's part of the reason I'm asking the question, is that in other presentations this committee has seen, some of the -- that was presented more clear, particularly the severe pain in bacteremic patients with insulin resistant isolates. So that's easier to see, and maybe you

could pull that data together yet today and let us see that in regards to helping us make judgment in the labeling.

CHAIRMAN RELLER: So, Dr. Chikami, could you --

DR. CHIKAMI: Let me just clarify what Dr. Hafkin said. What he showed on his slide for indications were the general sort of infection site indications. In fact, within the labeling the company is requesting specific wording for penicillin resistant Strep. pneumo., that is, infection due to Strep. pneumo. including penicillin resistant strains and infections due to Staph. aureus, including MRSA.

DR. TARPLEY: If I could just refer you also to page 6 of the brochure where the indications are listed and the pathogens associated with each of those indications are spelled out much more completely.

DR. CHIKAMI: Right.

DR. SORETH: It's on page 6 of your briefing document from the sponsor.

CHAIRMAN RELLER: To summarize the thrust

of those comments, I think the committee must elicit and ask all of the questions that the individuals would need to be able to address specifically the questions that we will vote on this afternoon.

And clearly, the issues regarding the resistant components of pathogens within the different indications is part of the task in which we will be asked to render advice to the FDA.

Dr. Wittes.

DR. WITTES: Yeah. I had three more questions in my series. Can I ask them?

CHAIRMAN RELLER: Please proceed with your questions, and bundling them is helpful to keep the continuity of thought going.

DR. WITTES: Yes. That's what I'll do. I'll put them all together and you'll see.

CHAIRMAN RELLER: They can be asked sequentially, but the related questions, we'll stick with the individual committee members so that we can round out the issue.

DR. WITTES: Okay.

CHAIRMAN RELLER: Please, proceed.

DR. WITTES: Well, then let me just tell you the series of questions and you can put them together the way you want.

The first has to do with definition of equivalence, that in many of the trials that you showed, it was pretty clear. You look at the lower end of the confidence limit. It's pretty clear that, you know, you wouldn't have -- whatever pre-defined definition you had, it would have satisfied it.

But in 48(a), it seemed to me that there was a very low lower bound, and I wonder whether -- how you, in fact -- whether you pre-define equivalence. How did it differ from indication to indication, and so forth? So that's question number one.

Question number two and three has to do with 54 and 54(a), and I actually was confused by the presentation today because it seemed different from what the briefing book said. My understanding from the briefing book was that there was a study whose name was either 54 or 54(a). You looked at the data early, reported that as 54(a), and then continued with

the study calling it 54, or it may have the labels wrong, and what we saw in the briefing book was, I think, only part of the rest of this 54, and there was going to be more.

That was my understanding. What my understanding today was that there was a preplanned study, 54(a), quite distinct from 54, and that what we see here is an interim analysis from 54, but I didn't see any discussion of what that interim means and what the alpha had and all of that sort of stuff.

So I need to understand what the study design is for the 54, 54(a) complex.

And the final question, which is, again, an overall question related to the studies, has to do with blinding. How much -- some of the studies are partially blind. Some are unblind; some of them are not, and some are blind, but the ones that are not where there's clinical outcomes, how much of the clinical outcome is subjective enough to be affected by knowledge of treatment?

DR. TARPLEY: Okay. Thank you.

Dr. Oliphant will start our responses on

the definitions of equivalency used, particularly in Study 48(a), and I presume he can also address the blinding issue.

Then we'll come back and try and clarify the Study 54. Is that acceptable?

DR. WITTES: Good, fine.

DR. OLIPHANT: Dr. Wittes, your question regarding our definition for equivalence, it was -- yes, it was study specific.

If I can have the slide on, please.

Basically as you indicated for most of the studies we had no problem meeting the requirement of the lower limit of the confidence interval exceeding minus ten percent. That was based on an assumption of 90 percent clinical cure rates in those studies.

The one exception was Study 48(a) where the assumption there was an expected clinical cure rate of 70 percent. So using sort of the guidelines in the FDA points to consider, their step function approach for what one should use for a delta based on expected cure rates, an expected cure rate of 70 percent translated to an equivalence margin of 20

percent. So for that study the lower confidence limit needed to exceed minus 20 percent for a declaration of equivalence.

Our next. Well, I'll address the next issue. You had a question about blinding and whether our outcomes were subjective enough to handle the fact that the blinding did differ from study to study. I guess I can best answer that by stating that all of the clinical outcome results that you've seen presented today are from a sponsor's clinical outcome, which was a generally conservative modification of the investigator's clinical outcome.

I can go through the various modifications if you'd like, but basically that was what we used for clinical outcome, was the sponsor's assessment, predetermined, done prior to breaking any blind; essentially involved sometimes downgrading an investigator's assessment of cure to failure or indeterminates, for instance, if not enough medication was received.

So that, I believe was our attempt to address any differences in blinding across studies.

Your third question regarding Study 54 and 54(a), I believe I'll let Dr. Hafkin begin to address that and may chime in if necessary.

DR. HAFKIN: The history of Protocol 54(a), the study that I called completed, was one of excruciating investment in time and effort. We had gone to more than 100 sites and had had the study up for more than a year, and our recruitment into the trial findings, solid clinical observations for VRE infections, were going badly.

We had been told by a couple of investigators that they simply didn't feel comfortable with the dose comparison design. We made the decision after more than a year in the field with this protocol that it was based on our need to know. We needed to know whether the design was working, whether the outcomes were going to be hopeful. We needed to know what was happening with this protocol in terms of patient outcomes.

We talked about this not only inside the sponsor's organization, but shared our intention to stop the study with the agency.