somebody either walks into the clinician's office with a community acquired pneumonia or when somebody comes into a hospital with one, and I think he'll have some reasonable observations to make.

In addition, we have three other experts' who have come along today to help enrich the conversation and help answer questions that you may have. Dr. George Drusano, professor and director in Albany, is here. He has been involved in the pharmacokinetics and the pharmacodynamic modeling of the data that's been derived from our clinical trials.

Dr. Charles Fogarty, Medical Director of Respiratory Therapy at Spartanburg, South Carolina, has been involved in clinical trial and actually produced cases that we have included in our presentation today.

And Dr. George Eliopoulis is here, Assistant Professor of Medicine and Director at Beth Israel Deaconess Medical Center at Harvard, because he comes with a wealth of experience in this field, and I'm sure he can help answer any questions you may have.

Finally, I'd like to remind you of our design to expand the labeling claim for levofloxacin. The highlighted words there are what we would like to

add to our current uses section of our labeling. It's the treatment of community acquired pneumonia due to Streptococcus pneumoniae, including penicillin resistant and intermediate strains.

So with that in mind, I would like now to hand over and start this substantial part of our presentation with Dr. Karen Bush.

DR. BUSH: Good afternoon. This afternoon I will be concentrating on the preclinical microbiological data that relates to levofloxacin, especially against penicillin resistant Streptococcus pneumoniae.

In my talk, I will be addressing the mechanism of action, the selection of resistant isolates, mechanisms of resistance. I will address some of the surveillance data very similar to some of the data that you have already seen, and briefly talk about the activity in animal models.

The overview of my talk indicates that we all have realized that penicillin resistance is increasing in Streptococcus pneumoniae, but high level levofloxacin resistance is slow to develop. It requires two mutations in topoisomerase and/or DNA gyrase, and these are unrelated to penicillin resistance mechanisms.

We have shown from our surveillance studies that throughout most of the world levofloxacin remains greater than 97 percent susceptible or the Streptococcus pneumonia isolates are greater than 97 percent susceptible to levofloxacin.

We have shown in vitro that levofloxacin is equally active against penicillin susceptible and resistant isolates, **and we will** show that it is efficacious in animal models predicting efficacy in humans.

Two of the major microbiological attributes of levofloxacin that we think contribute to its antibiotic activity indicate that this is a rapidly bacteriocidal agent. Time kill kinetics from Dr. Peter Appelbaum's laboratory indicate that there is no difference in time kill kinetics in Streptococcus pneumoniae regardless of penicillin susceptibility.

We show that there is a post antibiotic effect, again, that seems to be independent of the penicillin susceptibility of the organisms. The mean PAE is about two and a half hours.

These are all data that have been reported in the literature from Dr. Appelbaum's laboratory and also from data that we have internally.

If we look at the killing mechanisms that are required for beta lactems as compared to quinalones, we see that these are two unrelated mechanisms. Penicillins kill by inhibiting the essential cell wall synthesizing enzymes known as penicillin binding proteins or PBPs, whereas quinalones inhibit by one of two mechanisms or by both mechanisms, and that is inhibition of DNA gyrase.

In E. coli, this appears to be the primary killing target for quinalones, whereas -- or for levofloxacin -- and the inhibition of topoisomerase IV appears to be the primary killing target in Streptococcus pneumoniae.

Data that support this are reported for E. coli from Hoshino, et al., in 1994. Here we see that the IC-50 as determined for the topoisomerase IV activity and the DNA gyrase activity. The IC-50s are much lower for the DNA gyrase compared to the topoisomerase IV activity, indicating that gyrase is the primary target in E. coli.

However, for Streptococcus pneumoniae we see that in published data from Pan and Fisher, this is data on Streptococcus pneumoniae, topoisomerase, and DNA gyrase that was published earlier this year. A study was done with ciprofloxacin, sparfloxafin, and

clinafloxacin. However, levofloxacin was not included in this set of data. So we requested Dr. Fisher if he could generate this data for us to see how levofloxacin compared.

In the published study ciprofloxacin and sparfloxacin appeared to be using topoisomerase IV as the primary killing target compared to the activity against the DNA gyrase. Clinafloxacin appeared to have approximately equal **IC-50** values, as was seen in Staphylococcus aureus.

When levofloxacinwas tested in a separate set of experiments with ciprofloxacin and clinafloxacin as the comparators, again, ciprofloxacin appeared to have lower IC-50 value for the topoisomerase IV activity.

Levofloxacin paralleled the activity if ciprofloxacin, again, with a preferential inhibition of the topoisomerase IV activity. Clinafloxacin, again, appeared to be equal as it was in the previous studies.

In my talk today I will be using the current NCCLS interpretative criteria for defining susceptibility for penicillin, erythromycin, levofloxacin and vancomycin. The penicillin break points that we will be discussing, susceptible are

less than or equal to 0.06 micrograms per mL; intermediate, .12 to 1 micrograms per mL; resistant, greater than or equal to 2 micrograms per mL.

For levofloxacin, the break points are less than or equal to 2, 4, and greater than or equal to 8 micrograms per mL.

When we begin to talk about resistance, we see that the resistance mechanisms for penicillins and quinalones, as we would expect, are unrelated. Penicillins, the primary killing target is penicillin binding protein. The resistance mechanism that is operative for beta lactems is the incorporation of foreign DNA into the genes that encode the PBPs.

This results in lower binding affinities for beta lactems. In general, all beta lactems it was thought tended to parallel the activity of penicillins. We now know that there can be additional point mutations, such that there can be a differential in the binding affinities for the different beta lactems.

Quinalones havetargetmutations in either gyrase with the subunits of gyrA or gyrB, or in topoisomerase IV with mutations possible in either of the subunits for parC or parE. These are both chromosomal mutations that occur. They do not appear

to be related. It is not like Gram negatives where you can get plasma mediated linked resistances.

Recently there has also been an efflux mechanism that has been described for quinalone resistance. There are three different genes that have been named in the literature. At this point we don't know if some of these may be overlapping.

I'd like to talk about some of the studies that have shown the selection of resistance in in vitro studies using Strep. pneumoniae and various quinalones. This study, published by Fukuda and Hiramatsu this year in AAC, four of the quinalones that were examined included levofloxacin, ciprofloxacin and sparfloxacin.

The isolates were subjected to serial passages at one through 16 times the MIC, and the frequency of mutation was identified. At twice the MIC, levofloxacin had a measurable frequency of resistance of two times ten to the minus seventh. The other three quinalones in the list here had resistance that developed more rapidly than could be measured in this particular set of experiments.

At four times and eight times the MIC, no resistance was seen with levofloxacin that could be measured under these conditions, whereas even at eight

times the MIC with sparfloxacin there still was a very rapid selection of resistance.

In another set of studies using an in vitro model of Streptococcus pneumoniae infection, there was a study reported by Lacy from Charles Nightingale's laboratory, again, published this year in AAC.

This was a centralcompartmentmodelusing four Streptococcus pneumoniae isolates. It was a model that simulated the human pharmacokinetic parameters, and in the studies that I will show we will see a comparison of the pharmacodynamic profiles that have been compared for ciprofloxacin and levofloxacin.

In the data that I will be presenting, bacterial growth and susceptibilities were determined at 24 and 48 hours.

In this study, what I have shown here are the data for ciprofloxacin and levofloxacin, four strains of Streptococcus pneumoniae. Peak to MIC ratios for ciprofloxacin ranged from .5 to 4. AUC over MIC ratios for ciprofloxacin ranged from 3.8 to 28.

If we look at the initial MICs, these ranged from one to four for ciprofloxacin. The

studies were done in duplicate. So there are duplicate numbers for some of these.

We see the MICs at 24 and 48 hours. We see that in all cases, ciprofloxacin had an organism that was present with an MIC for cipro. of either four, eight, 16 after 24 hours; again, resistant isolates after 48 hours under these conditions.

With levofloxacin, the peak to MIC ratios ranged from 1.4 to 5.2. AUC over MIC ratios ranged from 14 to 55. MICs here ranged from one to four. These are fully susceptible. This is an intermediate strain.

After 24 hours, there was no growth with the first two sets of isolates. At 48 hours, there was no growth for the first three isolates. In the fourth isolate where there was growth, the MIC did not change from the initial isolate, indicating that resistant isolates were not being developed in this or not being selected in this particular set of experiments.

In a third set of studies looking at the selection of resistant isolates in an in vitro model, this is a set of studies from Peter Appelbaum's laboratory. There were ten different Streptococcus pneumoniae isolates that were examined. Serial

passages were done at sub-MIC levels, and the strains were passaged until a resistant isolate was identified.

The data I'm presenting are for ciprofloxacin and levofloxacin. As you can tell, in all of the ten strains, resistance developed more rapidly when ciprofloxacin was the selecting quinalone compared to levofloxacin, and in some cases you can see there's a very dramatic differential between the two agents.

When resistance develops, as I mentioned before, it can be due either to changes in the DNA gyrase in either gyrA or gyrB, or in topoisomerase in parC or parE.

In the study from Fukuda and Hiramatsu, this is an in vitro selection of strains. There was a set of analyses done showing that **a** single mutation in gyrA of either the serine to athenoalanine or a tyrosine did not alter the MIC for levofloxacin.

A single change in parC at either serine 79 or aspartic acid 83 resulted in a one dilution increase in the MIC. All of these are in the susceptible range.

In a study reported by Jorgensen and Tennover, again, this year in MC, there was a series

of clinical isolates that were analyzed for mutations in either gyrase or topoisomerase. In this set of studies there were attempts to find mutations in gyrA, gyrB, parC and parE.

Again, in the clinical isolates with a single change in parC, the MICs for levofloxacin were in the intermediate range, not in the fully resistant range. Double mutations in gyrA and parE or gyrA and parC gave higher MICs that now were in the fully resistant range.

So it appears that a single mutation does not give us a fully resistant levofloxacin MIC. It takes two mutations or more.

I had mentioned that there are efflux mutants that are now known to exist. This is a study from Zeller that was reported in 1997. There were a set of -- two sets of isogeneic strains reported in this particular study, one of which had an efflux pump which was defined as this FqA efflux pump, one which did not have efflux.

With ciprofloxacin, the presence of the efflux pump resulted in MICs that were elevated fourfold or 16-fold. Interesting, with ofloxacin, there was a fourfold or eightfold increase in MIC, whereas with levofloxacin there is only a twofold

increase in MIC in the presence of this efflux pump, suggesting that levofloxacin in the presence of efflux is not significantly affected.

If we move now into some of the surveillance data that we wanted to present, this is a slide very similar to that which was presented by Dr. Whitney. I've collected data from a number of different sources.

The major point that I think I'd like to reemphasize is that, again, penicillin intermediate strains began to be reported in the early to mid-1980s. Late 1980s we began to see some reports of macrolide resistance. By the time we got into the 1990s, macrolide resistance and fully penicillin resistant isolates, which are in the yellow here were definitely becoming very prominent in our surveillance studies.

These isolates are not only penicillin resistant, as was indicated by Dr. Whitney. There, again, is a strong multi-drug resistance character to the isolates, particularly those that are penicillin resistant.

As we look across the penicillin stratification from susceptible to intermediate to resistant, we see that with the beta lactems, with the

macrolides, and with trimetheprim sulfa in the fully penicillin resistant isolates at best we have 25 percent susceptibility.

This is based on data from the Internal Trust studies that I will discuss very shortly.

Thelevofloxacinsusceptibilityremains at 99 percent or better across the penicillin stratification, vancomycin fully susceptible as was shown by Dr. Whitney.

The Trust data that I referred to in the previous slide is tracking resistance in the United States today. These are studies that are sponsored by Ortho-McNeil Pharmaceuticals. They have been directed by Clyde Thornsberry. Dawn Sahm has been involved with this.

There have been three respiratory seasons in which surveillance has been conducted. 1996 to 1997 was the first respiratory season. Etest was used for the testing of the isolates. There were over 9,000 isolates in that particular study that were Strep. pneumoniae clinical isolates.

In 1997-'98 and '98-'99 thetestingmethod was microblot dilution. There were 98 common sites in the two years so that there could be a comparison of the change in susceptibilities over the same

hospitals. A total of 2,950 isolates in '97-'98 and almost 4,300 in '98-'99.

In a set of studies -- and I'd like to emphasize that the Trust studies are ongoing. We are not just stopping with these three years of Trust data.

In early surveillance data from other laboratories, we see that if we look at levofloxacin's susceptibilities compared to penicillin susceptibilities, that in these four studies in which there was a differentiation in terms of penicillin susceptibility, the MIC-50s and MIC-90s within a study remained constant regardless of whether the penicillin susceptibility was S, I, or R.

We see that there was no change in MIC-90s. In most cases we had almost 100 percent or 100 percent susceptibility. There was one study here where there were a few isolates greater than eight MICs.

In the Trust studies from the three respiratory seasons that I described previously, again, with stratification according to penicillin susceptibility, in 1996-'97, MIC-50s, MIC-90s remained constant across the various penicillin susceptibility stratifications.

In terms of percent susceptible, these were essentially the same numbers for all of the different stratifications. In '97-'98 and '98-'99, MIC-50s, .5; MIC-90s, 1. We see here that, again, there was 99.7 to 100 percent susceptibility in '97-'98, and in '98-'99 it's 99.0 to 99.6 percent susceptible.

If we look at the 25 levofloxacin resistant strains of Strep. pneumoniae in the last year of the Trust studies, this represented .6 percent of the 4,296 isolates that we had. These 25 isolates came from 18 out of 96 hospitals. Obviously no hospital contributed a major proportion of these isolates.

The hospitals that had the levofloxacin resistant isolates in 1997-'98 showed no resistance in '98-'99. Those hospitals that had resistant isolates in '98-'99 showed no resistance in '97-'98. Therefore, we did not see any clustering of levofloxacin resistance from the two years of these Trust studies.

Dr. Whitney addressed the paper in the New England Journal by Dr. Chen and Lowell and the Canadian Surveillance Network, and I'd like to give you a slightly different perspective of that study.

The first set of isolates from that study were reported in 1994-'95 respiratory season, reported in AAC in 1996. At that time, there were approximately 1,100 isolates that were identified.

In this particular population, there were four isolates that had MICs greater than four to levofloxacin. Total susceptibility was 99.6 percent to levofloxacin.

If we look at the latest data that were in the New England Journal article, there were 7,551 isolates, approximately seven times the number of isolates that were reported in this initial study. Twenty-five of these isolates were resistant to levofloxacin. Seventy-five of them were resistant to ciprofloxacin.

The paper that is entitled "Increase in Fluoroquinalone Resistance," as noted by Dr. Whitney, is based on ciprofloxacin MICs greater than four. If we look at the data for levofloxacin, the percent susceptibility has not changed from the initial reporting in this particular set of isolates.

We have conducted surveillance studies through the Trust studies throughout the world, and if we look at all of the countries, with the exception of Hong Kong, we see 99 to 100 percent susceptibility

throughout the world in terms of levofloxacin.

However, this study from Hong Kong that was reported last spring in AAC by Dr. Ho, et al., we have found out recently represents a clonal outbreak of ten isolates out of this 181 that are levofloxacin resistant. Overall, however, there is still a 95 percent susceptibility to levofloxacin.

So throughout the world we are seeing that there is still a very high susceptibility to levofloxacin.

Perhaps the question about the use of levofloxacin and the possibility of increased resistance is exemplified by these sets of data from Japan. This shows the number of quinalone prescriptions in Japan from 1993 to 1998. Levofloxacin began to be sold in 1994. Ciprofloxacin and ofloxacin were sold prior to that time. At this time levofloxacin is the largest selling quinalone in Japan.

However, if we look at susceptibility we see that there are still 99 percent of the Strep. pneumoniae isolates that are susceptible to levofloxacin even with the increased use of levofloxacin in Japan.

I'd like to finish by talking a little bit

about some of the animal models that have been done with levofloxacin and Streptococcus pneumoniae. What we see is that there have been a number of studies in which there were lower respiratory infections in mouse models. There have been at least four different studies in the literature showing that levofloxacin significantly decreased the CFUs in lung tissue compared to an untreated control.

The one study that I want to go into some detail about is a study by Vesga and Craig show that levofloxacin was efficacious in Streptococcal thigh infections.

In this set of studies neutropenic and normal mice were examined. There was one strain of penicillin intermediate Streptococcus pneumoniae and seven strains of penicillin resistant Streptococcus pneumoniae.

This is a set of isolates showing the dose response of levofloxacin that was administered every six hours against Strep. pneumoniae in the murine thigh model, again, reported at Vesga and Craig at ICAAC in 1996.

As you can see, there is a dose response that was seen both with the neutropenic mice and the normal mice.

Perhaps more important in this model was the pharmacodynamic examination of the data. Here we see a plot of the AUC over MIC and the drop in the log CFU per thigh at 24 hours.

The line that is drawn here represents a static effect, and if we look at the normal mice here, the static effect occurs at an AUC over MIC that is slightly higher than 20.

If we look at a more stringent set of criteria and use a one log drop, at this point the AUC of MIC is approximately 30. So we are seeing efficacy in this model with an AUC over MIC in the range of 20 to 30.

The implications of this for the human pharmacokinetics then show that in the static model an AUC over MIC greater than 20 should predict efficacy. In normal humans, the 24 hour AUC is 54.

If we use our MIC if two micrograms per mL, which is the break point for levofloxacin, then we see an AUC over MIC of 27, which is well within the range of the 20 to 30 that we had predicted from the mouse model.

Using an MIC of one, which is the MIC-90 from the Trust data, we have an AUC over MIC of 54.

The conclusion of the poster or of the

presentation at ICAAC was that levofloxacin would be effective against PRSP infections in humans.

So in conclusion then we see that penicillin resistance is increasing. High level resistance requires two mutations that are unrelated to penicillin resistance.

We see a slow development of resistance compared to ciprofloxacin. We see greater than 97 percent susceptibility to levofloxacin in most of the world. Levofloxacin is equally active in vitro against penicillin resistant and susceptible Streptococci.

And in murine models with penicillin resistant Strep. pneumoniae, we see efficacy with an AUC over MIC ratio of greater than 20, and I think this is a good point for me to lead into Dr. Corrado, who will show that these predictions will hold out as we go into our human model.

DR. CORRADO: Thank you, Karen.

I think probably I'd like to begin by reviewing a little bit about the history of these organisms, penicillin resistant pneumococci.

They were first described in Papua, New Guinea in 1967. I think most of us were ignorant of this at the time, but our eyes really were opened wide

and raised our eyebrows when we heard about the cases that came out of South Africa in the late 1970s from gold mines.

And at that time I think all of us were kind of hoping that this was going to be a novelty. It would go away. Strep. pneumo. was supposed to be a behaving son that we could deal with. We understood it.

It wasn't the case because in the '80s it became very apparent that in Europe there was a clear increase in the reporting of these organisms, and at that time I think we knew it was just a matter of time when it would be in North America. We just hoped it would take a little bit longer period of time.

And as you've heard today, in the early 1990s we began seeing fully resistant pneumococci in the United States, and in the mid-1990s to late 1990s, these have been increasing steadily.

The fact is that penicillin resistant Strep. pneumoniae lives among us, is pathogenic, and we need to consider our therapeutic options.

Why consider levofloxacin? Well, as you've heard, the overwhelming percentage of pneumococci have remained susceptible to levofloxacin after 15 years of quinalone use in this country.

There is no mechanistic linkage between susceptibility to penicillins and quinalones with respect to pneumococcus, and it is potentially true that use of Levaquin could decrease the amount of vancomycin we need to use for these organisms with an attendant benefit there.

Finally, the use of levofloxacin, because it is completely bioavailable when given orally, could decrease the number of hospitalizations, and at first blush, the benefit that could be derived there would be by decreasing hospitalizations, we decrease the burden of cost on the community.

But there's a second one. Pneumococci can be nosocomial pathogens, and to decrease the number of fully resistant pneumococci coming into the hospital could decrease nosocomial transmission among our most debilitated people.

What I'd like to do for you today is discuss the data for levofloxacin the way I would like to hear it in the information as regarding four distinct areas.

One, what is the pharmacokinetic profile? That's important because a drug needs to get to the site of infection and it's got to carry a big stick. If it doesn't get there in sufficient amount of

quantity or activity, it's not going to be credible.

Unfortunately, I can remember using drugs like colistin for therapy of Pseudomonas aeruginosa pneumonia, a drug that stayed in the vascular tree, but didn't get into the lung tissue, and we had abysmal, high percentage of failures with Pseudomonas aeruginosa pneumonia. So the drug has to get to the site where the infection is.

Secondly, what is the intrinsic activity of the drug and what is the clinical data for resistance potential? Proof of the pudding is always in the eating. So we're going to share with you the data on efficacy from clinical trials.

And lastly, as important as any is the safety profile of the drug.

Now, I'd like to share with you at this time -- you may be wondering why I'm here since I'm not with the company. It's not just because I'm another pretty face. It's because I knew the data, and I've been around the block two or three times, maybe four times, and I remember a drug that I used frequently in the late '60s and the early '70s, cephalothin. It was a great drug at that time. It was a cephalosporin, and because I'm not the most brilliant guy in the world, I compartmentalize things.

I said I understand cephalothin, and this is a cephalosporin. Therefore, I under cephalosporins, and cephalosporins don't cross the blood-brain barrier. Well, I was wrong. We've become known that most cephalosporins cross the blood-brain barrier. Cephalothin doesn't.

I also became aware of the fact that if you use a beta lactem, you can select your beta lactemase elaboration, and I thought any beta lactem will do that, and I have some to find out that some beta lactems are much better at that than others.

And so within a class some drugs can engender resistance more and some drugs are distributed differently, and I think we need to look at each drug independently, and that's what I'm going to do for you now with levofloxacin.

And I'm going to do that first on the pharmacokinetic data. I'd like to show you data that you will see from the package insert of levofloxacin and from data published by Drusano, et al. These are the data that you frequently see quoted. They are data in normal, healthy male volunteers.

And what one will see is an average Cmax of about 6.4 micrograms per milliliter, an AUC of around 54 to 55, and a half-life of about seven hours.

It's important to look at these data because when you see the data that are used to predict pharmacodynamics from animal models, these are the data that are typically used to derive AUC to MIC ratios and Cmax to MIC ratios.

What we observe, however, in patients treated, in some 270-odd patients treated, is that the Cmaxes ten to be higher in ill people. The area under the curve tends to be larger as well, probably owing in some part to the fact that ill people are somewhat more debilitated, somewhat smaller in size, but also to the fact that creatinine clearances in these volunteers are up around 130 cc's a minute, and in these patients are less than that, 70, 90 and the like.

So we do see higher levels for Cmax in patients and higher area under the curve.

That's plasma data. What about lung tissue since the overwhelming majority of pneumococci, even for people who have bacteremic pneumococcal pneumonia, most of the organisms are in the lung?

Well, these are data from lung tissue from biopsy or lobectomy, and what the data show you, the red dots are lung tissue -- the yellow are the simultaneous plasma -- is that we tend to see

levofloxacin in about twofold higher levels in the lung than in the plasma, but these data are often criticized because the bacteria are not throughout the lung, and this is homogenized lung tissue.

What is the meaningful date? What about the data in the fluids that are bathing the broncho alveolar space? That's where most of the pneumococci are, and to some degree within the alveolar macrophage.

So to that end a study was conducted which shows the following data, and I think this is very interesting data to review. This shows you levofloxacin, and this trial took volunteers undergoing BAL, bronchoscopy, and a 500 milligram dose of ciprofloxacin was given twice a day, a 500 milligram dose of levofloxacin once a day, and after three days of therapy, bronchoscopy was performed, and these are the data derived from them.

Four hours after the last dose of ciprofloxacin or levofloxacin you see that the Cmax for levofloxacin is still higher owing to the fact that it has greater bioavailabilitythan levofloxacin.

Twelve hours later, however, the plasma levels of levofloxacin are still higher than those for ciprofloxacin at four hours.

The most important thing from this data is, however, I'm going to ask you to remember this number for ciprofloxacin, the average level at four hours being a little bit above two micrograms.

When we look at the endothelial lining fluid levels, we see that, in fact, for ciprofloxacin those levels are lower than the plasma levels at the same time, but for levofloxacin they're about twofold higher than the plasma levels, showing a differential distribution into the pulmonary tree.

Now, are the exact numbers of micrograms important? This is an n of four patients in each of these groups of 12 patients in each one. What's most important is the relative relationship from plasma to lung and from drug to drug.

We still see that levofloxacin has appreciably higher levels 12 hours after in this lining fluid than ciprofloxacin even just four hours after.

And in the alveolar macrophage, important because it's the obligation of macrophages to phagocytize pneumococci, but they are want to have large capsules and don't cooperate in their own death. So we want to know about the ability for these drugs to get into the alveolar macrophage, and quinalones do

tend to get into intracellular tissues quite well, but once again, we see this disparity for levofloxacin having significantly higher levels.

Now, these data you've heard already from Dr. Bush some of the information from the Lacy data. I want to show you a little bit more and describe other things that they found. Ciprofloxacin, levofloxacin, ampicillin, the four isolates. This shows you the peak to MIC ratio, the AUC to MIC ratio, and the number of organisms that were still viable in their hollow fiber -- using their hollow fiber technique at 24 hours and 48 hours.

We see for ciprofloxacin there was some growth for one of the isolates even at 24 hours and for three of the four at 48 hours, and we did see resistance develop in all four of these.

For ampicillin, an excellent drug for pneumococci, we see that at 24 hours there was a significant drop of three logs or more, and at 48 hours no growth. The detection ability here was **100** CFUs per mL.

Forlevofloxacinwe see similar reductions compared to ampicillin, and we see that for one of the isolates there was still continued reduction at 48 hours with a resulting MIC being identical to the

progenitor isolate, and in three of those, sterility, the detection here being a little bit better than for ampicillin, detection down to ten CFUs per mL.

And what we look at and see here is that the AUCs to MIC ratio associated with this appears to be somewhere between **14** and 29, as would have been predicated by the Craig data, and the Cmax to MIC ratio somewhere between 2.9 and **1.4.** Let's call it three for the sake of argument.

We know that for Gram negative bacteria the AUC to MIC ratio that's important appears to be at around 120. For Gram positives, such pneumococcus, that answer appears to be somewhere between 20 and 30.

We also know that as you approach four Gram negatives, 120 as a ratio for AUC to MIC, and for the Gram positives around 20, that the efficacy rate is exceedingly steep as you approach that number.

Furthermore, when you reach that number the continued efficacy begins to flatten out such that the difference for Gram positives in AUC to MIC ratio of ten to 30 is greater than the efficacy between 30 and 50.

Recalling then in our patients that an **AUC,** a plasma AUC of 72.5 was the mean, for organisms with an MIC of two, that is, the break point for

levofloxacin, we have an AUC to MIC ratio above 36, well above the 30s, certainly well above the 20.

We also recall that in the surveys, the large surveys, 90 percent of pneumococci have an **MIC** to levofloxacin of one. In our clinical trials, which I will show you in a second, at an MIC of one 85 percent of our pneumococci were at that MIC or lower.

And so if we look for 85 percent of the pneumococci, the ratio of AUC to MIC would be 72.5. The ratios of Cmax to MIC will also be, using an MIC of two, be approximately 4.4.

We can conclude then on the pharmacokinetics of levofloxacinthat it achieves very high plasma levels and that it achieves even higher intracellular and ELF levels.

Also the plasma AUC to MIC ratio for levofloxacin is in the optimal range, exceeding 30 for all pneumococci with an MIC or two or lower to levofloxacin, and that the **Cmax** to MIC ratio easily exceed those predicted to retard resistance.

I'd like to now go through some of the clinical efficacy data. These are the studies that were conducted and form the basis of the data **I** will be presented for you today.

There were three studies conducted in the

United States for the original new drug application. One of those was a randomized comparative trial, and two were open, noncompetitive trials.

In addition, there was a single, double blinded comparative trial conducted in Europe.

At this time, these were all conducted, as you will see, up to between the years of 1992 and '96.

Additional study was conducted, which was a large, prospective, noncomparative study to garner more data with respect to penicillin resistant pneumococci, and other studies in severe community, moderately severe to severe community acquired pneumonia were also conducted, two of which are randomized, comparative studies and one noncomparative study.

Before we get into the data, I think it's important to review some data by Campbell. Campbell looked at the risk factors for having a penicillin resistant pneumococci, and these are what Campbell reported, and these are well known to us.

Most of these were not restricted from the protocols that I've just shown you. However, there are some caveats I would like to apply for these four.

Subjects who had received recent antibacterial therapy were excluded from the clinical

trials unless they had received at least 72 hours of therapy and were clearly failing previous therapy.

Subjects who had HIV disease were not excluded unless they had CD-4 counts below 200. All children were excluded from our trials, and because we were studying community acquired pneumonia we excluded people who were hospitalized or recently discharged from the hospital.

And so there are some people who were at risk to penicillin resistant pneumococci that we did exclude from our trials for various reasons.

Here are the trials again, and they show you the number of subjects enrolled, and we enrolled over 3,900 patients in community acquired pneumonia. It shows you how many receive levofloxacin, about 3,000 of them; how many had a pneumococcus; how many of those were intermediate susceptible pneumococci; and how many of them were fully resistant.

We had hoped to obtain more. We didn't. It wasn't through lack of effort, I think you can tell.

What were some of the reasons that that may have occurred? Well, I've already gone through the fact that some patients who had risk factors for pen. resistant pneumococci were excluded from trials,

and certainly largest among those are the pediatric population where we see significantly more fully resistant pneumococci than in adults.

And the fact is that while 40 percent of our data was derived in the early to mid-'60s, only about 28 percent of our fully resistant pneumococci and 17 percent of our intermediate occurred during that time. So as we had gone out later into the '90s, we were accruing a higher percentage of fully resistant and intermediate pneumococci.

A little bit about our subjects. These are the demographics. As you can see, 41 percent were women. Thirty-four percent were over the age of 65, were 65 or older. The mean age, however, was 55, and the range in ages was 18 to 91.

Thirty-nine percent of the subjects enrolled were classified as having severe pneumonia as judged by the following criteria. If they had bacteremia, diastolic pressure of less tan 60, using pressors, alteredmentation, intubated andventilated, or had a baseline respiratory rate of greater than 28, any one of those criteria would have been judged to have been a severe cause of pneumonia.

Now, in the clinical trials what was the susceptibility of the pneumococci that we encountered

and how does that compare to what we've seen in the very large surveys?

Here are the data. This shows the cumulative susceptibility to levofloxacin by MIC for susceptible pneumococci to penicillin, penicillin intermediate, and the resistant pneumococci. There are 22 here because they also include organisms that were treated with a comparator.

And we can see that 85.7 percent of these organisms had an MIC of one or less and 99.7 percent two or less, almost superimposable on the survey data.

Furthermore, we can see that there is no difference in what the MIC is going to be to levofloxacin based on the penicillin susceptibility. Independent variables.

That's not true though in our trials for other drugs. This shows the percent that were susceptible to other drugs from among the isolates that were tested, and you can see that 50 percent of these fully resistant pneumococci were susceptible to erythromycin, 50 percent to azithromycin, 39 percent to clarithromycin, 50 percent to sulfa trimetheprim, and 28 percent to ceftriaxone, all of them being susceptible to levofloxacin.

We can, therefore, statethatpneumococcal

susceptibility to levofloxacin has been consistently high over the 15 years of quinalone use in this country. There is no mechanistic cross-linkage in resistance between quinalones and penicillins. Currently greater than 99 percent of pneumococci within the United States are susceptible to levofloxacin, and our clinical data and the survey data both support the contention that organisms that are penicillin resistant are just as likely to be levofloxacin susceptible as organisms that are fully susceptible to penicillin.

Now, all of the data that I'm going to be presenting to you here on efficacy is based on subjects who received a single 500 milligram dose of levofloxacin once a day. They either received it as an IV dose and then were converted to oral or received oral dose entirely.

Those who received IV levofloxacin typically received one to three days of levofloxacin therapy before conversion to oral levofloxacin.

These data showyouthe efficacy outcomes, both clinical and microbiologic efficacy based on susceptibility to penicillin. As you can see, there are 160 fully susceptible pneumococci to penicillin, and 155 of those were successfully treated with 155 of

the cases having microbiologic eradication, for a success rate of 96.9 percent both clinically and microbiologically. Among the intermediate there were 44, all of them successfully treated both clinically and microbiologically.

And among the 14 of 18 cases that were evaluable among the fully resistant pneumococci, all 14 were successfully treated.

Now, regrettably 34 cases had their pneumococci that were not tested to penicillin, but among those 34 all of them were successfully treated once again.

Ourtotalexperience then forlevofloxacin is with 252 cases of pneumococcal pneumonia and 247 of them were successfully treated.

Now, I would like to look at the database on severity as well. So what I've done for you here is broken down the data not only by penicillin susceptibility, but by severity of illness as well, and as you can see, for the fully susceptible, penicillin susceptible pneumococci, the efficacy whether in mild to moderate disease or severe disease is basically superimposable, and when we get into the intermediate resistant and those without susceptibility to penicillin, we see that efficacy is

uniform regardless of severity of illness.

The other thing I would like to see is what about the bacteremic cases. There were 55. Among the 55 that had bacteremic pneumococcal pneumonia, 29 of them had a fully susceptible pneumococcus, all 29 successfully treated; six intermediate; six fully resistant; and 14 with unknown susceptibility.

All 55 cases of bacteremic pneumococcal pneumonia were successfully treated. All 55 of them had their organisms proven to be sterilized based on repeat blood cultures at the test of cure post therapy visit.

If we were to review then the data for severely ill patients and bacteremic patients, we see 99 patients had severe disease regardless of susceptibility, 96 of them successfully treated for a 97 percent success rate, and among the subcomponent of these that had bacteremia, all of them successfully treated.

Let's look at the bacteremia cases in a little bit more detail. This shows you the age, the gender, the MIC to penicillin, the MIC to levofloxacin, and their outcomes. Only one had an MIC above two to penicillin. Several had MICs of two, and

we can see that they were all successfully treated, and again, their susceptibility to levofloxacin is entirely independent of their susceptibility to penicillin.

If we look at just the cases with fully resistant pneumococci, whether they were bacteremic or not, in a little bit more detail, again, we see the wide range of ages, pretty similar distribution in gender. These are the sites of infection, the MICs of the organism. Again, susceptibility is independent of the penicillin susceptibility, and all 14 of these successfully treated.

One of the questions I would want to know is you had five failures among the total population of pneumococcal pneumonia treated by levofloxacin where the failures were all at the breakpoint of two. Now, these are the data by outcome by MIC to levofloxacin, and you can see there were 30 cases with an MIC of two. All 30 of these were successfully treated. In fact, we had one failure at .25, one failure at .5, and we had three failures at one. So they weren't at two, and in fact, this is predicted by the animal data, pharmacodynamics.

An MIC of two gives you that optimal range. A Cmax to MIC of 4.4 and AUC to MIC of around

37, and because at that point it really flattens out, the probability of seeing a difference in outcome for organisms with an MIC of two or .5 becomes vanishingly less common to the point where it would take a huge study to see any difference between those.

So these data are predicted, and we are very confident that this represents what we would see if there were 100 cases that would be comparable in efficacy to these other MICs.

The clinical summary then would be that 98 percent of patients with pneumococcal pneumonia were successfully treated; that susceptibility in our clinical trials to levofloxacin is independent of penicillin susceptibility.

Response to levofloxacin therapy is independent of penicillin susceptibility. It's independent of severity, with 82 of 85 severely ill patients being successfully treated, and that in total, 247 of 255 cases were successfully treated with 500 milligrams once a day of levofloxacin.

All 14 of our fully resistant pneumococci were successfully treated, whichyou'dpredictbecause there's no bearing on the -- the penicillin susceptibility should have no bearing on levofloxacin efficacy, and in total, of that most important

population, the bacteremic, 55 of 55 bacteremic pneumococcal pneumonia cases were successfully treated.

Now, the first rule in medicine is "primam non nichere," and what I'd like to show you now is the safety data because the safety data is part and parcel with how a doctor chooses a drug. It doesn't benefit you much that one of the first things I learned in reading X-rays **as** a young house officer seeing these stippled pelvises of men and I learned that sometimes if you spend an evening with Venus, you spend a lifetime with Mercury, and we want to know what benefit we're doing with patients when we give them therapy.

So now I'll show you the safety data for levofloxacin. What I would want to know first is what are the adverse events I'd likely see with levofloxacin. To do that, what I'm now showing you are all adverse events considered by our investigators to be drug related that occur with a frequency of one half of a percent or higher, and there are a total of four.

This is any adverse event. These are the comparators, and I will share with you that the comparators are primarily beta lactems with a

smattering of macrolide and to a much lesser degree quinalones. The majority of these are beta lactems, primarily cephalosporins, but also penicillins.

This data for levofloxacin are the data from these comparative trials. So it gives you a head-to-head comparison, and then I show you here the expanded database for levofloxacin, adding in the additional cases that were in noncomparative trials so that you see the full database.

There was somewhat more patients in the comparator that had any adverse event that was considered drug related, but when we get into the four common ones that occur with the frequency of a half a percent or more for levofloxacin, and I chose it if it were either a half a percent here or here, we see that they're pretty similar. There's a little bit more diarrhea in the comparator, a little bit more vaginitis in the comparator, but by and large they look pretty much alike.

That's for drug related, but sometimes we really need to look at regardless of drug relationship because one can never be sure what's truly drug related or not, and what I've chosen for you are adverse events that people really talk about when they talk about quinalones.

The first are seizure activity, and you can see that we had three in the comparative group for levofloxacin. They are by and large across the board similar between, once again, levofloxacin and the control.

I do want to point out two things though. I want to point out this one case on levofloxacin which occurred in the comparator, in the comparative trials and QT prolongation. For this patient with hepatic coma, this patient had an antecedent history of hepatic coma prior to coming into the trials; had endstage liver disease at entry into the trial; and had a GI bleed during the trial. The investigator thought the GI bleed was the cause of the hepatic coma and considered this to be unrelated to levofloxacin, but we did have one case.

For QT prolongation, we had none, but I'll tell you about what data we do have in evaluating patients. There were 150 patients who had either Holter monitor or an EKG done prospectively as part of the clinical trial. Eighteen of those had Holter monitors.

Of those people who had EKGs, EKGs were done at baseline and then between zero and two hours after the dose. So it would be at around the peak of

the levofloxacin.

There were, in those 150 patients, no episodes of QT prolongation.

Next.

Now, there are, as you've heard, 100 million prescriptions that have been written for levofloxacin worldwide, and ten million of those in the United States. Just globally I can tell you that the post marketing safety profile of levofloxacin looks to be consistent with what we've seen in clinical trials, but I'll show you some data on reporting rates.

What I've chosen here is to just give you American, U.S. reporting rates, and that's because reports, post marketing reports occur much more frequently in the United States. If we were to use the other, it would be 30-fold lower than this. So I'm going to concentrate just on American rates.

As you can see, the rates are uncommon. They are less than one in a million for most of these, and I've chosen the adverse events or the reports that I thought would be of most interest to you.

As is always the case with post marketing reporting, we don't know anything about drug relationship. They're all reported regardless of what

drug relationship might be.

We can then summarize the safety data as follows. Levofloxacin's safety profile appears to be similar to the comparators which were primarily beta lactems and to a lesser degree macrolides, and at the post marketing safety profile after about 100 million prescriptions closely mirrors what we've seen in our clinical trials.

Finally, I will conclude with my global observations. Levofloxacin is highly and differentially distributed to important pulmonary tissues. The safety profile of levofloxacin is well known, and it's similar to beta lactems and macrolides, and when given as a 500 milligram dose once a day, it's effective in treating pneumococcal disease regardless of its penicillin susceptibility and regardless as to whether or not it was involving severe pneumonia or bacteremic pneumonia.

At this time I would like to turn the podium over to Dr. Medeiros, who will give us a clinician's perspective.

DR. MEDEIROS: Thank you, Mike.

I'll be mercifully short. I'm a practicing infectious disease clinician at a teaching hospital in Providence, Rhode Island, and I only have

two slides.

(Laughter.)

DR. MEDEIROS: The point I want to make is to kind of emphasize what the clinician is facing now, and I do consider it somewhat of a dilemma, particularly when faced with severely ill, seriously ill patients who come in with pneumonia. Very often they're elderly, and they can't cough very well, and we can't get enough sputum. So we end up with no definitive pathogen isolated.

The clinical microbiology laboratory reports that about 27 percent of our pneumococcal isolates are resistant to penicillin, and as we saw from Dr. Whitney's data, the proportion of these that have MICs over one in the fully resistant category has been increasing every year.

As we saw from some of the earlier data, they're often resistant to macrolides andtrimetheprim sulfa, and the tetracyclines we don't usually consider in hospitalized patients.

We worry about chlamydia, mycoplasma, legionella, and there's no truly quick way to exclude that, certainly not immediately.

So our treatment options are limited. So what does the clinician do? And that's my next slide.

Well, a common default is to use third generation cephalosporins and a macrolide. If the patient's allergic to penicillin, then vancomycin gets used.

When I put on my hospital epidemiologist's hat, I worry about the ecological impact of these options. Extensive use of third generation cephalosporins has been documented to enhance selection of extended spectrum beta lactemases in many hospitals. We have a significant problem as do most hospitals in the country with vancomycin resistant enterococci.

As someone said, this issue of resistance is like a balloon. You squeeze it in one place and it comes out the other, and I'm not sure we know fully how to balance the use of these different antibiotics to minimize that overall.

So this is a consequence, and my basic and last point is that we have a need both clinically and epidemiologically at this point in time, now, for alternative antibiotics.

And with that I'll turn the podium over to Graham Burton.

DR. BURTON: Mr. Chairman, ladies and gentlemen, you've seen a lot of data, and I think

there are some points I'd just like to reiterate from our presentation this afternoon relating to this whole subject.

The first point here I'm not going to say again. It's, I think, an accepted observation.

But I would like to reaffirm that the pneumococcal clinical isolates that we have identified are susceptible to levofloxacin, and this applies to whether or not those isolates come from North America, Europe, Japan, and that levofloxacin, as we've shown you today, and we hope we've convinced you, is equally active in vitro against penicillin resistant and susceptible pneumococci.

It is highly and differentially distributed to important pulmonary tissue and fluids, and it is highly effective in treating penicillin intermediate and resistant pneumococci, including those patients with severe pneumonia and those patients with bacteremic pneumonia.

The safety profile of this antimicrobial is well known and similar to beta lactems or macrolides, as we've demonstrated from our clinical trials, and our post marketing experience suggests that there are no untoward events occurring in use of this product.

May I just finally remind you what our supplemental new drug application is here for. We'd like to add the words to the pneumococcal pneumonia treatment indication to include penicillin resistant and intermediate strains.

Thank you very much.

DR. RELLER: Thank you, Dr. Burton, and also to your colleagues for a clear, succinct, but comprehensive presentations.

We'd now like to have the entire presentation open for full discussion of the issues, and, Dr. Burton, you could help by directing the queries to the appropriate person on your team.

Questions? Celia.

DR. CHRISTIE-SAMUELS: I'm concerned, again, that all children were excluded from all of these studies, recognizing that the CDC data just told us that children represent one of the highest risk groups for drug resistant strep. pneumo. disease and colonization.

This is also on the background of two recent reports from the Cincinnati Children's Hospital which described a recent increase in the incidence of aggressive necrotizing pneumococcal pneumonias with lung abscesses and pleural empyemas in previously

healthy children from the community. These illnesses were associated with drug resistant and drug susceptible strains, and in the drug resistant group, these children tended to be bacteremic and tended to be younger at the time of presentation.

The disease also carried a high morbidity and a lot of concern. There were also anecdotal cases from all over the country, from other hospitals as well.

So the questions I have for the group this evening would be:

One, did you see this kind of presentation in your adults with this disease? In other words, did you see necrotizing pneumonias with abscesses and pleural empyemas in your adults?

How was severity of illness defined?

And also, in the studies by Kahn and by Bruggemann, did they evaluate the concentration or penetration of levofloxacin in the pleural fluid, in addition to lung tissue and alveolar macrophages?

Thank you.

DR. CORRADO: I'll try to -- remind me the questions if I don't remember them all.

The last one I'll take first. None of those subjects I'm aware of had pleural fluid. So

there were no pleural effusions to tap and to measure the levels.

The question about the presentation in our patients, did any of them have necrotizing pneumonia or lung abscess? One patient did have an empyema and a pericarditis, but there were no other cases which were similar to that which you've described in children.

And I apologize. I don't remember the third question.

DR. CHRISTIE-SAMUELS: How did you evaluate severity of illness?

DR. CORRADO: Severity? Severity was determined or defined, a case was defined as severe if the patient had altered mentation, if the patient had a diastolic pressure below 60, if they were intubated and ventilated, if they had bacteremia, or if they had a baseline resting respiratory rate of greater than 28 breaths per minute.

In the most recent studies we've used the FINE score, and FINE scores of 70 to 91 are considered moderate and above 91 would be Class IV, as moderately severe, and then above 120, I believe, being severe.

DR. RELLER: Dr. Burton, you categorized, and this came across at multiple times, the efficacy

according to susceptibility to levofloxacin and what the corresponding categorization was having to do with beta lactem susceptibility.

From the subset of patients who were in comparative trials that received a beta lactem alone, do you have from those data the side benefit of what the efficacy was by MIC for, for example, ceftriaxone or penicillin?

DR. BURTON: Dr. Corrado.

DR. CORRADO: Thank you, Dr. Reller.

We do have that. I hope to be able to find that. I can speak to it while I'm looking for it.

There were five cases that were treated with the comparator, all of them successfully, but none of them received a single drug. They received a macrolide plus ceftriaxone, and as I recall, Slide 151. Found it.

Four cases. I beg your pardon. This was the source. This was the MIC to levofloxacin, the MIC to penicillin. This one had an MIC -- received azithromycin, had an MIC of greater than eight, but also received ceftriaxone, the MIC to which was two. This patient received chlorythromycin with ceftriaxone. You see the MICs to both. This was

erythromycin, MIC of four; ceftriaxone of one; erythromycin, .03, MIC of one.

Here is the co-morbidity in those subjects. So none of them received monotherapy with the beta lactem, and all of them received at least one drug to which the organism was susceptible.

DR. SOPER: Mike, what were the total number of penicillin resistent Strep. pneumo. that you have experience with with levofloxacin.

DR. CORRADO: Eighteen.

DR. RELLER: Dr. O'Fallon.

DR. O'FALLON: Well, I wasn't exactly overwhelmed by seeing 14 cases, and if this is such a -- I mean 14 doesn't tell us a whole lot. If this is such a big problem why was it so hard to get 14 and why couldn't we see a whole lot more?

DR. CORRADO: I'd like to comment on the fact that 14 is not a whole lot of data. If the susceptibility to levofloxacin is independent of the penicillin susceptibility, one may legitimately look at the entire database en masse for pneumococci, and you have a database of 252 and 55 bacteremic cases, and that is a robust database to say this drug works for pneumococcus.

And furthermore, if the MIC is two, I

don't care what the MIC is to penicillin. If it's a MIC of two to levofloxacin, based on the animal dynamic data, the human dynamic data, and the clinical data, that supports the fact that it would work.

With respect to the second question, why didn't we find more, it will take a smarter person than I to explain that to you. It was not from dint of effort. There were almost 4,000 people enrolled.

There many reasons that people have speculated, and speculation is one thing. I can tell you we did restrict. We did not treat children. They do have a higher rate. We did restrict other people for various reasons that we do. We don't put people who are hospitalized in trials of community acquired pneumonia.

And because we do these for the purposes of submission, we don't enroll people who have had other drugs that may be responding because then you can't evaluate the drug. So that's part of it.

Part of it is certainly the fact that we have 40 percent of our database from 1996 or earlier when the rates were maybe five percent or lower. I can't explain more than that. I just don't know.

But I can tell you this. They're there, and they are pathogenic. They do cause bacteremic

disease. Particularly in some patients they do cause significant morbidity and mortality.

DR. MURRAY: I just wanted to talk a little bit about that. I'm not sure if you were at our meeting when we discussed this last year or not, but the question was raised at the time whether in some ways did this question have to be asked in this way. If the drug is approved for pneumococci, there's no exclusion for penicillin resistant organisms, and we don't ask does levofloxacin or any other drug work in the presence of a trimetheprim sulfa resistant pneumococcus. Does it work in the presence of -- I mean, because when there is an erythromycin resistant pneumococcus.

So those discussions, we waxed and waned about that as well, and my recollection is that there was a sentiment that if -- and so the question also came up what would we want to see in terms of data efficacy to approve a drug for a resistant organism.

Given the caveat that the question has been asked, not did we really think that an indication needed -- if there had to be one written because if it works for pneumococcus it should work for other pneumococci, but some of the things that were mentioned was if it works in non-penicillin resistant

disease, if there is animal data to support the fact that there is no difference using new Drug X against penicillin resistant orpenicillin susceptible strains of that species, and if there are a handful -- but we didn't define what a handful was -- of true resistant, severe disease treated with the new drug.

So in some ways they've -- I mean they have met those. I still think some fundamental questions exist in the sense of how necessary is it to have a separate indication. It's like you need a law to cover the people that are already included in the umbrella.

DR. CORRADO: We have someone with us if the chair would be interested who may want to comment on that, Dr. Charles Fogarty from South Carolina.

DR. FOGARTY: Thank you.

As to why it's so hard to document the penicillin resistant Strep. that we're so worried about, on clinical trials, and generally you're excluding someone who has had recent antibiotic therapy, and if you skip to your own personal practice, we frequently run into patients who had recent antibiotic therapy. They clearly are getting worse. They're bringing up any sputum, and you're not going to prove that the cause is penicillin resistant

Strep. pneumo. unless you have a pathogen.

Now, in a couple of the cases that I was involved with because they were on the study, because it was convenient, because they were in the emergency room where they had a bronchoscope around the corner, we used the bronchoscope to snake them, and indeed proved what we suspected.

But for the average practitioner, it's hard to prove that, and for the average clinical trial, you're excluding a lot of these patients up front.

DR. RELLER: Dr. Norden.

DR. NORDEN: I have two separate questions. One is for Dr. Bush.

Karen, do you think that based on what you've told us about the biology of the pneumococcus that if levofloxacin is used heavily, that quinalone resistance will emerge very slowly or moderately, rapidly, you know, compared to, say, how penicillin took forever?

And then I'll ask the second one after that.

DR. BUSH: This is something that we have obviously thought about. This is an item that we obviously have discussed extensively. I think our

best answer is based on the experience in Japan where the quinalones have been used for over a decade. We still see very high susceptibility to levofloxacin.

We've seen from three different in vitro studies that levofloxacin selects for resistance less frequently than ciprofloxacin, and ciprofloxacin certainly has been around much longer in clinical practice than levofloxacin.

Our hope would be that we would not select for resistance quickly. As a realist we know that there will be some increased resistance if we use a drug at all. So I think the data would suggest that we would see a slow development of resistance with levofloxacin.

DR. NORDEN: Thank you.

The other question, I guess, is really for Tony Medeiros.

I think we all face the dilemma of community acquired pneumonia and what drugs to use, but if you look at the data that has been presented and presented very clearly and nicely, I mean, there are very few cases of penicillin resistant pneumococcus, and even assume -- truly penicillin resistant, not intermediate -- and even assuming that the true rate is higher because you had so many

exclusions and so on, it's still a lower incidence.

And when do you start discarding beta lactem therapy and going to something like quinalones wholesale?

DR. MEDEIROS: Well, that touches on the question that was asked before. I mean, what is the threshold above which the physician anxiety level demands that you use something more aggressive?

I don't know exactly how to answer that. I can tell you that in my community it's there. You know, it takes a few cases.

About five years ago we had a patient sent up from Newport who had a meningitis from a pneumococcal. We'd never seen that in the community. All of the evidence indicated that it was a rare bird in our community, but he got it somewhere and probably from one of his kids that went to a day care center and nearly died.

So the accumulation of a few of those, plus. the laboratory telling us that they now have somewhere around **25** percent overall, in recognition of the fact that in the last few years -- and it's in the last three or four years -- we've been seeing an increase in the percentage of those with MICs over one. It's there. The anxiety level is there.

So do we want to use a lot of ceftriaxone and macrolides, or do we want to cut down on that and try to even out the balloon with a little quinalone?

I mean, not easy questions to answer, but there is clearly, I think, a clinical need for an alternative to what we have. We don't trust the macrolides. We've published one case of failure in a bacteremic patient treated with a macrolide, and out-patient who came in after treatment with a macrolide and has a bacteremia, and we're now looking at other cases. We have 11 accumulated so far.

So what do you do? And that's the physician's dilemma.

DR. NORDEN: I think your answer is a good one, and I don't mean to minimize the anxiety. I think we all have it. Just the trouble is now, and I guess I'm stating the obvious, but it's all, again, sort of post hoc reasoning.

If we knew the organism was penicillin resistant, it would be easy, but the trouble is we don't know that for --

DR. MEDEIROS: Right.

DR. NORDEN: -- 72 to 96 hours. So one of the obvious things --

DR. MEDEIROS: Right, and then in less

than half of the patients.

DR. NORDEN: Right. We still need an obviously more rapid diagnostic and sensitivity type of studies that would help us with this.

I just am nervous about -- because the obviously -- not the obvious. Sort of the extreme would be, well, we should give levofloxacin to every community acquired pneumonia, and I think that won't even out the balloon. It will just push it out the other side.

DR. MEDEIROS: I agree. I think there has to be some balance there.

DR. BURTON: Dr. Reller, is it possible for Dr. Fogarty to make a comment?

DR. RELLER: This is an open discussion, and in order, anyone who wants to comment or ask a question about what was presented will be addressed.

DR. BURTON: Thank you very much.

DR. MURRAY: While he's getting up, may I make a quick?

DR. RELLER: Please.

DR. MURRAY: Carl, back to your statement, I believe using a fluoroquinolone is already listed in IDSA guidelines for community acquired pneumonia. So it's already there. That already is a standard of

care.

DR. RELLER: Dr. Fogarty.

DR. FOGARTY: This is to follow up on Dr. Norden's question.

I don't think you can come up with a percentage. What I can tell you is what I do. Maybe ten percent of my practice is clinical trials. The rest of it is plain, old patient care.

In the clinical trials, the gold standard is a macrolide, and in most clinical trials there's no difference. So what I find in my community is that I use quinalones far more sparingly than the family practitioner in his officer.

Whom do I use quinalones, specifically levofloxacin, in a pneumonia? I use it in the patient with significant lung disease or co-morbidity in whom if I am wrong and I lose a couple of days I'm going to be in serious trouble.

That is not everybody. That is a subset of patients, and I think we run into other issues like educating the physicians.

DR. RELLER: Dr. Battinelli.

DR. BATTINELLI: Well, when we began, I think Dr. Bell from the CDC asked about addressing this issue of intermediate sensitivity and the

development -- well, addressing the honest confusion in the average clinician's mind about, in fact, what does that really mean, and I think people have just talked about some of those issues.

And I wanted either. Dr. Medeiros or Eliopoulis or one of the other clinicians -- how you would propose addressing that specific issue because I could see the average clinician hearing about an increase in intermediate sensitivity even if there is not an absolute increase in definite resistance, and them slipping into using the quinalone either all of the time or, in fact, switching from a drug that still would be useful in an intermediate resistance case, and that may accelerate over whatever period of time it is the development of the resistance.

DR. ELIOPOULIS: Dr. Battinelli, your question is a very complex one which I can begin to answer by saying that I agree completely with all of the things that Dr. Bell said in that I think it's in an attempt to circumvent some of the confusion that I think that this additional labeling actually carries some appeal to me in terms of pointing out both to the generalist and to the subspecialist where the data set.

Now, we know that at levels of penicillin

resistance that are intermediate we already start to see an increase in cross-resistance to several other unrelated classes of antibiotics, trimetheprim sulfa, macrolage, et cetera. So that there is something unique about those things.

But I would be the first to agree that if we had the data that a case had pneumococcal pneumonia and the MICs of that pneumococcus were favorable and that person did not have a closed space infection or meningitis or anything of that sort. Then high dose penicillin would, in fact, be a perfectly good drug, and that's the kind of thing that when our residents tell us, "We have a classic case with pneumococci in the sputum and a perfect story," and they started him on Penicillin G, we kind of give them the gold star for the day at residence report.

But unfortunately that's the minority of the cases because initially we know the patient has pneumonia. We're worried not only about pneumococcus and what the level of resistance is, but we're also worried about do they have Hemophilus influenza, do they have Moraxella catarrhalis, do they have legionella.

So at our place, a lot of people get put on ceftriaxone plus a fluoroquinolone. It's kind of

a style preference to macrolides, but lots of people empirically get the fluoroquinolone up front.

By the time you find out what the true susceptibilities are, the patients hopefully are ready for switch-over to oral therapy.

I think the reason that this sort of question actually helps sort out some of the confusion is that if you're a generalist, you've been hammered by our educational efforts for decades, being told, "Well, you know, this is methicillin Staph., and that means you can't use other beta lactems," and so forth. So we're being taught that in vitro susceptibility data do not always translate into clinical efficacy.

So the generalist can go to the labeling, whether it's in the PDR, the package insert, or anywhere else, and find out specifically that, yes, they might be able to use it for this indication, and therefore I can perhaps dispense with some of the other drugs that would be added to an empiric regimen.

And the specialist, the ID person looks at this kind of story as in vitro data kind of skeptically and says, "Well, you know, show me the evidence that it works because we know that there's something funny about penicillin resistant pneumococci. Maybe they wouldn't respond as well even

if in vitro they seem to be susceptible to a fluoroquinolone."

And it was my point of view that if there are data to support the fact that the agent works in that category of patients, especially people with bacteremia or other severe disease, then it can only help to get those data in the light of day.

DR. BATTINELLI: Do you worry about the issue thought in terms of the confusion of slipping backwards and using -- in other words, getting a report back on somebody who's got an intermediate susceptibility to penicillin, they're on a macrolide. It is susceptible, and their interpretation is to switch to a fluoroquinolone.

DR. ELIOPOULIS: That's certainly a definite risk, and that's another area in which I fully agree with Dr. Bell's comments, and I think that's something that needs to be addressed by education as well.

I think at that point in time, again, you're going to be thinking about an oral drug. We're further constrained by something that hasn't come up yet in this discussion, and that is that when you go to choose an oral drug, what are you going to choose?

YOU cannot go to a list of available

agents and pick one that you think is appropriate because your health plan, like my health plan sent me a list, and they said, "Well, you're second generation cephalosporin of choice is" -- and I won't mention the drug, but it's not one that would normally come up in discussion at least in my ID group of, you know, the treatment of choice for step-down oral therapy.

so I think under those circumstances going to an oral fluoroquinolone might not be a bad idea, especially if the alternative is one of those drugs that I really personally wouldn't have very much confidence in.

DR. RELLER: Dr. Norden, you asked or stated that if we knew the susceptibility of the organism to penicillin for pneumococci, it would be easy.

DR. NORDEN: Easier.

(Laughter.)

DR. RELLER: Would it? Do we know -- and I'm trying to link all of these comments with Dr. Bell's introductory comments in the open public hearing -- do we know for community acquired pneumonia that level of resistance where a beta lactem antimicrobial would be precluded from empirical therapy, as is so clearly delineated for meningitis

and the reason, at least to date, that the NCCLS has been so resistant or so conscientiously concerned with keeping the break point for susceptibility at .06, because know what that means?

Until we know, until we know that a pneumococcus is exceedingly susceptible to penicillin or to ceftriaxone or cefataxine, combination therapy must be used. Do we have similar objective data for the therapy and what should be done for pneumococcal pneumonia with a beta lactem?

DR. NORDEN: Well, Barth, I didn't think -- until Dr. Whitney gave her presentation, I'm not familiar with the Feikin study, but that's the kind of data that I think the pneumonia at least -- that would begin to answer the question that you're asking, and I think all outcome studies are difficult to interpret, you know, when they're not in sort of randomized controlled trials.

But I was impressed with the odds ratio at least for those isolates that were penicillin resistant. Now, what I didn't know and I don't think was answered and was able to be answered was what the therapy was and where you could show that those patients who have penicillin resistant isolate clearly fail on penicillin.

The other question, and Bill is standing at the microphone, would be based on animal data which we may also have.

DR. RELLER: Before we hear from Dr. Craig, the reason I pursued that is because Dr. Whitney presented data, whether it's at four or eight or somewhere around there, where the odds ratio really shifts.

The numbers that she presented was that the proportion of strains that fall into that category where one has an isolate is in the order of under five percent, and it gets down to Dr. O'Fallon's observation of why aren't there more patients who have highly resistant organisms who would be the ones who for reasons of resistance would need an alternative drug like a fluoroquinolone as opposed to those who might get the alternative drug because of not knowing about the possibility of legionella or chlamydia or some other reason.

And I think it's an exceedingly important, when we get to the questions, an exceedingly important distinction to make to try to encompass all of the concerns voiced by Dr. Bell, as well as the clinical realities of empirical decision making and the opportunities for education and what the package

insert ultimately says precisely.

Dr. Craig.

DR. CRAIG: I've been told I can't answer a question.

DR. RELLER: We recognize that you cannot comment, though I always love to hear what you have to say, but we won't hear it today.

(Laughter.)

DR. RELLER: Other questions or comments?

We'll have the opportunity to come back to these issues after the FDA presentation. It was originally scheduled that we would have our break at 3:45, and then have the FDA presentation. I think it would make -- choreography would be much better if we took our 15 minute break and we start the FDA presentation at 3:45.

A **15** minute break.

(Whereupon, the foregoing matter went off the record at 3:28 p.m. and went back on the record at 3:48 p.m.)

DR. RELLER: The three-quarters hour has come, and we're technically aright again and would like to begin the second half of the afternoon session with a presentation from the FDA that will be led by Dr. Edward Cox, a Medical Officer with the division.

Dr. COX .

DR. COX: Good afternoon. I'm Edward Cox. I'm a Medical Officer in the Division of Special Pathogens and Immunologic Drug Products, and I'll be presenting the FDA presentation of the clinical efficacy data for Levaquin for the treatment of penicillin resistant Strep. pneumoniae and penicillin intermediate Strep. pneumoniae in community acquired pneumonia.

And in the presentation I'll try to refer to the acronyms PRSP and PISP and also use CAP as an abbreviation, C-A-P, for communityacquiredpneumonia.

Can I have the next slide, please?

I know we've already heard a presentation from the folks from PRI. So I'll try and abbreviate my comments in areas that they've already covered.

You've seen a slide similar to this, and I just wanted to start just with a little bit of background. As we've heard, levofloxacin was originally approved in December of 1996, and included among the indications was community acquired pneumonia due to Streptococcus pneumoniae.

And the slide here shows an excerpted portion of the label. The text in white represents the current approved labeling for Levaquin, and the

issue that we're here to discuss today is the efficacy supplement that seeks to add the claim for PRSP and PISP in community acquired pneumonia for Levaquin, and the applicant's proposed addition to the current labeling is the yellowparentheticalphrase "including penicillin resistant/intermediate strains."

And then if I can have the next slide, please.

And then the way I'd like to approach my talk is, first of all, I'll talk about levofloxacin for the treatment of community acquired pneumonia, and this is community acquired pneumonia in general. So it includes both community acquired pneumonia secondary to Streptococcus pneumoniae, and then also community acquired pneumonia of other causes.

Then I'll focus further and talk about levofloxacin and community acquired pneumonia in those patients who had an emission isolate Streptococcus pneumoniae, and this data from the first two bullets comes from the data in the original NDA.

Then we'll move on and we'll talk about levofloxacin, the treatment of PRSP and PISP in CAP, and this is the subject of the efficacy that we're here to discuss today, and the way I'll approach this will be first to talk about the clinical trials from

which this data has been drawn, and then secondly I'll talk about the approach to the FDA efficacy analysis given that these data were drawn from a number of clinical trials, and then I'll move on and talk a little bit about the patient characteristics for the patients that are under study and then provide the efficacy rates for levofloxacin and then also for the comparator treated patients.

And I want to just go ahead and mention one caveat right up front, and that is that only some of the studies were comparative studies. So not all studies were able to contribute patients to the comparator group. So the comparator should be used to give an impression of the events that went on in the comparator arm, but may be less appropriate to use for direct numerical comparisons.

Can I have the next slide, please?

So we'll start out. We'll talk about data that was submitted in the original NDA with regards to Levaquin for CAP and Levaquin for CPA due to Streptococcus pneumoniae.

Next slide.

I want to just talk first about the two major clinical studies that were submitted in support of the NDA for community acquired pneumonia. The

first of these was K-90-071, and this was an open label, randomized study that was comparative, and it compared levofloxacinto a cephalosporin based regimen with the option to add either erythromycin or doxycycline to the cephalosporin arm of the study.

This study enrolled approximately 600 patients.

And then the second major study that supported the community acquired pneumonia indication was M-92-075, and this was a noncomparative study that looked at levofloxacin in the treatment of community acquired pneumonia and enrolled a total of 264 patients.

Next slide.

Now, what I'd like to first do is just give you an impression of the patient characteristics that were under study in these two major clinical trials, and the data here in this table is shown first of all by study, and here we have K-90-071 and we have the two treatment groups, levofloxacin and the cephalosporin based comparator regimen.

And then in this column we have the data from the noncomparative study M-92-075, which all patients receive levofloxacin, and then the selected patient characteristics here. We have severity of

disease at baseline and we see that approximately 16 percent of the patients across the board had disease that was classified as severe at baseline.

Then if we look at the category of hospitalization we see that across the board for the two arms of the comparative study, and then also in a noncomparative study, we see that approximately 40 percent of the patients were hospitalized across these studies.

Next slide.

Now, as far as the efficacy results from the K-90-071 study, this is the comparative trial of Levaquin that was in the original NDA. I want to talk about three categories of data.

The first one I'll talk about is clinical success in community acquired pneumonia, and clinical success includes both those patients who were classified as clinical cure at the test of cure visit and also those patients who were classified as clinically improved.

Then this is all comers with community acquired pneumonia. So it includes patients both with Streptococcus pneumoniae or other isolates in addition to Streptococcus pneumoniae. So this is all comers with community acquired pneumonia.

The next category of data I want to talk about will be microbiologic eradication in community acquired pneumonia, and this includes both those patients who had documented microbiologic eradication or the other category of microbiologic eradication which is presumed microbiologic eradication, which means that the patient was clinically improved and at the time of the test of cure visit was not able to produce an appropriate specimen for microbiologic analysis.

Then the third category of efficacy data that I'll talk about is the clinical success rate for those patients who had community acquired pneumonia and their emission isolate was Streptococcus pneumoniae.

And if we look across these three categories, we see that for the levofloxacin arm in this comparative study, the efficacy rates for clinical success, microbiologic eradication, and clinical success for those patients who had Strep. pneumo. as their emission isolate, we see they're approximately 96 percent.

Then in the comparator arm which used the cephalosporin based regimen, we see that the efficacy rates, again, for these three categories are in the

mid-80 percent range.

And then could we have the next slide, please?

Now, this slide is laid out much in the same way, and the same three categories are presented, and this is from the noncomparative study, M-92-075. And we see that for this study the rates for clinical success, microbiologic eradication, and clinical success for patients who had Strep. pneumo. is their emission isolate. We see rates that are similar to what was observed in the comparative study. The rates are approximately 94 percent for these three efficacy categories.

And then the next slide.

And I've talked about that **data** from the original NDA just to provide an impression of the efficacy of Levaquin in the treatment of community acquired pneumonia and in those cases where community acquired pneumonia is secondary to Strep. pneumo., and most of these isolates are susceptible Strep. pneumo. from the original NDA.

Now we'll move on, and you know, with that as a framework, move on and start talking about the data in the supplemental NDA which focuses on PISP and PRSP in CAP.

Next slide.

And first of all, I just want to talk a little bit about where the data have been derived from that are the subject of the supplement here today. They are drawn from eight clinical trials and four of these studies were randomized comparative trials. Three were open label. One was double blind, and then four of the studies are open label, noncomparative studies.

Next slide.

And from the four randomized comparative studies, four levofloxacin treated patients were identified who had PRSP isolated. Six levofloxacin treated patients had PISP isolated.

And if we look at the comparators for these studies that had comparators, we see that there are approximately a similar number of patients was also found in the comparator arm.

Then if we move on and look at the four open label, noncomparative studies, a total of 14 levofloxacin treated patients with PRSP were identified and 43 levofloxacin treated patients with PISP were identified.

And then if we look at data just to get an overall impression of the rates of PRSP and PISP in

these clinical trials, the rates are roughly five percent and 15 percent for PISP.

Next slide.

And this slide provides a little more detail as to where these patients were derived from that had PRSP and PISP. First of all, in this column we have the study identify by the study number and the slides divided into two sections. The first three studies are the NDA studies that supported the CAP indication with the top two being the major clinical studies that supported the CAP indication.

And then in the bottom portion of this slide are the other studies that are included as part of the efficacy supplement that provided additional patients with PRSP and PISP isolates.

The first column designates those studies that had comparators. The second column designates those studies that were randomized. The third column designates those studies **that were double blind, and the next, those** studies that were open label.

And then in the last two columns, the number of patients who had PRSP or PISP by study as designated in this column, and we see the total number of levofloxacin treated patients with PRSP, **18,** and the total number of levofloxacin treated patients with

PISP, totaling at 49.

And I haven't shown data here for the comparator patients, but as you'll see as we get a little further in, the numbers are small. So I think this gives a pretty good impression of where the levofloxacin treated patients with PRSP and PISP were derived from from the clinical studies.

Next slide.

And then I want to talk a little about the approach to the FDA efficacy analysis, and just sort of to start out, the reason why it's important to consider the approach. You know, first of all, as you've seen, there's a number of studies that we're drawing patients from here.

The studies have some differences in study design. Some of the studies had only one test of cure visit post therapy. Other studies had more than one visit following the completion of therapy, and these visits could occur at different points in time following the completion of therapy.

Because of these variations, it was important to try and standardize the approach to how the data was analyzed and also, secondly, to try and establish clinical successes that were durable clinical successes, and that is those clinical

successes that are far enough removed from the time of completion of antimicrobial therapy to designate true durable clinical success.

so two categories were defined: supportive cases and pivotal cases. Now, in order to be either a supportive or a pivotal case, first of all, patients had to meet the protocol specified evaluability criteria, and then if a patient had only a single test of cure visit and that test of cure visit occurred two to four days post therapy, that patient was classified as a supportive case.

For those patients that had a test of cure visit five to 21 days post therapy or had two post therapy visits with one being two to four days post therapy and then a second visit that occurred on the fifth day or later post therapy, that patient could be in the pivotal group of cases.

And then with regards to failures, all failures were considered pivotal, and in order for a patient to be considered eligible for failure, that patient would have had to receive 48 hours of therapy.

Next slide.

And one thing I'll mention, too, just before I get to this slide is that in the studies, some of the studies were non-IND studies that data are

derived from, and had post therapy evaluations that per protocol specifications could occur as early as two days post therapy.

As far as the rational for pivotal versus supportive cases, in order to allow time for drug to clear and also in order to allow time for inadequately treated disease to recrudesce, pivotal cases are defined as being those cases that undergo their test of cure visits five to **21** days post therapy, and the idea here is that we're trying to designate those cases where success is a durable outcome and drug has had a chance to clear and disease that's merely suppressed would have time to recrudesce.

And then next slide, please.

And then I've got this slide here really just to provide a handle on the populations that I'll be talking about in the subsequent slides regarding patient characteristics, and across the top row here we see levofloxacin treated patients, comparator treated patients who had either **PRSP** or **PISP,** and this number 18 reflects the total number of levofloxacin treated patients with **PRSP** that were identified, and then of these 18 patients, 11 of the cases were considered pivotal. Four were considered supportive, and three were nonevaluable.

And then for the levofloxacin treated patients who had PISP, there were a total of 49 patients identified. Thirty-seven were considered pivotal. Four were supportive, and eight were nonevaluable.

And then if we look at the comparator treated patients, we have three pivotal comparator treated PRSP cases and four pivotal PISP cases in the comparator arm.

Now, in the subsequent slides I'll be referring to an n of **15,** and that represents the patient characteristics for the pivotal and supportive **cases** combined, and then an n of 41 for the levofloxacin treated patients with PISP, which represents the pivotal and supportive cases combined.

May I have the next slide?

And then this is a slide that's got a lot of information on it. So I'll just try and focus you on a couple of the locations.

First of all, in this column is the data for the levofloxacin treated patients with PRSP, and this column is the data for the levofloxacin treated patients with PISP.

And we see with regards to the patient characteristic of hospitalization we have nine of 15

patients who were in-patients, and then in the PISP levofloxacin treated patients, we had 28 of **41** for approximately 68 percent.

And then if we look at disease severity at baseline, we have five of 15 levofloxacin treated patients who were classified as severe, and then **12** of 41 PISP levofloxacin treated patients who had their disease categorized as severe at baseline, and I also not that there's a significant number of patients whose disease classification was unknown.

And then if we look at the number of patients who had bacteremia, we have six of 15 of the levofloxacin PRSP patients who were bacteremic at the time of study entry, and in the PISP arm we have six of 41 for approximately 15 percent.

And then in the bottom column, this designates those patients who received pre-study antibiotics for less than 24 hours, and typically this is a single dose of an active antimicrobial that the patient receives prior to study enrollment, and we have four of **15** levofloxacin PRSP treated patients who got pre-study antibiotics for less than 24 hours and ten of 41 of the levofloxacin PISP patients who got less than 24 hours of pre-study antibiotics.

And the next slide.

And this is the same table essentially for the comparator treated patients, and I'll just sort of quickly just go through a couple of the categories here. For the comparator PRSP treated patients, we see that all three of three were in-patients, had severe disease, and were bacteremic, and of the four PISP patients, two were in-patients, one had disease classified as severe, and one was bacteremic.

Next slide.

And then one other comment I'll make about the data is that, you know, this data was derived from a total of eight studies, but one additional note that I'll make is that one center contributed six of the **11** pivotal levofloxacin treated PRSP cases and this same study center also contributed **11** of the 37 pivotal PISP cases that were levofloxacin treated.

Next slide.

Now I'll move on and talk about the efficacy results for PRSP and PISP in CAP that were observed with Levaquin, and I'll present the clinical efficacyandmicroefficacyessentiallysimultaneously, and that is because the numbers were the same.

And for the levofloxacin treated patients with PRSP, those cases that were defined as pivotal successes, we have 11 of **11** pivotal successes for an

efficacy rate of 100 percent.

And for those cases that were defined as supportive successes based on the timing of their test of cure visit, we have four of four patients for 100 percent for levofloxacin treated patients who had PRSP.

And then we have three patients who were nonevaluable.

And then if we look at the levofloxacin treated patients with PISP for the pivotal successes, we have 37 of 37 for 100 percent, and then for those cases that were considered supportive successes, we have four of four, and then eight nonevaluable patients for the levofloxacin treated patients with PISP.

And then next slide.

And then I'll present the data for the comparator again just to give an impression of the events in the comparator arm of the study.

And then for those patients who received comparator therapy, and that was only -- these patients only were from some of the clinical trials because not all trials had a comparator arm -- for those patients with PRSP and PISP with CAP we see that three of three patients were defined as pivotal

successes, and then in the comparator treated patients with PISP four of four were defined as pivotal successes, and five of the PISP comparator treated patients were nonevaluable.

And then next slide, please.

And then I present this information really just to give an impression of the cross-resistance that was observed in the levofloxacin treated patients, from their isolates from the clinical trials, and we'll start out here at the bottom.

For the penicillin intermediate Strep. pneumo. isolates, the total of 49 that we've talked about for the total number of patients identified who were levofloxacin treated who had PISP, we see that 48 of these isolates were levofloxacin sensitive. One was levofloxacin resistant.

And then if we move over to the penicillin resistant column, we have **18** total isolates and **18** of the **18** isolates were sensitive to levofloxacin.

And then the next slide, please.

So now I just want to summarize. In the data from the original NDA that supported the approval of Levaquin for the treatment of community acquired pneumonia, the clinical and microbiology success rates that were observed in the treatment of community

acquired pneumonia of all causes were in the approximately 95 percent for levofloxacin, and then for the comparator were in the mid-80 percent range.

And then if we look specifically at the patients who had Strep. pneumoniae as their admission isolate from the NDA clinical studies, we see clinical success rates for Strep. pneumo. for levofloxacin in the mid-90 percent range, and then for the comparator we see 85 percent in the one study that had a comparator. And this is all data from the original NDA.

The next slide.

And then just to summarize the data that's the subject of the discussion for today, this is the supplemental NDA data looking at Levaquin for the treatment of PRSP in CAP. The clinical and microbiologic success rates that were observed for levofloxacin were **100** percent with **11** of the cases being pivotal and four supportive.

And then for the levofloxacin treated patients who had CAP and PISP as their isolate, the clinical and microbiologic success rates for levofloxacin were **100** percent, with 37 of the cases being pivotal and four supportive.

And then the comparators for both

categories, the numbers are small, but the success rates were 100 percent.

And that concludes my presentation, and now we'll just go -- go to the next slide. And then one more slide.

Before I finish, I just wanted to just touch on the questions that we'll be asking the advisory committee to address, and then I'll try and answer any questions with regards to my presentation.

The first question for the advisory committee is:

Are the data sufficient to demonstrate that levofloxacin is safe and effective for the treatment of CAP due to PRSP?

And then if the answer is no, what additional data would be required?

If the answer is yes, are there any caveats about its use that you would recommend be included in the product labeling?

And should any mention of PISP be made in the indications and usage section?

And then next slide.

And the question number two: do you have any recommendations regarding Phase 4 studies or data collection that the applicant should be requested to

perform?

And question number three: do you have any recommendations for future clinical trials for this indication? Such recommendations might address, but are not limited to the issues of the supportive value of isolates from other body sites and the usefulness of data from penicillin intermediate isolates.

And just any questions for me now? I'd like to open up.

Dr. Murray.

DR. MURRAY: Just for curiosity, your numbers were slightly different from their numbers. In one case you had one or two more isolates, and the PISP had one or two, a couple less. Was that lumping more trials or --

DR. COX: They're all the same trials. They're all the same 49 and 18. There's one patient for the levofloxacin treated patients with PRSP that was included among my supportive plus pivotal cases that was outside of the test of cure window in the analysis done by PRI that fell into the test of cure window for my analysis. So there are differences of that nature that lead to slight differences in the numbers in the denominators that we're referring to.

Yes.

DR. PARSONNET: Do you have confidence intervals around the cure rate, what the lower confidence interval would be?

DR. COX: For the PRSP and --

DR. PARSONNET: Yeah, for the PRSP.

DR. COX: We didn't calculate confidence intervals, and I think, you know, we're dealing with small numbers here. Certainly you could. We did not.

DR. RELLER: Barbara.

DR. MURRAY: I just wondered if you or someone else at FDA or even Barth could sort of remind us of the discussions of a year or more ago about the ten percent or ten isolates being resistant out of the big subset or the big set of clinical isolates.

DR. COX: Do you want me to try to address that is that a question --

DR. GOLDBERGER: You're welcome to try.

(Laugher.)

DR. COX: I think Dr. Goldberger might do a better job if that's okay.

DR. MURRAY: I'm not saying that we should be held bound to what we discussed ad hoc at an earlier date because people may change their minds about things, but nonetheless to refresh us what we

did say.

DR. GOLDBERGER: Well, there's, first of all, a standard that has been used in a number of trials for anti-infective products for some time of looking at the microbiologically evaluable patients that for a given organism, ten percent or ten, whichever is more, of the given organism should be present out of the total group of microbiologically evaluable patients.

So, for instance, you had **150** microbiologically evaluable patients. You ought to have **15** at least of a given isolate.

So there are the rules like that that exist.

One of the reasons for the degree of discussion, I think, last year at the advisory committee about resistant isolates goes back to even before at another advisory committee about the concerns that were already being raised about the ability to enroll sufficient numbers of penicillin resistant Streptococcus pneumoniae cases.

And, therefore, were there other options that might be considered in terms of getting a sufficient number of information or a sufficient amount of information?

YOU will recall, you know, some of the remarks I made earlier today about the issue of the use of preclinical data, MIC data, PK/PD data, and the importance, for instance, of susceptible pneumococci if one doesn't believe that cross-resistance is an issue.

Ultimately, of course, the amount of information that's here is one of the questions we're really asking the committee about for its opinion at this point in time when we ask if there are sufficient data about safety and efficacy.

But, in fact, one of the goals of having a lot of the discussions we've had is to think in the absence of the usual number of isolates, depending on the given circumstances of the situation, are there other types of data that would also be helpful in coming to a decision?

My sense from the meeting last year is that most people felt that that was the case, but ultimately we have to decide at this moment in time what people think about the body of information that has been collected here.

DR. RELLER: At the end, we will have a vote on these questions and then the sections for recommendations.

Before getting to the questions, is there any comments or discussion that people would like to make before tackling the questions?

(No response.)

DR. RELLER: Before doing so, I would like to clarify. The sponsor presented their information and has requested action that is embodied in the questions, but slightly different from. Dr. Goldberger, Dr. Kweder, are we to address these questions?

DR. GOLDBERGER: The sponsor basically asked for a modification in their labeling, which means, in essence, they would like to add to their indication the terms "penicillin for community-acquiredpneumonia," "penicillin resistant Strep." and "penicillin intermediate Strep."

And in essence we have restated it in the traditional way: is levofloxacin safe and effective for the treatment of CAP due to penicillin resistent Strep.? That is tantamount to placing that phrase in the indications and usage section. So I would like to think what we're asking is the same thing basically.

They wanted to basically show you how their label would be impacted. What we're asking you, in essence is: is there sufficient information to

warrant making this change in the label, which is adding this one phrase to their indication section?

DR. **RELLER:** **I** think that it may be worthwhile to discuss this point because when the committee members vote, it must be certain what they're voting for.

Dr. Chesney was not able to be here this afternoon owing to previous commitments, but it has been the tradition in the past that a voting member of the committee who has comments that they want to make is able to leave for the record written comments, and I would like to read her comments for inclusion in the discussion.

She wrote, "I have several issues/concerns. Of the 14 penicillin fully resistant available case provided in the material, only two cases had penicillin MICs greater than two micrograms per mL, and none has MICs greater than four micrograms per mL. These are very small numbers, particularly as there were no failures with resistant organisms in the control group, ceftriaxone plus or minus erythromycin," and that's been affirmed in what we've just been presented.

"Other than meningitis and otitis media" -- second point -- "there have been rare or no clear-

cut failures of beta lactem drugs to treat penicillin intermediate or even resistant organisms when usually recommended doses and durations are used for community acquired pneumonia.

"3. The role of fluoroquinolones for resistant pneumococci or the rate of fluoroquinolone resistant pneumococci is increasing rapidly as the CDC, Dr. Whitney, has indicated. Increased use will only emphasize this, and we will lose almost our last resort class of antibiotics.

"4. As clinicians are unclear as to the difference between intermediate and resistant, if this drug is approved and marketed as the first and only antimicrobial for penicillin resistant strains, it will be widely used for everything, including by pediatricians, family physicians, ENT surgeons, et cetera, in children for recalcitrant otitis sinusitis.

"Even though fluoroquinolones are not intended for children, 12,000 courses were prescribed in children less than one year of age in 1996 alone." These are ciprofloxacin, not levofloxacin data. "There will be even less hesitancy to use 'a better drug.'

"Lastly, we badly need new antimicrobials for these common penicillin resistant organisms. I am

concerned that based on only **14** patients with no evidence for activity better than we already have, physicians will not use levofloxacin prudently.

"Perhaps it would be fair to advertise it as comparable to ceftriaxone, but not better."

And those are the comments that if she were here, Dr. Chesney would state in the discussion.

Are there any other points?

DR. NORDEN: I guess I'd also like to ask some clarification perhaps from Dr. Goldberger, but the present label, community-acquired pneumonia due to Streptococcus pneumoniae, without specifying anything about resistance or intermediate penicillin, encompasses. I mean it doesn't say anything about penicillin resistance in the present. So it doesn't imply that it isn't effective.

Dr. Murray raised this question earlier this morning, I think. It isn't encompassed, and what bothers me, I guess, is then all other drugs, like ceftriaxone, should -- or amoxicillin -- be effective against penicillin intermediate based on what we know.

Does everybody have to come in and reapply? I guess I'm not sure why we would change this label.

DR. GOLDBERGER: Well, let me try to

address that. There is a term in the law that is "ripeness," that is, when an issue is sort of ripe for discussion, and we have probably reached that point with this particular topic.

There has been a growing amount of interest in the pharmaceutical industry about the issue of drugs, for instance, beyond resistance specifically for this issue of penicillin resistant Strep. pneumoniae, and as a consequence we are sort of obliged to consider that issue to gain the, you know, opinion of the committee.

I would think that there is enough information in the scientific literature, as well, to say that the time has come to discuss whether it is reasonable to grant such an indication, and I'll come back in a moment to the significance of that.

I think one can certainly argue about present significant of penicillin resistant Strep. pneumoniae, but it would seem reasonable at this point scientifically, as well as from a regulatory perspective, to at least have the discussion.

As far as the issue goes of putting it in the label, ultimately, of course, one of the major issues here is a promotional one, and in fact, that placing it in the label does influence what a

pharmaceutical company is able to do in terms of their promotional material.

Now, we need to keep in mind the specific issues here since this can vary from case to case. This is, for instance, an already marketed product. Whether or not a change is made in the product label, the product is available for physicians to use. It may be used in any way, you know, that physicians deem appropriate.

I think that one could make at least a reasonable case that sometimes putting information in the label, including and as you'll notice in our questions appropriate caveats, actually is more helpful than leaving out information and then leaving it solely to the physician's discretion as to how to proceed without, for instance, the type of promotional and educational material which may, for instance, provide a broader picture.

I think all of us have been -- were impressed by the thoroughness with which the company approached this problem. I would be surprised if, for instance, they haven't considered some of the issues that we're talking about now in terms of how one might influence physician prescribing to avoid some of the problems that have been brought up, and I think if

committee members are interested, you can certainly inquire of the company as to what their thinking is currently.

But realistically this is a promotional issue. One must also keep in mind that even within the issue of promotion, there are certain types of promotion currently that are available even without the indication.

So, on one hand, granting this allows a certain type of advertising. On the other hand, it may also grant a certain type of control over that.

Nonetheless, at the end of the day you need to decide whether the data is sufficient to support such an indication. Your reservations about this issue should obviously come out very clearly.

If you feel the data is sufficient, then any caveats you have -- and we spoke specifically in our question about the issue of any modifying statements in the labeling -- under certain circumstances labeling may say for patients who have had certain microbiologic tests, for patients who may be at high risk for such-and-such, even if there is some information about how one might define that, et cetera.

We leave that to your discretion to make