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FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

67TH MEETING

THURSDAY,

OCTOBER 21, 1999

The meeting took place in the Kennedy Ballroom, Holiday Inn, 8777 Georgia Avenue, Silver Spring, MD, at 8:00 a.m., L. Barth Reller, M.D., Acting Chairman, presiding.

Present:

L. Barth Reller, M.D., Acting Chairman
Rhonda Stover, R.Ph., Executive Secretary

Gordon L. Archer, M.D., Member
Celia D.C. Christie-Samuels, M.D., M.P.H., F.A.A.P., Member
Robert L. Danner, M.D., Member
Barbara E. Murray, M.D., Member
Carl W. Norden, M.D., Member
Judith R. O'Fallon, Ph.D., Member
Julie Parsonnet, M.D., Member
David E. Soper, M.D., Member

Keith A. Rodvold, Pharm.D., Consumer Rep.

David Battinelli, M.D., Guest Expert
J. Thomas Bigger, M.D., Guest Expert
Richard Platt, M.D., Guest Expert
Jeremy Ruskin, M.D., Guest Expert

Allen Brinker, M.D., M.S., FDA Representative
Mark Goldberger, M.D., FDA Representative
Robert Hopkins, M.D., FDA Representative
Sandra Kweder, M.D., FDA Representative

Andrea Meyerhoff, M.D., M.Sc., DTMH,
FDA Representative
Leonard Sacks, M.D., FDA Representative
Robert Temple, M.D., FDA Representative

Carl E. Calcagni, R.Ph., Sponsor Representative
Deborah Church, M.D., Sponsor Representative
Alan Hollister, M.D., Ph.D., Sponsor Representative
Joel Morganroth, M.D., Sponsor Representative
Stephen Zinner, M.D., Sponsor Representative

Also Present:

Eckhard van Keutz, D.V.M., Ph.D.
John Lettieri, Ph.D.
Dr. Dagmar Kubice
John DiMarco, M.D., Ph.D.

A-G-E-N-D-A

OPEN SESSION

Issue: Avelox(TM) (moxifloxacin), Bayer Corporation Pharmaceutical Division, for the treatment of community-acquired pneumonia, acute bacterial exacerbations of chronic bronchitis, skin and skin structure infections, and acute sinusitis.

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

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

8:03 a.m.

DR. **RELLER:** Good morning. I'm Barth Reller in the Division of Infectious Diseases and Director of Clinical Microbiology at Duke University Medical Center, Acting Chairman for today's meeting of the Anti-Infective Advisory Committee.

I would like to call the meeting to order. At the outset I would like to ask all speakers to talk directly into the microphone. One doesn't have to get real close. They are very sensitive but direct the voice toward it, not immediately into it so that we can have an accurate transcription of all of the deliberations today and that all can hear your cogent comments.

Next we'll have the Conflict of Interest Statement read by our Executive Secretary, Rhonda Stover.

MS. STOVER: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based cn submitted agenda for the meeting and all financial interest reported by the committee

participants, it has been determined that all interest in firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for the appearance of a conflict of interest at this meeting with the following exceptions:

Dr. William Craig is excluded from participating in today's discussion and vote concerning Avelox. In addition, in accordance with 18 U.S.C. 208(b) full waivers have been granted to Drs. Robert Danner, Carl Norden, Julie Parsonnet, and Keith Rodvold.

A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A30 of the Parklawn Building. In addition, we would like to note that in 1996 Dr. Rodvold consulted with Johnson and Johnson regarding levofloxacin.

Further, he has had interest in Eli Lilly, Rhône-Poulenc Rorer, Bayer Corporation, and Bristol-Meyers Squibb unrelated to their competing products.

We would also like to note that Dr. Gordon Archer's employer, Virginia Commonwealth University, has an interest in Bristol-Meyers Squibb which is unrelated to the firm's competing product.

Although the interest of Dr. Rodvold and Dr. Archer do not constitute a financial interest in the particular matter within the meaning of **18** U.S.C. **208,** it could create the appearance of a conflict. However, it has been determined notwithstanding these interests that it's in the agency's best interest to have Drs. Rodvold and Archer participate in the committee discussions concerning Avelox.

Further, one of our committee members has had an interest relating to Avelox that we believe should be disclosed. FDA believes that it is important to acknowledge the participants' involvement so their participation can be objectively evaluated.

Dr. Barbara Murray previously participated in an in vitro activity study of moxifloxacin sponsored by Bayer. With respect to FDA's invited guest speakers, Dr. Jeremy Ruskin and Dr. Richard Platt have reported interests which we believe should be made public to allow the participants to objectively evaluate their comments.

Dr. Ruskin would like to disclose that his wife owns stock in Johnson and Johnson. Dr. Platt would like to disclose that he has led or participated in studies funded by Merck and SmithKline Beecham. He has also participated in discussions about potential

studies funded by Parke Davis and Bristol-Meyers Squibb. Further, he has had fees paid to his department for Merck consulting.

In the event that the discussions involve any other products or firms not already on the agenda which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

DR. RELLER: Thank you, Rhonda.

I should next like to have each member of the committee, as well as our invited experts and consultants who will contribute so much to the discussions. I'll begin on the right with Dr. Battinelli.

DR. BATTINELLI: David Battinelli, Vice Chairman for Education, Boston University School of Medicine.

DR. RUSKIN: Jeremy Ruskin. I'm Director of the Cardiac Arrhythmia Service at Massachusetts General Hospital, Boston.

DR. PLATT: I'm Richard Platt. I'm a professor of ambulatory care and prevention at Harvard Medical School.

DR. O'FALLON: Judith O'Fallon, Biostatistics, Mayo Clinic.

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

DR. CHRISTIE Celia Christie, Department of Child Health, University Hospital of the West Indies, Jamaica.

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

DR. DANNER: Bob Danner, Critical Care Medicine, NIH.

MS. STOVER: Rhonda Stover, FDA.

DR. PARSONNET: Julie Parsonnet, Stanford University, Division of Infectious Diseases.

DR. ARCHER: Gordon Archer, Medical College of Virginia Campus, Virginia Commonwealth University, Division of Infectious Diseases.

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

DR. NORDEN: Carl Norden, Division of

Infectious Diseases, Cooper Hospita1, University of New Jersey Medical School.

DR. MEYERHOFF: Andrea Meyerhoff, Medical Officer, Division of Special Pathogens, FDA.

DR. HOPKINS: Bob Hopkins, Medical Team Leader, FDA.

DR. SACKS: Leonard Sacks, Medical Officer, Division of Special Pathogens, FDA.

DR. GOLDBERGER: I'm Mark Goldberger, Director of the Division of Special Pathogens.

DR. KWEDER: I'm Sandra Kweder. I'm the Acting Office Director, Office of Drug Evaluation IV.

DR. RELLER: Thanks. It's now time for the open public hearing. Are there any remarks to be made? Since there is none, we'll move to the sponsor presentation.

DR. GOLDBERGER: Barth, can I just make a couple of remarks?

DR. RELLER: Yes.

DR. GOLDBERGER: Thank you. I would like to just join in the welcome of everyone, Dr. Reller, advisory committee members, invited consultants, members of Bayer Pharmaceuticals. Today we are here todiscuss Bayer Pharmaceuticals marketing application for the quinolone antimicrobial moxifloxacin.

Individuals who have worked in infectious disease are certainly aware over the years of how modifications, for instance, in the beta lactam antibiotics have led to significant changes in the activity spectrum.

More recently we have become aware of the potential for doing the same thing with fluoroquinolone antimicrobials and in response to growing problems with infections, particularly resistant infections due to gram positive organisms, an effort has been made to modify many of the newer fluoroquinolone antimicrobials to enhance their gram positive activity. We'll be talking about such an antimicrobial today.

Not surprisingly when one does structural modifications, one changes not only activity but sometimes one changes the toxicity profile as well. We have become increasingly aware over the last few years of the broad range of toxicities associated with the fluoroquinolone antimicrobials. We will, of course, be discussing the safety profile of this drug as well.

As part of that discussion we will be having some commentary about the issue of QT prolongation associated with this antimicrobial. It

is important to note that QT prolongation occurs with a wide range of noncardiac drugs and including a range of antimicrobials beyond simply the fluoroquinolones. Assessing the significance of such prolongation is not an easy issue.

We are extremely fortunate that in addition to our invited guests the company also has Dr. Joel Morganroth, an extremely well-known expert who as part of the company's presentation will be giving an overview of this issue to hopefully provide those of us who are infectious disease specialists with some reasonable understanding of the issue.

We are looking forward to an interesting discussion today. We thank you for your attention. Thank you.

DR. RELLER: Thank you, Mark, for helping me read the agenda in the right order and for that broad overview.

Dr. Kweder, do you have anything you want to say at this time?

So having had the stage set by the FDA, we will now move to the sponsor presentation. This will be led by Carl Calcagni who is the Vice President for Regulatory Affairs at Bayer Corporation Pharmaceutical Division.

It has been requested and worked well yesterday that we have the entire sponsor's presentation. Then there will be an open discussion on all issues raised by this presentation with assistance from Carl in directing the questions to the appropriate members of his presenting team, as well as consultants to Bayer.

Carl, please.

MR. CALCAGNI: Thank you, Dr. Reller. Thank you, Dr. Goldberger. I think you set the stage. I will probably repeat some of the things you said and you will probably hear about the agenda once again. I apologize for the repetition but I think it's important to set the stage for today.

My name is Carl Calcagni as you see before you. I'm the Vice President for Regulatory Affairs at Bayer Pharmaceutical Corporation in West Haven, Connecticut. I wish to thank the members of the advisory committee, the FDA, and the other participants for this opportunity today to present Bayer's new drug, moxifloxacin hydrochloride to be known commercially as Avelox.

Bayer submitted its NDA 21-085 application approximately 10 months ago. Bayer corporation is a global leader in the development of quinolones and

anti-infectives. Cipro, or Ciprofloxacin hydrochloride known by most of you, was approved in 1987, quite a long time ago. It has over 12 years of marketed clinical experience in the USA.

Over 200 million patients have been treated worldwide. Today Bayer presents this advanced generation of quinolone that was synthesized at our Bayer AG Leverkusen, Germany facility.

Moxifloxacin was synthesized with a purpose and developed with a purpose; to cover respiratory tract pathogens for enhancing gram positive and atypical activity; to provide longer half life to ensure once daily dosing; to improve compliance by shorter course of therapy and good tolerability; to potentially minimize antibiotic resistance; and to provide a new alternative for community respiratory tract infection treatment.

Moxifloxacin has current approval status in the listed countries. It has been recently marketed in Germany and is currently in process for the mutual recognition procedure in Europe.

Bayer's objectives today are to demonstrate that moxifloxacin is safe and effective for acute bacterial exacerbation of chronic bronchitis, acute sinusitis, community acquired

pneumonia, uncomplicated skin and skin structure infections, and to review the observation of the QTc prolongation with moxifloxacin, **assess** its relative risk factors, and present submitted labeling that is appropriate and responsible.

Moxifloxacin dosage administration is once-a-day for the following indications and duration of therapy. Acute bacterial exacerbation of chronic bronchitis, five days; uncomplicated skin and skin structure infections, seven days; acute sinusitis, **10** days; and community acquired pneumonia, **10** days.

The agenda today will reflect our review of the efficacy and safety by Dr. Deborah Church who is the director at Bayer for the anti-infective group, followed by a backgrounder on the QTc by Dr. Joel Morganroth, clinicalprofessorof medicine, University of Pennsylvania, presenting the background.

Then for purposes of our data presentation, Dr. Alan Hollister, who is the deputy director of our clinical pharmacology group. Following that, and providing the risk benefit and conclusion, will be Dr. Zinner who is the Charles S. Davidson Professor of Medicine, Harvard Medical School, Chair of the Department of Medicine at Mount Auburn Hospital.

In addition, Bayer has in attendance today the listed experts for consultation by the advisory committee, the FDA, and Bayer if needed.

I would like to present Dr. Deborah Church to present the efficacy and safety section.

DR. CHURCH: Good morning. My name is Deborah Church and I'm here today to speak to you about the efficacy and the safety of moxifloxacin, a new 8 methoxy quinolone developed by Bayer.

What I would like to do is start off by just setting the stage and going through the items that I'll be discussing during my presentation. I'll discuss with you the rationale for development, the microbiology, the pharmacokinetics and pharmacodynamics of the compound.

We'll talk about the findings of moxifloxacin and drug resistance. I'll share with you the clinical and bacteriological results submitted in the NDA for the four indications we are seeking approval for; acute sinusitis, acute exacerbation of chronic bronchitis, community acquired pneumonia, and skin infections.

I'll also share with you outcome analyses that we did, particularly with the morbidity parameter. When speaking about safety, I'll discuss

with you drug interactions, excretion, and metabolism. When discussing exposures of patients we'll talk about adverse events, serious adverse events, premature discontinuations, deaths. I'll compare moxifloxacin with the controlled drugs when talking about selected quinolone related events.

For the particular topic of QTc prolongation and the observations with moxifloxacin, Dr. Morganroth and Dr. Hollister will go on to talk about that later in the presentation.

Despite the predictions that infectious diseases were on the decline, we have actually seen today that respiratory tract infections still account for significant mortality and morbidity. Drug resistance has increased over time. We know that is the case with the organisms which you'll hear today; haemophilus influenzae, moraxella catarrhalis, and in particular with streptococcus pneumoniae or know as strep. pneumo.

It thus makes sense that new antibiotics and a change in selection and use may be needed to alter these trends of resistance. Potent new fluoroquinolones such as moxifloxacin should have an important place in the management of infectious diseases.

I have put this slide here that you have seen yesterday also just to show the impact of decreasing penicillin macrolide susceptibility of strep. pneumo in the United States.

This diagram goes through the last two decades. Looking at the left-hand side of the slide, you'll see that the number of macrolides suspectable to penicillin in 1979 approached about 97 percent. A year ago that percent went down to about 64 percent. With respect to resistance in 1979 was about a 0.2 percent. As of a year ago that increased to 14 percent.

That's not only the case with penicillin but also the case with the macrolides. An example being on the slide, erythromycin. In 1979 100 percent susceptibility. Looking at 1998, down to about 77 percent.

So why did Bayer set out to design moxifloxacin? We had an increased knowledge of quinolone structure activity relationships which facilitated the following. We had excellent gram negative coverage but we wanted to look for enhanced gram positive, atypical, and anaerobic activity.

We'll share with you an innovative approach to resistance in terms of efflux as well as

other mechanisms of action. We wanted to look for the optimal pharmacokinetics and pharmacodynamics.

We wanted to select the appropriate dose not only for therapeutic efficacy, but we also wanted to look for a compound that had a low propensity for resistance and, of course, a favorable safety profile.

This is the structure of moxifloxacin. This is the apparent ring of the quinolones. We now know by changing some of those side chains on quinolones we can actually do a number of things. The first thing is we can enhance the antibacterial profile. The second part of it, we could try to look for mechanisms to minimize resistance. How do we do that?

This part of the chain is the C-7 which is the bicyclic amine which actually enhances gram positive activity as well as minimizes efflux, particularly for strep. pneumo and staph. aureus. This is the C-8 position which is the methoxy position which actually enhances anaerobic activity, as well as minimizes development of resistance through DNA gyrase as well as topoisomerase **4.**

We have done a number of in vitro experiments with moxifloxacin. I would like to share with you some of those highlights. This is the in

vitro activity of moxifloxacin against the key respiratory tract pathogens, strep. pneumo. Unlike the beta lactams regardless of whether the strain is penicillin susceptible or penicillin resistant, the MICs for moxifloxacin are identical at 0.25.

A very similar case with haemophilus influenzae, moraxella catarrhalis. Regardless of whether there is production of beta lactams or not, those MICs are identical at 0.06. We certainly know that atypicals are on the rise. They are important pathogens in community acquired pneumonia, once again with very favorable MICs for moxifloxacin.

How about with regards to other respiratory tract pathogens? Well, with haemophilus parainfluenza and strep. pyogenes the MICs are 0.25. With regards to staph. aureus methicillin susceptible at 0.125 and for MRSA and MIC at 4.

We also know that moxifloxacin is active against a wide variety of clinically important anaerobic species. For the sake of brevity I've just placed two examples here, bacteroides with an MIC of 2 and peptostreptococcus with an MIC of 0.25.

It is important to note in general that the MIC value is less than **2** for the minority of the anaerobes. Moxifloxacin in contrast to other

quinolones is very active against M. tuberculosis with an MIC of 0.5.

I've placed this slide here to reinforce that the MICs for moxifloxacin and for strep. pneumo is unaffected by resistance by penicillin. I'll tell you about a second item I would like to bring in also. We have a list of three quinolones here; moxifloxacin, levofloxacin, and ciprofloxacin. Macrolides, examples are clarithromycin and azithromycin and the beta lactams with amoxicillin, clavulante acid and cefuroxime axotal.

You can see as I go down the macrolides that if the organism is a pen. susceptible strep. pneumo to a pen. resistant strep. pneumo that the MICs do increase. The same thing happens with the beta lactams. Certainly not the case with the quinolones. The second important feature is when looking at the three quinolones here the most active of the three quinolones is moxifloxacin with an MIC of 0.25.

Now, I would like to tell you a little bit about the findings with moxifloxacin and drug resistance. What I'll do is give you two findings and actually give you an example of an in vitro experiment and some in vivo examples.

With regards to the mechanisms of

resistance mutations in nor A gene that up regulate the membrane associated drug efflux pump despite increased antibody efflux from nor A containing strep. pneumo and staph. aureus, moxifloxacin MICs remain identical to the wild type. That is, identical wild type MICs to mutant MICs.

Mutations in topoisomerase **4** and DNA gyrase, simultaneous independent mutations in both grl A and gyr A are required to increase the moxifloxacin MICs. Even when this occurs, though, the MICs are still near the clinically observed minimum concentration of the drug.

This is just an example to give you differential emergence of resistance between levofloxacin and moxifloxacin with one particular strain of strep. pneumo 4241. If you look at the X axis we have the number we have the number of passages from serial exposures at 0.5 times the MIC which is also the same as the number of days.

If you look at the Y axis you actually have the MICs. If we look at zero we'll see that the MIC for moxifloxacin, which is designated by the yellowish green line here, you'll see that the MIC is about 0.25. Levoquine or levofloxacin the MIC is 1.

If you look at a particular day such as

day four, you'll see that the MIC for moxifloxacin is less than or equal to 1. If you go to levofloxacin you'll see there's an increase of about 10 fold. If I go out to day six, what I'll see is there's a plateau for moxifloxacin. If I look at levofloxacin, there's about an MIC of about 100. What I've tried to show you here is there's slow development of resistance to moxifloxacin and to a lesser extent for levofloxacin.

How about with staph. aureus? Same type of diagram here, the isolate being strain 133. Once again the MIC for moxifloxacin about 0.125. Higher for levofloxacin. If I look at, for example, day four, I see that it's less than 1 for moxifloxacin, higher than that, close to 10 for levofloxacin. Moxifloxacin plateaus here and about a 64 when going out to day six to eight for levofloxacin. Once again, showing you the slow development of resistance to moxifloxacin and to a lesser extent than levofloxacin.

This is an example of an in vivo model. This actually is a rat granuloma pouch model looking once again at the two pathogens that I've just shown you, staph. aureus 133 and strep. pneumo 4241. The items here are the type of mutants created whether it's the first step or multi-step for both the

pathogens. The MIC for moxifloxacin from day zero to day eight are identical across the board. Therefore, there's no development of moxifloxacin resistance in the rat granuloma pouch model.

I would like to summarize what we've said so far. We've targeted both the DNA gyrase as well as topoisomerase 4. There's been minimization of resistance that has been demonstrated in vivo by the example that I've given you with levofloxacin. The animal studies have shown no emergence of resistance in the rat granuloma pouch model. These important results are achieved via the methoxy group at C-8 which significantly delays the selection of resistance in the bicyclic amine at C-7 which minimizes drug efflux.

Let's talk a little bit about the pharmacokinetics and the pharmacodynamics of moxifloxacin. They are pretty straightforward. The half life at steady state is **12** hours which actually supports once daily oral dosing of 400 milligrams. The Cmax is 4.52.

Another important item if you look at the concentration over a 24-hour period, you'll see the concentrations above the MICs of the relevant pathogens I've just spoken to you about, strep.

pneumo, staph. aureus, haemophilus and moraxella.

I would like to talk to you not only about the pharmacokinetics and pharmacodynamics and also tissue penetration. Here basically is respiratory as well as sinus tissue. Looking at the plasma concentrations once again from 3.3 to 3.7, way above the MICs of the relevant pathogens that I've shown you. Tissue are fluid concentrations.

Particularly I would like you to note the macrophages which have a 61.8, as well as the epithelial lining fluid at 24.4. I would like to show you that ratio. Looking at the ratio between tissue and plasma at 21.2 for macrophages and 8.7 for the epithelial lining fluid.

Just in the form of a comparison, I would like to show you levofloxacin. This is at 2 and 4 hours. If I look at the 2 hours 21.2 for moxifloxacin versus 7.3 and 8.7 versus 0.8.

Those are two other parameters that are well known to look at correlations with quinolone efficacy. There are the Cmax or maximum concentration to the MIC 90 which should be at least eight to 10. Looking at the area under the curve divided by the MIC 90 of greater than 100. I would like to show you how moxifloxacin compares to other quinolones with this.

Just on top just to go over this, moxifloxacin, levofloxacin, ciprofloxacin, sparfloxacin, and grepafloxacin. This is particularly looking at the Cmax over the MIC 90. We know for optimal antibiotic effect and to minimize development of resistance that the Cmax to MIC 90 ratio should be at least eight to 10.

For haemophilus influenzae, moraxella catarrhalis if you look across the board those are pretty much above eight to 10. Let's look at strep. pneumo, a very important pathogen. You can see that looking at levofloxacin, ciprofloxacin, sparfloxacin, and grepafloxacin, these numbers are less than the eight to 10. Moxifloxacin is above that with an optimal number of 18.

Now, what if I wanted to look at AUC and MIC 90, once again looking at the same quinolones, haemophilus influenzae, moraxella catarrhalis, once again those numbers for optimal antimicrobial effect and to minimize resistance should be greater than 100. Across the board those are over 100. If I want to look at strep. pneumo, once again looking at the other quinolones less than 100, moxifloxacin at 192.

so far what I've shown you about pharmacokinetics and pharmacodynamics, moxifl.oxacin

PK, certainly supports once-a-day dosing. It provides plasma and tissue levels above the MIC for the relevant respiratory pathogens for the entire 24-hour period. A **400** milligrams once-a-day dose of moxifloxacin provides optimal pharmacokinetics and pharmacodynamics. Moxifloxacin pharmacokinetics results in the optimal overall pharmacodynamic characteristics that you just saw, Cmax over MIC area under the curve over MIC compared to the other four quinolones.

Now, I would like to take you a little bit through the general aspects of the clinical development program that we did as well as go into the individual indications.

We did Phase II and Phase III studies that were performed in the four indications you'll hear about; acute sinusitis, acute exacerbation of chronic bronchitis, community acquired pneumonia, and skin infections. We used the FDA/IDSA guidelines as well as the primary efficacy variable with clinical outcome. That was assessed at test of cure which we defined it some number greater than or equal to seven days after the last dose of drug. We also looked at secondaryvariables whichincludedthe bacteriological responses as well as safety.

As provided in the points to consider, the treatment groups were tested for equivalents and the intent to treat population and safety population included all patients who took at least one dose of study drug.

Just to give you the idea of how many studies we did and how many patients were in these trials, we did 15 trials in respiratory tract infections plus three for skin for a total of 18 studies. With regards to the number of patients, there were 8,306 patients in the NDA of which 3,109 received comparator, which I'll talk what comparators we used later on in the presentation, and 4,015 patients were on moxifloxacin at 400 mg.

Now, what I would like to do -- these slides are pretty much set up the same way -- I'll talk to you about each indication individually. I'll show you the clinical responses and the bacteriological responses.

This is for acute sinusitis and we're looking at the clinical resolution at test of cure. I just want to start out by telling you that D96-024 and D96-023 were the first sinusitis studies that we started off with. **024** was a double-blinded prospective multi-sentry trial performed in the United

States. We found the drug to be efficacious at 81 to 80 percent. But when doing this trial against cefuroxime 250 milligrams BID for 10 days, the seven days of moxifloxacin did not show equivalence to cefuroxime.

We did a very similar trial outside the United States in Europe and we found this study to be equivalent to cefuroxime. We then proceeded to do a sinusitis study at 10 days which is 100, 107, a doubled blinded prospective multi-sentrytrialdone in the United States with a 90 percent cure rate.

I want to mention that these are not taking into consideration improvements. These are true cure rates. Ninety percent versus 89 percent for cefuroxime at 10 days.

One hundred and sixteen is the study I mentioned which was actually the seven-day study in Europe which had a 90 percent cure rate for seven days of moxifloxacin versus 84 percent for cefuroxime did show equivalence. 116 is the 10-day study which is quite similar to the U.S. study with a 94 percent cure rate, 95 percent for cefuroxime.

What about microbiology? Three target pathogens here; strep. pneumo for moxifloxacin at seven days had a 98 percent eradication rate, 95

percent for cefuroxime. With regard to haemophilus influenzae, 86 percent versus 85 percent. For moraxella catarrhalis 88 percent versus 67 percent, although there were small isolates for that arm.

So for acute sinusitis both in North America as well as outside North America the studies demonstrate equivalence between the 10 days of moxifloxacin and the 10 days of cefuroxime. The microbiological efficacy of the seven days of moxifloxacin was demonstrated against the three targeted pathogens. Moxifloxacin given for 10 days is clinically and bacteriologically effective for the treatment of acute maxillary sinusitis.

Now, I would like to go on with acute exacerbation of chronic bronchitis. We have two studies there I would like to talk to you about. The first one is D96-027. It's a double-blinded prospective multi-sentry trial done in the United States and the 124 which was done in Europe doubled blinded also.

With respect to the 027 we actually looked at 10 days of moxifloxacin versus five days of moxifloxacin and saw almost identical rates of 91 percent versus 89 percent.

When looking at the five days of

moxifloxacin in the control which was clarithromycin given over 10 days. It was 89 percent versus 89 percent, identical rates.

For the ex-US study at five days moxifloxacin had identical numbers with the U.S. trial. And with regards to clarithromycin given over seven days, that was 89 percent versus 88 percent.

I know this is a busy slide but these are the organisms that we are looking for approval for; haemophilus influenzae, 90 percent for moxifloxacin versus 64 percent for clarithromycin; strep. pneumo 89 percent versus 95 percent; moraxella catarrhalis 86 percent for moxifloxacin versus 98 percent for clarithromycin; staph. aureus 94 percent versus 84 percent; kleb. pneumo 85 percent versus 91 percent; haemophilus parainfluenza 84 percent versus 100 percent.

I've told you so far for acute exacerbation of chronic bronchitis that moxifloxacin is consistently demonstrating equivalence to the comparator. It's effective against the major pathogens associated with this disease. A five-day treatment arm is recommended based on the favorable clinical and bacteriological results. The shorter duration may increase the compliance and facilitate

patient convenience.

There were also a number of studies that were done in community acquired pneumonia. The first two studies, D96-026 and D96-025 were actually studies done in North America. **119** and 140 were done outside of North America.

Just to take you through them, 026, a doubled-blinded prospective multi-sentry trial with moxifloxacin over 10 days having 95 percent cure rate versus a 95 percent cure rate with clarithromycin over 10 days.

The open study, 025, had a success rate of 93 percent with moxifloxacin over 10 days. The 119, the European study, was 93 percent with moxifloxacin versus 92 percent with clarithromycin. **140,** 89 percent for moxifloxacin versus 89 percent with the comparator which here was amoxicillin given one gram three times a day.

Just to give you an idea about pathogen eradication rate for community acquired pneumonia, strep. pneumo 89 percent, almost identical to the control, 88 percent; haemophilus influenzae 90 percent, once again higher than the control at 74 percent; moraxella catarrhalis 86 percent versus the identical number for the control 86; kleb. pneumo 87

versus 80 percent; staph. aureus 94 percent versus 90 percent.

With mycoplasma as well as chlamydia we did also cultures as well as serological testing and those numbers are for mycoplasma 94 percent versus 95 percent for the control; for chlamydia 92 percent versus 96 percent.

so moxifloxacin is clinically and microbiologically effective in community acquired pneumonia. It shows favorable activity against typical as well as atypical target pathogens associated with the disease.

Now, we talked about enhancement of gram positive activity and I want to show you some of the results of our skin trial. Two trials, once again 97005, the U.S. trial, and 0131, both double-blinded prospective multi-sentry trials with clinical cure rates 89 percent for moxifloxacin given over seven days in the U.S. versus the control which was 90 percent with cephalexin. Looking at 131 it was 95 percent for moxifloxacin given over five to 14 days versus 93 percent for cephalexin plus or minus metronidazole.

Just to give you some of the eradication rates for the particular pathogen seen there, the

predominate pathogen was staph. aureus at an 82 percent eradication rate in the U.S. study versus 93 percent for the control. For the ex-U.S. study 92 percent versus 88 percent for the control.

Once again, moxifloxacin is clinically effective, microbiologically active for uncomplicated skin infections, 400 milligrams once a day for seven days as recommended for optimal patient compliance and convenience.

So I just want to show you the indications and durations in doses and the different indications we just talked about. I've shown you evidence for the efficacy of acute sinusitis over 10 days for the targeted pathogens seen here; acute exacerbation of chronic bronchitis for five days for the same pathogens plus haemophilus parainfluenza, kleb. pneumo, as well as staph. aureus, and for community acquired pneumonia for a 10-day duration, same organisms with the atypical, and skin infections for seven days with gram positive coverage.

I want to show you two additional analyses that we did. The first one is looking at penicillin intermediate and resistant isolates to strep. pneumo from our pivotal trials using 400 milligrams of moxifloxacin in control. Overall there were 146 of

207 isolates. 71 percent of the strep. pneumo were actually penicillin susceptible.

This chart goes through penicillin intermediate as well as penicillin resistant strains. Those were defined as intermediate, an MIC of greater than 0.1 to less than 2 and resistance was an MIC of greater than or equal to 2.

I've done this by the particular indications; sinusitis, community acquired pneumonia, acute exacerbation of chronic bronchitis. I'll ask you to look at all studies which is the combination of all these results.

For intermediate isolates we had 31 isolates for an eradication and cure rate of 87 percent. There were 11 isolates in the control arms and those controls once again were clarithromycin and amoxicillin at 1 gram TID for an eradication and cure rate of 82 percent.

For those isolates that were resistant we had 15 isolates for an eradication rate and a cure rate of 87 percent. With regards to the control arm, there were five isolates and 80 percent eradication and cure rate.

So 46 or 37 percent of the strep. pneumo isolates were recovered from patients treated with

moxifloxacin, had MICs in the penicillin intermediate or resistant range. The high clinical success rate that was observed in patients with penicillin intermediate and resistant strep. pneumo suggest that these infections respond to moxifloxacin at 400 milligrams. These clinical and eradication success rates were either comparable or higher than those observed for comparators.

Now, I want to show you one additional outcome analysis which basically has to do with morbidity. We wanted to examine additional benefits of moxifloxacin. We did a retrospective analysis of the data from acute exacerbation of chronic bronchitis patients and community acquired pneumonia patients with the intention that these patients being, of course, outpatients.

The data was analyzed for overall hospitalization rates and we pulled the studies across the U.S. as well as internationally and we compared those data with our control drugs.

Now, this is looking at worsening of respiratory conditions which resulted in hospitalization. Remember that these are outpatients with acute exacerbation of chronic bronchitis and community acquired pneumonia patients.

We selected adverse events based on COSTART terms of worsening of bronchitis, worsening of pneumonia, or lung disorder. Lung disorder, for example, was exacerbation of COPD would be a good example and any of the above.

Just to let you look at this one particular line of any of the above, there were **18** patients that worsened their condition and resulted in a hospitalization of the moxifloxacin arm. That was versus 30 patients in the control arm. so hospitalization rates were lower and the acute exacerbation of chronic bronchitis patients as well as the pneumonia patients treated with moxifloxacin when compared to the control. The P value of that was 0.02.

So I just want to conclude with efficacy saying that moxifloxacin is microbiologically and clinically effective in the treatment of acute sinusitis, acute exacerbation of chronic bronchitis, community acquired pneumonia, and skin infections.

The clinical and eradication success rates that you've seen for penicillin intermediate as well as resistant strep. pneumo were either comparable or higher than those observed for the comparators. The data from the additional morbidity analysis

demonstrated favorable results from moxifloxacin versus the comparators. With respect to the hospitalization rates in patients that had acute exacerbation chronic bronchitis and community acquired pneumonia.

I'd like to give you a short review of moxifloxacin safety profile just in the form of a summary.

Moxifloxacin dosage adjustment is not necessary to the elderly, particularly speaking here about age, gender, race, either mild, moderately, or severe renally impaired patients, or mild to moderate hepatically impaired patients.

An important feature which you'll hear Dr. Hollister speak about in his presentation is moxifloxacin is not metabolized by cytochrome P450 enzyme system. It also has no apparent clinical effects on the cytochrome P450 enzyme system. Unlike other quinolones, for example, levofloxacin which is primarily exceeded from the kidneys and trobofloxacin from the liver, moxifloxacin exhibits a balanced excretion by both renal and biliary routes.

There are no clinically significant drug/drug interactions and I've placed here a number of them; theophylline, warfarin, digoxin, probenecid,

ranitidine, and glyburide. As with other quinolones, although this is not an issue of safety, reduce moxifloxacin bioavailabilitywith antacids and iron if given concomitantly.

Just to give you an idea of what safety profile we have, worldwide 5,233 patients were enrolled in either the 200 or 400 milligram arm of moxifloxacin. 99.2 percent of these patients were evaluated for safety and 89 percent of these patients were treated with the 400 milligram dose. Of the 400 milligram moxifloxacin treated patients valid for safety, 4,008 patients, 87 percent were enrolled in the control trials. You'll see that number when I show you some of the safety tables.

To give you an idea of what safety procedures we did, we monitored clinical evaluations, laboratories including chemistries, hematology, electrolytes, urinalysis, PT/PTT, additional studies such as theophylline, 12-lead ECGs which you'll hear those results with Dr. Hollister. We monitored adverse events. We did this during baseline and during end of therapy and the follow-up was usually four weeks after the last dose of drug.

Just to give you an idea of the number of patient exposures, we had a total of 21 studies. With

regards to the 400 milligram controlled studies, there were **4,008** patients; all moxifloxacin treated patients, 5,189; and with comparators 3,689.'

What I would like to do is go through the incidents of adverse events by individual events. What I've done here is placed any adverse effect which has been greater than or equal to 2 percent. This also does not take into account whether the investigator thought it was drug related or not so we have all the adverse events here.

I've also placed them in the frequency of highest frequency to lowest frequency. I'll show you the comparison of moxifloxacin with the controlled drugs. Overall any event, **46** percent for moxifloxacin versus 45 percent for controlled drug. The most frequent events were nausea, diarrhea, headache, and dizziness, quite similar with the controlled drugs. All the events past dizziness were 3 percent or less.

Now, if you were wondering what that adverse event profile looks with any individual comparator, I've placed that also. Quite busy but just to point out a number of items. When looking at something, for example, as GGTP, the highest values were in the amoxicillin **1** gram TID as well as the cefuroxime 500 milligram BID arms.

When looking at something, for example, as liver functions, 11 percent with amoxicillin, 1 gram TID. If I was to look at this particular study with moxifloxacin the comparison would be 6 percent there.

How about premature discontinuations. Once again, the rates are quite low and similar to the comparators. Moxifloxacin had a 5 percent premature discontinuation rate to adverse events. That was versus 4 percent for the control. When looking at any individual event., as you can see they are quite low, less than **1** percent for moxifloxacin.

With regard to serious adverse events, once again quite similar. Four percent for moxifloxacin and 5 percent for the control. Looking at any individual event, once again those were less than 1 percent.

So, in summary, just the part of the adverse event profile, the incidents of adverse events were quite similar; 46 percent for moxifloxacin at 400 milligrams versus 45 percent for the control. We're looking at serious adverse events, 4 percent versus 5 percent. Premature discontinuations due to adverse event, 5 percent versus 4 percent.

So moxifloxacin was comparable to the FDA well established control drugs. Most adverse events

reported were mild to moderate in severity and required no therapy.

Now, what I would like to do is show you some mortality rates. What I'll do is consider deaths that we recorded through 30 days post study drug administration. I'm going to show you three subsets. The first subset will be those patients that were enrolled in the indications we are seeking approval for; respiratory tract infections and skin infections.

If you look at the moxifloxacin arm, there were seven deaths versus 15 deaths in the control arm for a P value of 0.056. Now, if I wanted to look at those patients that had acute exacerbation of chronic bronchitis as well as having community acquired pneumonia, those deaths were five in the moxifloxacin arm versus 15 in the control for a P value of 0.009.

What if I just wanted to look at those pneumonia patients? You would see there are four deaths from moxifloxacin versus 12 from the control. The P value is 0.045.

The mortality rates were lower in the community acquired pneumonia patients and the combination of those patients with acute exacerbation of chronic bronchitis. Rates were lower with moxifloxacin than those that we're seeing with the

control drugs.

Now, there are a number of selected events that have been associated with some of the quinolones and I have selected some of those to show you the rates we have with moxifloxacin versus control drugs, the first one being CNS. I selected seizure. One patient on moxifloxacin 400 milligrams versus 2 for the control. This particular patient actually had a preexisting condition of seizures.

With respect to pain in the achilles tendon, there were two versus zero for the control. Neither of these patients had any action taken for the pain in the achilles tendon and there were no tendon ruptures.

With regard to phototoxicity, two with moxifloxacin versus three for the comparator. I must mention that these two patients actually had more of a sensitivity to bright light than actually phototoxicity.

Being such an important issue with quinolones we did in vitro and in vivo studies that did not show any evidence of phototoxicity. We actually did a double-blinded placebo controlled clinical phototoxicity study and we looked at moxifloxacin at seven days and saw it was comparable

to the placebo.

Certainly with the recent events with trobofloxacin and elevated liver functions, we looked at that. **1.6** percent adverse events associated with liver functions abnormalities withmoxifloxacinversus 1.9 percent with the comparators. I just want to give you a little bit more information on the next slide.

Preclinical in Phase I hepatic safety that we looked at, the morphologic liver alterations were seen in monkeys only at lethal doses and they were not seen in the dogs which are considered the species sensitive to this situation of hepatic safety.

Elevation of liver enzymes were slight and transient in nature. As we stated previously, liver impairment did not influence the pharmacology of moxifloxacin in our Phase I studies.

Once again, as we mentioned previously, moxifloxacin is excreted via multiple routes. **20** percent renal, **51** percent hepatic, and 25 percent transintestinal.

I would like to show you the liver functions that we collected during our Phase III program. I have divided this into three parameters and t iree functions. SGBT, SGOT, and bilirubin. The three parameters were greater than upper limit of

normal. It actually means that anything that is up with the limit is normal. Greater than 1.8 times the upper limit of normal or greater than three times the upper limit of normal for each of the parameters.

If you look across the board with moxifloxacin in control, you will see that the rates are identical and very similar, I should say, between moxifloxacin and the control.

There was the other important issue that there's no difference noted when comparing this by gender, race, or age group, and that the premature discontinuations, that were due to the elevations of LFTS that were greater than three times the upper limit of normal, were equal numbers both in the moxifloxacin treated patients and with the controlled treated patients.

So summary of safety. So far we've heard that only adverse effects occurring in greater than 5 percent of the patients were nausea and diarrhea. Premature discontinuations were less than 1 percent for any single adverse event.

The mortality rates in community acquired pneumonia and the combination of those patients with acute exacerbation of chronic bronchitis for the moxifloxacin treated patients were lower than those

observed with the comparators.

When looking at those selected events associated with quinolones such as phototoxicity, liver function abnormality and seizures were rare with rates comparable to the control drugs.

Before I end I just want to give you a summary of all the attributes I have spoken about. Excellent pneumococcal activity. Activity against haemophilus influenzae, moraxella catarrhalis including beta lactams positive. Activity against atypicals. We even talked about activity in vitro with MTB.

Optimal PK/PD for the major respiratory tract organisms. The important issue here, once daily dosing for short duration of therapy of five to 10. Minimization of resistance. No dose adjustments in special populations including the elderly and hepatically and renally impaired patients.

No interaction with the cytochrome P450 system. No significant clinical drug/drug interactions. Favorable morbidity and mortality trends. And a favorable safety profile including hepatic safety as well as phototoxicity.

In conclusion, moxifloxacin is safe and effective in respiratory tract infections as well as

skin infections. The favorable pharmacokinetics and dynamics of moxifloxacin enhances efficacy as well as safety. The once daily short five to 10 duration offers a patient compliance, convenience, and safety advantages. Thank you.

I would like to leave the podium and give this to Dr. Joe Morganroth who will talk to you about the background of QT prolongation.

DR. MORGANROTH: Thank you very much, Dr. Church. Mr. Chairman, ladies and gentlemen, it's my pleasure today to provide you some information about the QT interval on the electrocardiogram, a topic which actually, I think, is quite timely in light of the increased regulatory interest that this particular ECG wave form change has engendered over the last few years and is now the subject of points to consider in Europe and draft guidelines at the FDA.

The QT interval is an important electrocardiographic safety measure in drug development. It's important as you look at drug development data to ask some very critical questions about the methodology and the form of interpretation of the QT interval. I think it's no longer necessary to assume that with a couple of hundred ECGs randomly selected in clinical trials, hopefully on the drug and

not before and after, that you can, in fact, be able not to make a lot of proper judgments about the QT unless you have a form of development that 1'11 describe to some degree and is present in some of the new guidelines.

The first thing that I wanted to show you is an electrocardiogram. I show you this principally to remind you that we're not going to be talking about the kinds of ECG information that relate to morphology and PR interval QRS interval, heart rates, etcetera, which are all valuable pieces of information. We are going to concentrate only on one of the wave forms which is the QT. I remind you that the EKG has a background of a grid in order to measure the interval durations. The waveform itself can be subjected to a lot of different measurements. Again, we are going to concentrate only on the QT interval which I remind you is made up of both depolarization, the QRS, and repolarization, the junction of the QRS and the ST segment, the J point to the end of the T, the so-called JT interval. Historically and conventionally we measure the entire depolarization, repolarization sequence rather than just repolarization which is the part of the ECG complex we are most interested in today.

The grid itself is important because the tiniest of the little boxes that you can see on an electrocardiogram when obtained at 25 millimeters a second standard speed that the paper runs through the EKG machine. That smallest little box has a duration of milliseconds of 40, a number I had asked you to remember as we get into what this particular duration of various drugs do to the QT interval.

It's obvious from just what I've shown you that one should think about how the QT is measured in a drug development set of electrocardiograms. This is not an interval that is simple and easy to measure such as heart rate. That's because one is looking at a T wave which may have low amplitude. There may be noisiness to the baseline. There can be low amplitude signals.

In fact, the T wave can be distorted by the presence of a U wave which is when abnormal and bizarre, in some cases, may in fact indicate the early after depolarization that is the hallmark of the beginning potential for repetitiveness of ventricular beats that can form a ventricular tachycardia, and if associated with a polymorphic form and a long QT has gone under the name of torsade de points which we'll talk a bit more in a moment.

In terms of the difficulty of measurement, it's important to remember that you still need a human being for this process, I believe. The use of computers that think that they can find the end of the T wave and differentiate it from the U wave, we're still not there. Taking the measurements off of a routine computer reading of an electrocardiogram is generally potentially faulty and it requires some experience to differentiate U waves from T waves and some degree of art to that rather than pure science by any means.

In terms of the quantitation of QT durations, the normal value accepted in the United States is approximately **440** milliseconds. The variability of the QTc duration in man over the day is really quite marked. It can range from **15** to 70 milliseconds with trivial changes in time or position or food or what have you.

Actually, if we look at multiple measures that have been made in a group of normal volunteers, the average was 75 milliseconds over a day when ECGs were taken on an hourly basis and 5 percent of those electrocardiograms had levels of 500 milliseconds or greater, a level that there is some concern in terms of the clinician's feeling about significance in terms

of drug discontinuation.

Cardiac patients tend to start with longer QTc. They tend to be a bit more variable. As you recall, the QT interval duration is very dependent on the heart rate. As you heart rate slows, the QT gets longer. As your heart rate speeds, the QT gets shorter. So if you're dealing -with an infectious disease patient who may have fever and tachycardia in the initial electrocardiogram may show a short QT.

As the treatment breaks in and the patient's depheresces and the heart rate slows, the QT can lengthen. It's very important to do a correction of the QT. The classic correction is the Bazett formula from the 1920's which is a square root function of the heart rate. This breaks down very frequently when you get to tachycardiac rates so the Fredericia Q group function generally tends to do a better job.

There are linear regression formulas. Often in the research mode of QT, if you will, we are beginning to look at QT dynamicity, looking at the RR as it relates to every QT and perhaps defining a specific square root function.

Remember Bazett is .5 and Fredericia is .33. Something between .33 and .5 may, in fact, be

the best number to correct for an individual study in an individual patient. Again, I mention that it's a research mode. The importance is that we're not sure exactly yet how to correct in all settings.

Let me spend a moment because I know one of the questions this committee is going to address, which I think is No. 4, at the end of the day is to provide some guidance on drug development and QT issues. I'll just spend **a** moment to emphasize what the committee on proprietary medicinal products in Europe have issued as points to consider in terms of the QT interval. This came out essentially about a year ago -- a year and a half ago. Excuse me. Some of the points that were emphasized in terms of drug development and QT issues are, No. 1, that a centralization of the electrocardiograms is greatly encouraged because of the site to site variability. This is such a difficult measure if you put in the variation of how individuals read electrocardiograms at various sites. That produces so much noise that you can find a great deal of false/positive and false/negative. Centralization is important and that the ECGs, in fact, should be read by experienced cardiologists that have looked at and thought about U wave issues versus T waves.

The committee has recommended that the standard 12-lead electrocardiographic intervals be done in a manual mode avoiding automatic QT measures meaning as the computer prints it at the top of the ECG. Or to try to obtain QT data from Holter monitoring and that the manual reading is needed in order to provide a precise mechanism.

Digitizing a pad with point to point computer digitized human readings with five millisecond resolutions are possible. I remind you that if you use an eyeball cardiologist and calipers, that the point of the caliper can be as wide as maybe half of those little tiny boxes or about 20 milliseconds.

We're going to be talking in a few minutes about drug changes in the zero to 10 millisecond range. It's important to use digitizing methods and not eyeball calipers and automatic readings.

Obviously the fifth point that the committee is making is that you should probably try to measure your EKG while you have as much of the drug on board as possible rather than getting an EKG before and after. That really tells you whether the drug has caused permanent damage to the heart rather than actually looking at effects. Still we see many data

sets that have not adequately sampled their ECGs.

I must point out that the Bayer presentation on moxifloxacin despite the fact that their program began before the CPMP guidelines has adhered to these policies in terms of using centralization to their ECG reading set and using the single cardiologist in applying a good number of these principles and, therefore, their data set as well as their timing of the ECGs were appropriate to understand their QT effect.

Now, the QTc change that's important in many people's minds from a regulatory point of view is any QTc change like one millisecond, you know, or anything that's real is sufficient to be of concern because it's an effect. The question is at what level of QTc duration do you have something to worry about in terms of clinical relevance and importance.

A second issue is how do you tell whether if you have a very small mean change in the QTc like one, two, three, four, five, six milliseconds which is, you know, half of a little box or less than half a little box. It's like quarter of a box. To determine whether that mean change is, in fact likely to be of significance.

Well, you look for outliers like in many

phases of drug development safety issues. You try to find how many patients go beyond a certain limit that are important like going above 3x on your liver function test.

Well, the committee decided to pick numbers that are derived from our terfenadine variability data that actually suggest that if a drug causes a QTc change, it is more likely that it's the drug doing it rather than spontaneous variability if, in fact, you reach 60 milliseconds or more.

It's a clear concern that the drug is causing that effect. Less than 30 milliseconds is more likely than not due to spontaneous variability. Obviously between 30 and 60 would be the borderline zone.

At the FDA in many divisions a **15** percent criteria is used. One usually cuts the data at 10, **15,** and 20 percent. If you ask clinical cardiologists, their concern tends to be at **500** milliseconds because it's at that level when a cardiologist sees a QTc duration increase that consideration for a drug reduction or discontinuation is often made. Again, there's great variability among cardiologists.

The QTc dispersion which is really simply

taking the longest QT in any one of the 12 leads and subtracting the shortest QT. There's a great deal of controversy right now as to whether it really reflects repolarization of the heart of maybe just a quantitative means of determining T wave changes on the electrocardiogram.

Nevertheless, it's an interesting measurement in which if the committee felt that if your dispersion increases by **100** milliseconds on drug from baseline or changes by **100** percent, that would be considered a significant effect.

I must remind you that the QT interval prolongation doesn't cause the individual patient at the time that that occurs any notice. It doesn't cause any symptoms of any kind whatsoever. It does not effect the cardiac function in any way. Until it **as a** risk factor adds with some other factors; hypokalemia, ischemia, heart failure, changes in sympathetic tone, something has to develop in addition to QT in order to produce an important clinical event, the worst of which, of course, is Torsade de Pointes, a polymorphic ventricular tachycardia which can be **short enough to just** cause no symptoms, occasionally; dizziness, potentially severe enough to cause fainting with self-remission or can go on to degenerate to

ventricular fibrillation and death. There is a wide spectrum of potential effects of the QT prolongation with other cofactors.

I have already mentioned to you that the clinician believes that the QTc often has to hit a 500 or greater before this becomes an important risk factor. However, we need good epidemiological data to try to link the degree of QTc prolongation with torsade and the degree of risk.

At the present time from a public health point of view, any effect on the cardiac repolarization is considered something worth discussing, something worth putting into the risk benefit assessment of the drug to determine whether or not it should be approvable or not.

There are many things that cause the QTc to prolong and they are listed on this board. I'm not going to go through them other than to point out it's a wide cascade of events whether it's metabolic, congenital, potassium channel, genetically based deficiencies in the congenital long QT syndrome, CNS disorders, electrolytes, ischemia, etcetera.

There are also, if you will, a whole host of types of drugs that have been well studied and well reported to effect the QT interval. Antiarrhythmics,

of course, historically being the most concern but we have now learned in the last decade and emphasized the fact that noncardiac drugs are very frequently potential actors in this realm from all kinds of various classes, as you'll see, and a whole host of miscellaneous classes.

I must point out that is why the CPMP guidelines are suggesting that every single new chemical entity and biologic should be studied for a QT effect preclinically with, for example, herb potassium channel model. There's a great debate as to which is the best screening methods preclinically, but that one should consider what the preclinical risk of your drug is just like one would do other toxicological studies.

In man despite what you find preclinically, because there may not be good correlation between preclinical models and humans, that in man one should include electrocardiographic study for QT interval in all drugs, particularly in Phase I and in an intense way if there is a positive or equivocal preclinical study.

I thought you would find this interesting, and this is in your handouts, to look at what the Food and Drug Administration in the United States has done

with the labeling of QT prolongation or a drug that has had Torsade de Pointes which implies QT prolongation and has mentioned it or pointed it out in the label.

You'll see that erythromycin, clarithromycin, and you can read these, etcetera, are drugs that have QT notice in the label. The azoles, ketoconazole and itraconazole specifically not only have it in the label but there are black box warnings. That's probably because and I suspect more appropriate because of the 3A4 P450 system interaction which is profound, although, of course, erythromycin has that interaction.

In fact, an intravenous study with erythromycin has shown as many as half the patients that receive that drug may have QT prolongation of important note. Dr. Hollister will give you more information about that.

There is a whole host of -- I'm going to ignore the antiarrhythmics for a moment, of course, but there's a whole host of CNS drugs, more than it seems to me any other class seems to be the ones that are popping up all over the place. But there are many, many drugs that have QT prolongation. They are noted in the label. Some are emphasized, as I

mentioned. Most are not.

This is the interesting slide. This is a slide of over 60 drugs that have in the literature, have in other drug labels or with other regulatory agents -- we could focus that a bit but you have it in your handouts so that's fine -- have QT prolongation known or torsade association with it. Mostly QT prolongation.

Drugs like, for example, imipramine which no one questions has a QT interval prolongation and is an important drug. Most of these drugs -- excuse me, all of these drugs have no mention in their label of a QT effect whatsoever which is interesting. There's a great deal of heterogeneity about how one warns physicians in the label as to the QT interval. A lot of it has to do with historical relevance of once drugs are on the market to come back and change the label with less data is not **easy**.

Let me point out that drugs that prolong the QTc, of course, are the antiarrhythmics. We have the most information about them. This may be not relevant in terms of the discussion today or more noncardiac drugs but I give it to you as a bench mark that when you are dealing with drugs that prolong the QT from the antiarrhythmic point of view, and this is

giving it to cardiac patients, often with arrhythmias, like ibutilide being given to patients with serious supraventricular arrhythmias for acute conversion.

The rate of Torsade de Pointes per year; how often that problem occurs is extraordinarily high for this type of class in this setting. It can be in the one to 10 percent. That's one out of 10, one out of 100 people. I'll ask you to remember that huge number because from a public health epidemiologic point of view that's huge.

Compare it to terfenadine because terfenadine was the noncardiac drug that I think got all of us interested in this issue of QT prolongation. The first thing that was clear is that terfenadine in the early '80s was released around the world as the first antihistamine that had no sedating activity and had a good antihistaminophinic profile. It was very popular and very successful. Two hundred million patients approximately were on the drug by the first 10 years.

In the 1989 to 1991 range there were 83, and maybe now more than 150 in that early period, instances of cardiac issues, fainting. In fact, some cases of Torsade de Pointes and some reports of prolonged QT despite the fact that no one had noticed

on any of the electrocardiograms any QT effect done in the usual way, not as the CPMP recommends.

If one looks at the reported incidents, which of course is always underreported, and obviously this is probably the best case for the drug, it's about one in 200,000 patient months. I've heard other estimates as much as high as one in 10,000. The number is probably, in my opinion, somewhere around one in 100,000. That's a lot different than one in 100 or one in 10 that you may get with an antiarrhymic.

That rate needs to be compared to the benefit and the risk. The amount of QTc prolongation that terfenadine produced after one looked at this very carefully with a digitizing manual method at its clinical dose of 60 milligrams BID was six milliseconds. By the way, the same number you're going to be seeing today from moxifloxacin.

Of course, what was interesting about terfenadine and what is very different about terfenadine and moxifloxacin is that this drug, terfenadine, has a major interaction at P450 3A4. In fact, the parent compound terfenadine is where all the QT effect occurs.

If you block its metabolism by co-

administering ketoconazole or erythromycin in blocking 3A4, you don't convert terfenadine until it's acid metabolite fexofenadine, now on the market as an antihistamine called Allegra. What happens is that with blockade by the drugs that you see on the bottom, or an overdose or other problems with the liver, you can get a QTc that goes up nice and linearally with drug dose or with this metabolism.

In fact, you can induce a rate of Torsade de Pointes that is in the one to 10,000, one in 100,000 rate. If you're giving it for sniffles as an antihistamine, that was considered largely unacceptable from a risk benefit.

Today you will be discussing the risk benefit of moxifloxacin and the QT effect. I think that you will, and I'll summarize very briefly and quickly, that the effect on the QT at therapeutic doses, 400 milligrams per day of moxifloxacin, is this six millisecond number. You'll see that it's similar or less than most of the other antibiotics, particularly of the macrolide class, and, of course, of the conazole class, and frankly of sparfloxacin and many other of the fluoroquinolone class.

What's important in my mind personally as you distinguish this drug in a risk benefit, is it's

not used for months or years but it's used for five to 10 days. This short duration is the most salutatory anti-concern that I would have about the QT prolongation. The other thing is it is being used for not sniffles but for potentially life threatening bacterial infections.

Another, and probably the second most important reason that I'm not as concerned about this issue, is that there are no drug interactions at 3A4 which, therefore, make the likelihood of the QT going longer on this drug less obviously than on most of the metabolic issues save, of course, by giving another drug that prolongs the QTc with it.

I think these issues can be easily worked out in appropriate cautionary labeling as you'll hear. This issue of QT prolongation will become something that won't be as difficult to deal with as the day progresses. Thank you very much for your attention.

Let me ask Dr. Hollister to come up and give you the data in detail about the QT effects of moxifloxacin.

DR. HOLLISTER: Thank you, Dr. Morganroth. This morning I would like to talk to you about moxifloxacin and our evaluation of its effect on the QT interval.

During the early development of moxifloxacin in our preclinical and Phase I we found a mean six millisecond prolongation of the corrected QT interval. We decided to initiate a series of prospective studies and retrospective analyses of the data to try to identify what the level of risk was and what cofactors in terms of the risk might be present.

As Dr. Morganroth has pointed out, why is QT prolongation an issue? Experientially it is a risk factor for ventriculary arrhythmias including Torsade de Pointes. The magnitude of the risk, particularly in these short intervals, the magnitude of prolongation does not predict risk. Obviously there are limits. If you have something that prolongs **100** milliseconds, that's likely to be a much greater risk than something that prolongs a very short time.

I think the issue here is that these small prolongations are neither necessary nor sufficient for determining risk, and it's the other things that go along with the prolongation that help you evaluate clinical risk.

The risk is greater with drug accumulation. Dr. Morganroth talked about the terfenadine story. In many other situations with noncardiac drugs the issue is the drug that causes the

QT prolongation accumulating.

There are specific subpopulations that are more sensitive to the QT prolongation effect of drugs. It is appropriate for us to evaluate the subpopulations that have received moxifloxacin to see if there is any signal for risk in those subpopulations.

So what I'll go over, Dr. Morganroth has done a lot of QT background. There is some that leads into my preclinical studies that I will cover just briefly in terms of evaluation of the moxifloxacin effect on the QT interval and the mechanism that's involved here.

Then I will show you our analyses of the electrocardiogram and clinical subpopulation risk factors or risk predictors that are taken from the literature as being associated with QT prolongation and/or the onset of ventriculary arrhythmias. In addition, I will give you an evaluation of those that our outliers; that is, those that have greater QT prolongations, adverse events, and deaths.

So we are all on the same page, we are talking about the QT interval, as Dr. Morganroth has explained from the beginning of the Q wave to the end of the T wave.

This QT interval represents the depolarization/repolarization time of the myocardium and the normal range is 300 to 450 milliseconds. Females tend to have a little bit wider range at 470 milliseconds as "normal." There is a lot of spontaneous variation as you've seen from Dr. Morganroth's studies.

The issue of correcting for heart rate is quite important because in this setting we're treating ill patients who have an elevated heart rate often times at the onset of therapy and with successful therapy their heart rate will shorten. As Dr. Morganroth told you, as you slow the heart rate, the QT interval will prolong.

The corrections that are used in the majority of the data that I will show you are this Bazett's correction, the square root of the RR interval divided into the QT measurement.

Now, in terms of an individual myocardial cell, this is a tracing of the action potential in the myocardial cell and in time link fashion the potassium channels are currents that are involved in some of the phases of the depolarization/repolarization. This is the familiar Phase 0, Phase I, plateau Phase II, and repolarization Phase III of the myocardium.

During this period of time repolarization of the cell is dependent on the outward movement of potassium, the so-calledpotassiumrectifier channels, the Ikr and the IKs channels you'll hear them termed. Sometimes I believe Dr. Morganroth used the genetic term for the channels as well.

These outward going channels are responsible for repolarizing the cells to their resting potential. Interruption, a blockade of these channels will prolong the action potential duration perhaps in a fashion like this. With sufficient prolongation, what may happen is you have summation of the heterogeneity of repolarization in the myocardium that gives you these so-called early-after depolarizations.

Theseearly-afterdepolarizationsaretime related to the appearance of U **waves** so when a lot of early-after depolarizations are occurring and summating, you see changes or appearance of a U wave and sometimes giant U waves. This can lead to a progressive, a repetitive depolarization of the cells and a ventriculary arrhythmia.

Now, in our preclinical studies we looked at these repolarizing or rectifying potassium channels, Ikr and IKs. These do vary by tissue

preparation and our results varied by tissue preparation. The bottom line we feel is that moxifloxacin is a weak blocker of the Ikr channel relative to sparfloxacin, for instance. It's one-third the potency of sparfloxacin. We have other data currently underway that has not yet been reviewed by the FDA.

In the classic guinea pig myocardiummodel IV action potential duration, there is a concentration dependent prolongation of the action potential with an apparent threshold for moxifloxacin in the order of 50 micromolar as opposed to sparfloxacin, around three micromolar.

During the course of these studies there was no appearance of early-after depolarizations with moxifloxacin which indicates there is no presence of that risk factor from an electrophysiological point of view.

Moving on to the animal arrhythmia studies, we have the classic animal arrhythmia study is an anesthetized methoxamine infused rabbit. Methoxamine, the alpha agonist, is infused to induce reflex bradycardia because that potentiates the onset of arrhythmias, particularly arrhythmias of the long QT form and Torsade de Pointes.

Moxifloxacin and sparfloxacin in this model were infused at two milligrams per kilogram per minute for an hour. I'll show you a slide of the actual data in a moment. With moxifloxacin one of six animals showed PVCs after a total cumulative dose of moxifloxacin of **96** milligrams per kilogram. No ventricular tachycardia arrhythmias occurred with moxifloxacin.

Incontrast, sparfloxacinshowedpremature ventricular contractions in half of the animals at earlier time points. Three animals showed ventricular tachycardias including one that had classic Torsade de Pointes during the course of the infusion with sparfloxacin.

In another even higher dose preparation in an anesthetized dog, we were able to obtain ventriculary arrhythmias but only at extreme concentrations of the drug, greater than **200** milligrams per liter or approximately 50 fold the Cmax that we're talking about in humans. This is not possible in the conscious dog because CNS toxicity occurs at lower concentration than these concentrations and these concentrations cannot be reached orally.

This is a slide of the data of the rabbit

arrhythmia model with plotting the QT interval in milliseconds against the time of infusion of the test drug here at two milligrams per kilogram per minute of either moxifloxacin or sparfloxacin. Methoxamine infusion was actually begun **10** minutes before the zero time point.

Here in the sort of yellowish is sparfloxacin, the actual data and a regression line with indications of the time points at which ventricular tachycardia and Torsade de Pointes occurred during the sparfloxacin infusion. Moxifloxacin, in contrast had no events of ventricular arrhythmias with the infusion. Somewhat less of a slope in terms of the effect on the QT interval.

Now, the literature tells us that clinical studies of patients with QT prolongation and arrhythmias associated with QT prolongation show a number of ECG risk factors that can be monitored. Amongst them are the magnitude of QT prolongation which is about the only thing that we have looked at clinically in the past.

Now we know the dose dependency or concentration dependency of QT prolongation is another way to help assess risks. Using this committee for proprietary medicinal products criteria, if you have

a high frequency of patients exceeding limits in that criteria, that may be a signal for a risk issue, the increased dispersion of the QT interval.

I'll give you my definition of that when we get to the slide and Dr. Morganroth as alluded to it. In addition, reverse rate dependency is another characteristic that has been described with drugs that prolong QT interval and cause arrhythmias. I'll define that when we get to the slide. There are several others that I will give you as well.

This is our worldwide and North American experience in terms of moxifloxacin and the effect of moxifloxacin on the QT interval. This is the change in the QT plus or minus the standard deviation here in our data set of all paired valid ECGs. In order to meet those criteria, we had to have a base line and on-drug ECG. **The** on-drug ECG had to be obtained during a window of time during which we were confident drug concentrations would be high.

This shows the all comparators with the average changes here. Then for your interest the comparator drugs are broken out. This is not all the comparator drugs but many of them to show you the size of change here.

Now, to put this in perspective in terms

of antibiotics, the next slide shows some literature values that we found for erythromycin, clarithromycin, grepafloxacin, and sparfloxacin. The erythromycin orally, a mean prolongation in a study with approximately 160 patients in it of 13.8 milliseconds. The IV study that Dr. Morganroth mentioned showed very large prolongations in the QT interval and a high frequency of patients exceeded 500 milliseconds.

Withclarithromycinthevarious references in the literature range from three to 11 milliseconds of QT prolongation. Grepafloxacin in its registration data, 10 milliseconds. Sparfloxacin has in its label 11 milliseconds. Other references will give you a range of that data.

Very pertinent to these drugs is the fact that there are important drug interactions because of metabolic issues. I will show you some of the data with respect to moxifloxacin.

There is the potential for drug accumulation because of the drug's route of elimination sometimes interacting with the drugs that may be co-administered with the drug as well. For perspective, I'll show you where the moxifloxacin mean six millisecond falls with respect to these other commonly employed antibiotics.

I took the data from our Phase I trial base to try to determine whether or not there might be a concentration effect relationship. Plotted here are the QTc for our 211 patients -- 211 subjects, mostly Phase I normal subjects, plotted against the moxifloxacin concentration that was drawn at the time the EKG was obtained. As you see, there is an upward slope as we regress this data. There is a lot of scatter around the data. These are the 95 percent limits. This is the limit of normal for males.

This regression is significant. The ability of this regression line to account for the variability, though, is poor. The R squared is only about three percent of the variability is accounted for by a regression.

Now, another way to look at these kinds of data are the outlier frequency. This committee for proprietary medicinal products provided a guidance document about two years ago giving these definitions for normal, borderline prolongation, prolongation, and risk of arrhythmia here in terms of the corrected QT interval.

In terms of the change in the QT, as Dr. Morganroth showed you, those that changed less than 30 milliseconds implies no concern with respect to a

drug. Thirty-one to 60 possible drug effect and greater than 60 is concern for arrhythmias. In addition, this parameter QT dispersion, should that exceed 100 milliseconds or increase more than 100 percent, are also criteria for concern.

So using these data, or these criteria, and some of the ones that have been employed by the FDA, we have made a table here of the frequency of outliers. Here with greater than 500 milliseconds. Here a change in the QT interval of more than 60 milliseconds. Here a change more than 30 milliseconds to an abnormal value be it male or female. Then a simple change in the QT of greater than 15 percent.

This is the moxifloxacin database, the all comparators in our all paired valid database. You see there are minor differences here and here in terms of the frequency. If you take any of those outliers overall, there is very little difference between moxifloxacin and all comparators. For your interest, the other drugs that are underneath this all-comparator category are shown there as well.

The QT dispersion is defined as the greatest difference in the QT interval between any two leads in the 12-lead EKG. Again, it's considered a risk if the QT dispersion exceeds **100** milliseconds.

In a Phase I study that was cross-over administering placebo, 400 milligrams moxifloxacin, **800** milligrams moxifloxacin orally, and EKGs obtained repeatedly after administration of these drugs, the QT dispersion, whether it's the absolute QT or the Bazett's correction of the QT, were measured. This is the mean and standard deviation for values of placebo, on moxifloxacin **400,** moxifloxacin **800.**

As you see, there is no difference in QT dispersion on what we think are therapeutic doses and super therapeutic doses of moxifloxacin. We have no evidence that moxifloxacin increases QT dispersion.

Another characteristic of drugs that are associated with QT prolongation and caused Torsade de Pointes is this co-called reverse rate dependency. Basically this is a prolongation of the QT interval that does not shorten proportionately as the heart rate increases leading to the possibility that you can have the R on T phenomenon and arrhythmias.

In such a drug you would expect plotted on this sort of a graph an upward going curve. Our data with moxifloxacin determined over multiple heart rates at **400** milligrams and at 800 milligrams show the opposite direction of the slope of the curve. Our expert interprets this as no evidence for reversed

rate dependency with moxifloxacin.

Another potential risk group are those that start with long QT intervals. We tried to address this issue by taking the top quartile of people in terms of the duration of their QT interval prior to drug therapy. Then we ask the question **what** happens to the QT in these people when they are treated with moxifloxacin or the comparator drugs.

These are the data from our largest database and it shows that if you start with a longer QT, in fact you have a shortening of the QT interval on average, the so-called regression to the mean. Patients with longer baseline QT intervals are not at greater risk for QT prolongation. This is in contrast to data that has been generated with erythromycin, for instance.

So to summarize these electrocardiographic risk factors for QT prolongation that we took from the literature and applied to our data set, we have a magnitude that is a mean of approximately six milliseconds prolongation. There is a concentration dependence to that prolongation. It's a shallow sloped curve and does not account for the vast majority of the variation in QT interval.

In terms of the QT outliers using the CPMP

and other criteria, there's no overall difference in the frequency of outliers with moxifloxacin versus comparators. We found no effect on QT dispersion, no reverse rate dependency of QT prolongation. Those patients that started with lung baseline QTs actually decreased the duration of their QT interval.

Now, other factors have been published in the literature that are pertinent to risk evaluation of drugs that may prolong QT are QS widening, T wave abnormalities, appearance of new U waves. There is no QRS widening with moxifloxacin. T wave abnormalities are not different between the moxifloxacin and comparative groups. There were no differences in the appearance of U waves pre and on therapy with moxifloxacin.

Now, there are a number of clinical subpopulations that are recognized as being at higher risk for QT prolongation and arrhythmias with drug administration. The ones that are published in the literature include cardiovascular disease, age - older age, gender. Females are more susceptible than males to this effect.

Electrolyte abnormalities, particularly low potassium, bradycardia, particularly profound bradycardia associated with increased frequency of

arrhythmias and Torsade, and as you are well aware, drug interactions that increase the concentration of the relevant drug.

In addition, reduced organ function that can increase the concentration of the relevant drug also are issues in terms of evaluating risks. The co-administration of drugs that themselves prolong the QT interval. Is there a synergistic action. Clearly with some drugs there may be.

Then finally the accumulation of metabolites that may be associated with an increased risk of arrhythmia that may accumulate in organ dysfunction. A good example is the hydroxy metabolite of quinidine.

So in a series of slides here 1'11 show you these clinical risk factors, their presence or absence or the parameter and the effect on the QTc, corrected QT interval, here plus or minus the standard deviation. Here for cardiovascular disease, the presence of cardiovascular disease, we had about 122 subjects in our population. They did not show more QT prolongation than subjects without cardiovascular disease. This, again, is in contrast to a drug such as erythromycin.

Here with **age, age** greater than 65 years

is associated in the literature with excessive QT prolongation and increased risk of arrhythmias. We did not find an increased QT prolongation in elderly patients treated with moxifloxacin.

Similarly in terms of gender the females in the literature are more susceptible to QT prolongation and arrhythmias. There is no difference in those patients treated with moxifloxacin in the change in QT interval.

Electrolyte imbalance, hypokalemia. Here very small numbers of patients if we take the cut at 3.5 milligrams per liter. The mean, plus or minus standard deviation, here is small and there is no interaction effect in terms of the prolongation of the QT interval with moxifloxacin.

With heart rate bradycardia is recognized as being -- profound bradycardia -- a risk factor for QT prolongation and for the onset of arrhythmias. These show the mean change in the QT interval in 80 of our subjects that had bradycardia at entry into the study.

We find no effects of the hypokalemia or bradycardia.

Now, moxifloxacin does not inhibit the cytochrome P450 enzymes as Dr. Church related to you earlier. This means that it's very unlikely that

there would be Phase I drug/drug interactions. Our data with a variety of drugs that I'll show you on the next slide indicate there are no significant drug/drug interactions with cytochrome P450 metabolized drugs.

In addition, moxifloxacin itself is not metabolized by the cytochrome P450 system including the specific 3A4 isoenzyme that is the most problematic to us clinical pharmacologists. Because it's not metabolized by this system, there's no risk for accumulation of moxifloxacin during co-administration of other inhibitors which are so common.

This slide shows an abbreviated list of the drug interaction studies that we performed with the enzyme system within the cytochrome P450 system, the specific isozymes that are responsible for the primary metabolism of these drugs and just a brief comment on the results.

Theophylline is metabolized by the 182 isozyme. Co-administration of moxifloxacin with theophylline does not result in increases or changes in theophylline levels nor changes in moxifloxacin levels. Co-administration of moxifloxacin with glyburide does cause a slight decrease in glyburide concentrations, nonsignificant in terms of glucose

control, and no change in moxifloxacin levels.

Warfarin, which is stereoisomerically metabolized predominately by the 2C9 isozyme of cytochrome P450 has neither of its metabolites. The stereoisomers or the metabolites are changed by co-administration with moxifloxacin and moxifloxacin levels are not changed during co-administration.

Ranitidine is recognized as a weak inhibitor of the cytochrome P450 system and co-administration of moxifloxacin with ranitidine does not alter moxifloxacin concentrations.

We have additional data that are not yet reviewed by the FDA, and our in vitro data that all support the concept that there's no interaction at the cytochrome P450 system with moxifloxacin.

Looking at additional clinical risks factors, co-administration of moxifloxacin with drugs that are known to prolong the QT interval in a small number of subjects in our largest data set had co-administration of these drugs. They did not show excessive QT prolongation with the addition of moxifloxacin.

Also, renal dysfunction and hepatic dysfunction. I'm showing you here the extremes of our renal dysfunction data in Phase I studies less than 30

milliliter per minute creatinine clearance does not influence the effect of moxifloxacin on the QT interval. With hepatic dysfunction, again with reduced hepatic function we studied child pew class A and B patients. There is no increase in the QT effect of moxifloxacin.

Now, with renal dysfunction there is some accumulation of the M2 metabolite of moxifloxacin, the glucuronide metabolite. Despite that accumulation, there is not excessive QT prolongation. With hepatic dysfunction there is some accumulation of the sulfate metabolite moxifloxacin. Again, there is no apparent effect of that metabolite on the QT change with moxifloxacin.

So to review these data in terms of clinical subpopulations that might conceivably be at risk during co-administration of moxifloxacin, with cardiovascular disease, age, gender, concomitant administration of QT drugs, organ dysfunction, electrolyte imbalances, specifically potassium imbalances, and bradycardia, there was no change in the effect of moxifloxacin on the QT interval.

Importantly there are no metabolic interactions that are likely to increase the concentration of moxifloxacin. There were none. Nor

are there any interactions that moxifloxacin is likely to cause any accumulation of another drug that might conceivably effect the QT interval.

Finally, organ dysfunction is not a risk for drug accumulation with moxifloxacin. That also is an important factor in terms of risk assessment of this drug.

Another way to approach the whole issue is from the other direction. You say let's take those people that really did show the QT prolongations and ask whether or not they had adverse events. What I've done here is with our largest safety database is looked at the people that met any criteria as being a QT outlier by the CPMP criteria and the others for which in our largest database we have **38** with moxifloxacin and 28 with all the comparators.

Then we ask the question did they have cardiovascular events. One of 38 subjects exhibited sinus tachycardia rate 130 about three days into therapy of her community acquired pneumonia. That's the only cardiovascular event associated with these QT prolongations with moxifloxacin.

In contrast with our comparators, four subjects had cardiovascular adverse events. Two were sinus tachs. One was an atria1 flutter. One was a

ventricular arrhythmia resulting in death. We found no evidence of a signal here. In those patients that have QT prolongation with moxifloxacin we found no clinical risk for cardiovascular adverse events that exceeded those of comparator drugs.

If we look at the broader database, too, we also ask the question are there other cardiovascular events going on that might conceivably be a signal for arrhythmia or other problems with moxifloxacin. We called these surrogates for QTc prolongation.

We searched the database withmoxifloxacin and all comparators and these were terms that had the most frequent. Your briefing document has a larger table of all of these terms and shows that the frequency of tachycardia, evidence of myocardial ischemia, palpitations, heart failure, episodes of syncope, or arrhythmias were no different between moxifloxacin treated subjects and the all-comparator treated subjects.

I would remark that amongst these arrhythmias with moxifloxacin the three arrhythmias that we had were -- in fact, if you look closer the data were atria1 fibrillation. One was a sinus arrhythmia which is a normal heart rate. One was the

appearance of a solitary PCV on an EKG. In contrast with our comparators, two of those were ventricular arrhythmias that resulted in death.

If we take our data and look at it in terms of deaths whether It's any death in the treatment program, deaths within 30 days, deaths within seven days, or deaths on therapy, comparators here in red, moxifloxacin in blue, in each cut of the data for deaths there is a favorable trend for moxifloxacin.

So to conclude our evaluation or risk factors here, we do know that moxifloxacin produces a mean six millisecond QT prolongation. In our evaluation of the database, we could find no electrocardiographic or clinical subpopulations that were predictors for excessive QT prolongation by moxifloxacin.

Those patients who had the greatest changes in QT interval with moxifloxacin did not experience more cardiovascular events. Finally, deaths were less common in moxifloxacin treated patients than in the comparator treated subjects.

So to try to give you a benefit risk evaluation here, Dr. Church has given you information regarding broader spectrum of coverage for

moxifloxacin compared to many of the other quinolones. In fact, other antibiotics to some extent. We think there are in vitro improved efficacy ratios for moxifloxacin with some indication in vitro superior resistance characteristics.

The pharmacokinetics are straightforward and reliable in that they are not affected by organ dysfunction or interaction with other drugs. Elimination is by multiple systems so that drug does not accumulate.

The short duration of therapy has been mentioned before. It's once daily therapy. There's one peak per day for five days or maybe 10 days, depending on the indication. Also, factors into low risk compared to other drugs. No dose adjustments are necessary because we didn't find things that cause drug accumulation. There are no interactions with the cytochrome P450 system which is central to so many of the noncardiac drugs that cause Torsade de Pointes.

We found no liver, CNS, or phytotoxicity in comparison to the background rate in comparator drugs and we have favorable morbidity and mortality trends in data that Dr. Church showed you.

Against this benefit here, we do have some risk that is difficult, if not impossible, to quantify

in terms of QT prolongation. As we look very closely at the population, we could find no electrocardiographic or subpopulations that were at particular risk and that's in contrast to many other drugs. Overall our database shows no clinical evidence of risk with moxifloxacin in terms of this QT prolongation.

With this benefit risk ratio in mind, we propose the following label for moxifloxacin. Moxifloxacin as with some other quinolones and macrolides has been shown to prolong the QT interval of the electrocardiogram. The degree mean plus or minus standard deviation of QT prolongation with moxifloxacin in our clinical trials was six plus or minus 26 milliseconds, compared, for example, to two plus or minus 23 in patients treated with clarithromycin.

Consequently, moxifloxacin should be used with caution in patients with congenital or acquired syndromes of QT prolongation, or in patients taking concomitant medications known to prolong the QT interval, examples are Class IA and Class III, even though our database found no evidence of risk in those populations. Thank you.

Now, it's my pleasure to introduce to you

Dr. Stephen Zinner, the Charles Davidson Professor of Medicine at Harvard Medical School and Chair of the Department of Medicine.

DR. ZINNER: Thank you very much. In addition to my new job, I'm a rapidly aging infectious disease doctor.

It's my task to very rapidly and briefly summarize for you some of the principles that have been seen with moxifloxacin. I just want to start with my disclosure list of companies for whom I'm a consultant and those companies that have supported some of my research studies over the years.

I believe you've heard today that moxifloxacin is safe and effective for the treatment of acute exacerbations of chronic bronchitis, community acquired pneumonia, acute sinusitis, and skin structure infections.

In addition, I believe that the moxifloxacin does have excellent in vitro activity against all of the common respiratory tract infective organisms. I believe it has pharmacokinetics and pharmacodynamics that promote rapid killing. It has some novel properties that might minimize the development of antibiotic or antimicrobial resistance.

I think also there has been demonstrated

a possible positive impact on mortality and hospitalization in patients with lower respiratory tract infections.

I think we still need new antibiotics today in our current clinical environment. We certainly heard yesterday, and are well aware, that resistance among the respiratory tract to infective organisms is certainly increasing. In some cases in some parts of the world and in some parts of this country a high-level penicillin resistance among pneumococc may be seen in up to **10** or **15** percent of strains. We continue to see penicillin and beta lactam resistance among strains of moraxella catarrhalis with roughly 30 percent of strains being beta lactamase producing.

And we have also seen some increase in resistance to the microlides in vitro. In some studies among strains of penicillin resistant strep. pneumoniae as many as 40 and in some cases 50 percent may also be resistant to the microlides.

The respiratory tract continues to be a site of infections that are associated with significant morbidity and mortality. We have been bombarded with new pathogens including Legionella and some other atypical pathogens.

Unfortunately for those of us in infectious diseases who like to think we can make the diagnosis in most of these cases, therapy is usually empiric and directed against the broad range of common causative organisms.

Moxifloxacin has an excellent in vitro activity against these common respiratory tract infections with low MICs well within the drug concentration range for this drug.

In addition, if you look at these organisms, pneumococcus, haemophilus, and moraxella, the common bacteria causing these infections, with respect to whether or not they are resistant to beta lactams, here are two quinolones, moxifloxacin and levofloxacin. You can see that their MICs do not change with or without penicillin or beta lactam resistance.

However, with respect to clarithromycin, amoxicillin, clavulante, and cefuroxime you can see that certainly penicillin resistant strains have a much higher MICs for those antibiotics.

Now, with respect to antimicrobial resistance, I think common properties for the fluoroquinolones is that they are in general not affected by beta lactamase or other mechanisms

including those that affect microlides or aminoglycosides for example.

However, there are some differences that do exist among the fluoroquinolones with respect to resistance mechanisms. You've heard about the nor A mutations and the efflux pump, as well as topoisomerase mutations. Really that should be DNA gyrase and topoisomerase 4.

With respect to moxifloxacin's resistance perspective, the efflux pump mechanism virtually do not affect moxifloxacin, at least with strep. pneumo and staph. aureus. In fact, one needs more than two mutations to show resistance in in vitro situations.

In vitro passage studies have shown a low propensity for resistance and in the rat granuloma model did not show in vivo resistance development during exposure to moxifloxacin.

I think one of the particular properties of this drug that is particularly of interest to me and particularly useful are its excellent pharmacokinetics and pharmacodynamics if the drug is greater than 90 percentbioavailable when administered orally and achieves a Cmax at steady state of 4.5 milligrams, well above the MICs for the pathogens under consideration.

In addition, it has a long half life, elim nation half life of 12 hours. It achieves high levels in serum tissue and the levels of which are greater than the MIC, 90 for most of the respiratory tract organisms over the entire dosing interval.

Of these pharmacodynamic parameters of Cmax to MIC, which has a bench mark of eight to **10** in some circumstances, and the AUC/MIC 90, which has a bench mark that seems to change over time, at least whether you use a low one of 20, a high one of 125, or anything in between, certainly both of these parameters are far exceeded by moxifloxacin. And the drug is rapidly bactericidal against the bacterial pathogens that have been studied.

The clinical profile has been well presented to you. As you know, the development was focused on acute sinusitis, acute exacerbations of chronic bronchitis, communityacquiredpneumonia, skin and skin structure infections. The studies were designed to show equivalence according to the FDA approved study designs. A single dose of 400 milligrams once a day is useful for either five to 10 days depending on the indication. I'm particularly attracted to the shorter course possibilities with this drug.

And as you know and have seen, these studies showed equivalence with the comparators for acute exacerbations of chronic bronchitis with clarithromycin, community acquired pneumonia with clarithromycin and amoxicillin, sinusitis with cefuroxime and skin structure with cefuroxime.

The safety profile, as you have heard, over 5,000 patients have received 400 milligrams once a day, roughly 39,000 exposure days. The adverse effects, there were no surprises with respect to the quinolone class of drugs. Most events were present in less than five percent except for nausea at nine percent and diarrhea at seven percent. This continuation and serious adverse effects on moxifloxacin were similar to that of comparators.

In addition, there was no hepatotoxicity, no nephrotoxicity, no phytotoxicity seen with this drug. The QTc prolongation, about which we have heard a great deal, is comparable to commonly used antimicrobials. No cardiac events were seen at increased rates related to QTc with the drug.

I think that the moxifloxacin's clinical pharmacology really does support the entire safety profile in that it has a balanced metabolism in elimination. It is not metabolized as we've heard by

the P450, which I think may be important with respect to minimizing any risk associated with the slight prolongation of the QTc. No drug/drug interactions have been seen other than iron and antacids similar to the other members of the class.

No dosage adjustments are needed in either renal or hepatic insufficiencies and there appears to be no risk of serious adverse effects due to interactions with other agents because of the metabolism.

Some unanticipated positive outcomes that turned out -- although the studies were clearly not designed to show this, there was a slight lowering in overall mortality rate in patients with respiratory tract infections treated with moxifloxacin compared with comparators and some lower rates of hospitalization or rehospitalization than the comparators in this patient group.

So, in summary, I think moxifloxacin demonstrates safety and efficacy for its proposed indications, acute sinusitis, acute exacerbations of chronic bronchitis, community acquired pneumonia, and uncomplicated skin structure infections.

I believe that the benefits of this new drug balance any theoretical risks attributed to the

small prolongation of the QTc interval especially given its metabolism, excretion, and its short course of therapy.

Any potential risk attributed to this QTc prolongation I think is appropriate addressed in the proposed labeling that you've just seen.

Despite limited clinical data, moxifloxacin is effective in infections caused by penicillin resistant streptococcus pneumoniae. I believe this drug is a useful addition to the antimicrobial armamentarium in addition to its clinical success.

It might also provide beneficial effect on hospitalization rates and mortality rates in respiratory tract infections and may have a different effect, at least, on antimicrobial resistance. Thank you. Carl.

MR. CALCAGNI: Dr. Reller and the advisory committee, this now concludes our official presentation. If there are any questions, we can triage those questions to the participants or the experts that are available that we have in the room.

DR. RELLER: We're now ready for discussion questions for the sponsor presentation. Dr. Ruskin.

DR. RUSKIN: I don't know what sequence you'd like to deal with this. Perhaps if there are efficacy questions, they should come first. My questions obviously relate to the cardiovascular issues. I'm happy to ask them at this point or wait until later.

DR. RELLER: I don't think that we need a particular sequence of taking. We'll take them as they come up to be focused on the data presented by the sponsor and issues raised by it. Of course, after the **FDA** presentation there will be a combining and we'll get to voting on the questions. Please go ahead.

DR. RUSKIN: I have a couple of questions for Dr. Hollister. The con med data is of particular importance. The concomitant medication data is particularly interesting and important. I only have the briefing document so I was unable to tell precisely what medications you were talking about when you referred to other agents that prolong the QT interval. The numbers are small but obviously it's an area of great interest. Can you educate me as to which agents were used and in how many patients?

DR. HOLLISTER: Sure. There were **61,** I believe, in patients on that slide with concomitant

medications that are generally accepted to cause QT prolongation; that is, with moxifloxacin. Amongst those there were two with amiodarone and one with sotalol. We have a list of the other medications that correspond, in fact, to a number of the medications that were shown on Dr. Morganroth's list as ones commonly recognized as causing QT prolongation.

DR. RUSKIN: Is that available in slide form? Is it possible to look at that?

DR. HOLLISTER: Yes, it is. Carousel five, slide 32, please.

DR. RUSKIN: Oh, I'm sorry. This is Dr. Morganroth's slide. I was asking if you have specific numbers of patients.

DR. HOLLISTER: These are the drugs.

DR. RUSKIN: Okay.

DR. HOLLISTER: Our patients were co-administered during the course of the study with moxifloxacin.

DR. RUSKIN: So there were three patients in the entire database who were receiving a Class III anti-arrhythmic agent. Is that correct?

DR. HOLLISTER: That's right. When we first identified a QT prolongation, we modified the entry criteria for the protocols, the Phase III

protocols, to not allow those patients in who were taking the Class IA and Class III antiarrhythmics.

DR. RUSKIN: When did that exclusion begin? How many patients had been entered into your trials before that exclusion came into effect?

DR. HOLLISTER: I think about one-third of our Phase III patient database could have had these drugs on board when they entered into our trials of moxifloxacin so 2/3. It was an exclusion criteria.

DR. RUSKIN: And the exclusion criteria applied only to antiarrhythmic agents?

DR. HOLLISTER: Yes, that's right. To these Class IA and Class III antiarrhythmic agents.

DR. RUSKIN: And can you tell me how many patients were exposed to cisapride or any of the major psychotropics?

DR. HOLLISTER: Not off the top of my head but we would be happy to provide that data to you.

DR. RUSKIN: I think it would be important to look at.

Two other questions and then a comment. I guess one other question and two comments. The other question is how did you define cardiovascular disease?

DR. HOLLISTER: We used the ICD 9 codes