FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

NINETY-NINTH MEETING OF THE

CARDIOVASCULAR AND RENAL DRUG ADVISORY COMMITTEE

8:08 a.m.

Thursday, May 29, 2003

Holiday Inn - Silver Spring
8777 Georgia Avenue
Silver Spring, Maryland

ATTENDEES

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DOUGLAS THROCKMORTON, M.D.
MARCEA WHITAKER, M.D.

REPRESENTATIVES ON BEHALF OF SANOFI-SYNTHELABO:

SYLVAIN DURRELMAN, PH.D.
PIERRE MAISON-BLANCHE, M.D.
JIM OPPERMANN, PH.D.
CLAUS ROEHRBORN, M.D.
JEREMY RUSKIN, M.D.
DOMINIQUE SALLIERE, M.D.
JON VILLAUME, PH.D.
WOJCIECH ZAREBA, M.D., PH.D.

ATTENDEES (Continued)

REPRESENTATIVES ON BEHALF OF BAYER PHARMACEUTICALS:

JOHN CAMM, M.D.
BOB CLARK
GERALD FAICH, M.D.
PAUL MacCARTHY, M.D.
JOEL MORGANROTH, M.D.
DR. P. SUNDARESAN
MARY TAYLOR, M.P.H.
THOMAS SEGERSON, M.D.
UDHO THADANI, M.D.

ALSO PRESENT:

CULLEY CARSON, M.D.
RODNEY FALK, M.D.
KATHERINE McCOMAS, PH.D.
WILLIAM SHELL, M.D.
MICHAEL SWEENEY, M.D.

C O N T E N T S

QT PROLONGATION ISSUES ASSOCIATED WITH TWO NEW DRUG APPLICATIONS: NDA 21-287, ALFUZOSIN HCl, SANOFI-SYNTHELABO INC., FOR THE PROPOSED INDICATION OF TREATMENT OF THE SIGNS AND SYMPTOMS OF BENIGN PROSTATIC HYPERPLASIA; AND NDA 21-400, LEVITRA, VARDENAFIL HCl, BAYER PHARMACEUTICALS CORPORATION, PROPOSED FOR THE INDICATION OF TREATMENT OF ERECTILE DYSFUNCTION

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C O N T E N T S (Continued)

P R O C E E D I N G S

(8:08 p.m.)

DR. BORER: Welcome to the 99th meeting of the Cardiovascular and Renal Drugs Advisory Committee of the U.S. FDA.

We'll begin the meeting which will deal with issues relating to QT prolongation on the electrocardiogram by drugs that are not antiarrhythmic drugs.

We have a number of special government employees sitting ad hoc on the committee today because of the nature of the drugs we're going to be talking about and the problems we're going to be discussing. So I'd like to begin by having everybody at the table introduce him or herself. John, why don't you begin.

DR. NEYLAN: I'm John Neylan. I'm Vice President of Clinical Research at Wyeth Research. I serve on the committee as the industry representative.

DR. ARTMAN: My name is Mike Artman. I'm a pediatric cardiologist at New York University School of Medicine.

DR. CARABELLO: I'm Blase Carabello, a cardiologist from the Baylor College of Medicine and the Houston VA.

DR. BARBEY: I'm Toby Barbey, clinical pharmacology from Georgetown University.

DR. HIRSCH: My name is Alan Hirsch. I'm an associate professor of medicine and cardiovascular specialist and vascular medicine clinician at the University of Minnesota Medical School in Minneapolis.

DR. PICKERING: Tom Pickering. I'm at the Cardiovascular Institute at Mount Sinai Hospital in New York.

DR. ARMSTRONG: Paul Armstrong, cardiologist, University of Alberta.

DR. RODEN: Dan Roden, clinical pharmacology and cardiology at Vanderbilt.

DR. BERNITSKY: Gay Bernitsky. I'm a clinical urologist.

DR. LORELL: Beverly Lorell, a cardiologist at Harvard Medical School and Beth Israel Deaconess Medical Center.

DR. CUNNINGHAM: I'm Susanna Cunningham. I'm a professor in the School of Nursing at the University of Washington in Seattle.

DR. LINDENFELD: I'm JoAnn Lindenfeld. I'm a cardiologist at the University of Colorado.

DR. BORER: Jeff Borer. I'm at the Weill Medical College of Cornell University.

MS. PETERSON: I'm Jayne Peterson. I'm the acting Executive Secretary of the advisory committee for

today.

DR. FLEMING: Thomas Fleming, University of Washington, Seattle.

DR. HANNO: Phil Hanno, urologist at the University of Pennsylvania.

DR. KOWEY: Peter Kowey. I'm a cardiologist and electrophysiologist from Philadelphia.

DR. NISSEN: Steve Nissen, cardiologist, Cleveland Clinic Foundation.

DR. KENNA: Leslie Kenna, clinical pharmacology reviewer, FDA.

DR. JARUGULA: Venkat Jarugula, clinical pharmacology reviewer, FDA.

DR. WHITAKER: Marcea Whitaker, medical officer, FDA.

DR. BENSON: George Benson, urology team leader, FDA.

DR. GRIEBEL: Donna Griebel, Deputy Director of the Division of Reproductive and Urologic Drug Products.

DR. THROCKMORTON: Doug Throckmorton. I'm the Director of the Division of Cardio-Renal Drug Products.

DR. BORER: In addition, we have one voting ad hoc member of the committee, Edward Pritchett, who is a consulting professor of medicine in the Divisions of Cardiology and Clinical Pharmacology at Duke, and Dr.

Pritchett is on the telephone and can hear us and participate, though he's not physically present.

Before we move on, I want to remind everybody that what happened just now is important to happen throughout the meeting. That is, if you're going to say something, press the button on your microphone and speak into the microphone please. It will help us to know that you have something to say and it will be possible for the transcriber to hear you.

Jayne Peterson will now read the conflict of interest statement.

MS. PETERSON: Good morning. It's quite a long one today, so bear with me.

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

Dr. L. Gay Bernitsky has been granted a waiver

under 21 U.S.C. 355(n)(4), an amendment of section 504 of the Food and Drug Administration Modernization Act, for ownership of stock in one of alfuzosin's competitors who also makes an alpha adrenergic blocker, and this is valued at less than $5,000. Because this stock interest falls below the de minimis exemption allowed under 5 C.F.R. 2640.202(a)(2), a waiver under 18 U.S.C. 208 is not required.

Dr. Jeff Borer has been granted a waiver under 18 U.S.C. 208(b)(3) for his consulting with one of the sponsors of Levitra. The firm also makes competing products to alfuzosin and Levitra. Dr. Borer consults on unrelated matters, for which he receives $10,001 to $50,000 annually.

Dr. Susanna Cunningham has been granted waivers under 18 U.S.C. 208(b)(3) and under 21 U.S.C. 355(n)(4), an amendment of section of 505 of the Food and Drug Modernization Act, for ownership of stock in one of alfuzosin's competitors which is valued between $25,000 and $50,000. The 21 U.S.C. 355(n)(4) waiver also includes ownership of stock in one of Levitra's competitors valued between $5,001 and $25,000. Because this stock interest falls below the de minimis exemption allowed under 5 C.F.R. 2640.202(a)(2), a waiver under 18 U.S.C., section 208 is not required.

Dr. Thomas Fleming has been granted a waiver under 18 U.S.C. 208(b)(3) for membership on three unrelated data monitoring committees supported by one of the sponsors of Levitra who is also a competitor of both Levitra and alfuzosin. He receives between $10,001 and $50,000 per year. Dr. Fleming's waiver is also for his membership on two additional unrelated data monitoring committees supported by a competitor to both Levitra and alfuzosin. He receives less than $10,001 per year.

Dr. Alan Hirsch has been granted a waiver under 18 U.S.C. 208(b)(3) for his consulting with the sponsor of alfuzosin. Dr. Hirsch consults on unrelated matters for which he receives less than $5,000 annually and for his membership on a speaker's bureau for the sponsor of alfuzosin. Dr. Hirsch does not receive any personal remuneration from this interest. However, his employer receives less than $5,001 annually in support of the Vascular Medicine Research Fellowship.

Dr. Peter Kowey has been granted a waiver under 18 U.S.C. 208(b)(3) for the following interests: Consultant to the sponsor of alfuzosin on unrelated matters for which he receives less than $10,000 annually. Consultant to a firm that makes competing products to alfuzosin and Levitra. He consults on unrelated matters and receives less than $10,000 annually. Consultant to one

of the sponsors of Levitra on unrelated matters. The firm also makes competing products to alfuzosin and Levitra. He receives between $10,001 and $50,000 annually. Lectures for one of the sponsors of Levitra. The firm also makes competing products to alfuzosin and Levitra. And lectures for a firm that makes competing products to alfuzosin and Levitra. He receives between $5,001 to $10,000 a year from each.

Dr. Edward Pritchett has been granted a waiver under 21 U.S.C. 355(n)(4), an amendment of section 505 of the Food and Drug Administration Modernization Act, for ownership of stock in a competitor to alfuzosin and Levitra. The stock is valued between $5,001 to $25,000. Because the stock interest falls below the de minimis exemption allowed under 5 C.F.R. 2640.202(a)(2) a waiver under 18 U.S.C. 208 is not required.

Dr. Dan Roden has been granted a limited waiver under 18 U.S.C. 208(b)(3) for the following interests: Stock in a competitor of alfuzosin. The stock is held in a trust fund and is valued between $50,001 to $100,000. Consulting with one of the sponsors of Levitra on unrelated matters for which he receives $10,000 annually. The firm also makes competing products to Levitra and alfuzosin. He receives less than $10,001 per year. Under the terms of the limited waiver, Dr. Roden will be permitted to

participate in the committee's discussions concerning alfuzosin and Levitra, but will not be voting.

A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, room 12A-30 of the Parklawn Building.

In addition, we would like to disclose that Dr. John Neylan is participating in the meeting as an acting industry representative, acting on behalf of regulated industry.

In the event that the discussions involve any other products or firms not already on the agenda for 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.

Thank you.

DR. NISSEN: Are we ready for a coffee break yet?

(Laughter.)

DR. BORER: The meeting is open for public

comment, and I think we have one, Jayne, that you want to introduce.

MS. PETERSON: Yes, if I could introduce Mr. Katherine McComas. This is really not public comment. Katherine is conducting a survey, a conflict of interest survey, for the University of Maryland, and she'd like to say a few words.

DR. McCOMAS: Good morning. My name is Katherine McComas, and I'm working with the FDA on a study of public understanding of the conflict of interest procedures that the FDA uses to monitor and manage its real or potential conflicts of interest of its advisory committee members. This study is being conducted across multiple centers at the FDA and across multiple meetings.

I also have a separate survey that I'll be distributing to the advisory committee members under separate cover.

I realize you have a very busy day today. The survey takes about 15 minutes to fill out. If you have a chance to complete it today, there's a box on the registration desk where you can drop it. Otherwise, there's a business reply envelope that you can drop it and it will make its way to me.

We really appreciate your taking the time to fill this out. The more responses we get, the more valid

and reliable our results and the better we are able to make recommendations to the FDA about ways to improve, if necessary, the conflict of interest procedures to improve overall satisfaction and understanding with the process.

I'll be around today. If you have any questions, please seek me out. And thank you again for your time and thank you for letting me address the group.

DR. BORER: Thank you.

If there is no public comment, we'll move on to the agenda. There is an introductory statement on the agenda. I'll summarize it here, read it in part. QT prolongation issues associated with two new drug applications: NDA 21-287 for alfuzosin hydrochloride from Sanofi-Synthelabo for the proposed indication of treatment of the signs and symptoms of benign prostatic hyperplasia; and NDA 21-400 for Levitra, or vardenafil hydrochloride, from Bayer for the proposed indication of treatment of erectile dysfunction.

We're asked to focus our discussion on the clinical trial designs which may be used for the assessment of QT prolongation and the pros and cons. The approaches to the correction of QT interval for drugs that affect heart rate. And I'm sure we'll be discussing the positive negative characteristics of each of the correction algorithms that's being used now. And risks of cardiac

arrhythmias associated with different degrees of QT prolongation, which is really the meat of the discussion. Pre-marketing clinical safety data from these applications and post-marketing safety data relevant to cardiac QT prolongation from drugs in the same two drug classes, that is, alpha adrenergic blockers and phosphodiesterase type 5 inhibitors, will be considered.

As an introduction to this discussion, Doug Throckmorton, Director of the Division of Cardiovascular and Renal Drug Products, will welcome us and provide some background.

DR. THROCKMORTON: Dr. Borer, thank you very much. I have two general things that I'd like to say. The first is just to sort of provide a little bit of context for the meeting today.

Detecting proarrhythmic risk for drugs that are not antiarrhythmics has emerged as a real concern in drug development and has occupied a lot of attention and a lot of concern both within and without the agency and the sponsors that we regulate. That concern has emerged in two different ways.

One, there has been the release of a preliminary concept paper of thoughts that will potentially lead to a guidance document from the agency or the international regulatory community about how to think about

looking for this proarrhythmic risk using primarily the biomarker QT prolongation on the electrocardiogram, although obviously the use of post-marketing as well and other adverse events. That release of that document led to a public meeting in early January where public comment was solicited and received.

Today we have an opportunity to look at two trials that have been conducted following some of the suggestions that were discussed in both that paper and at that meeting in January. It will be interesting to have feedback from the committee with regard to the wisdom of that suggestion, whether or not they believe this particular trial design gives them the answers that they feel they need as regards QT interval prolongation.

The one other thing that I need to mention, Jeff, is I'd like to take the opportunity to thank three members of the Cardio-Renal Committee. This is their last meeting, and I'd like to use this opportunity to personally thank them and thank them on behalf of the agency for really terrific service that they've rendered over the last several years. Dr. Hirsch, Dr. Lindenfeld, and Dr. Fleming have all really contributed materially to the discussion and the assistance that the agency has received from this committee, and I'd just like to thank them because it's been a real pleasure to work with them and I think they've

really helped us a great deal.

Thank you.

DR. BORER: I think all of us sitting around the table, as well as the sponsors, would add to your note of thanks to the three people who are leaving.

With that, we'll move on to the formal presentation, first from Sanofi-Synthelabo. Dr. Jon Villaume will introduce the presentation.

DR. VILLAUME: Good morning. My name is Jon Villaume. I'm representing Sanofi-Synthelabo Research, the developer of alfuzosin hydrochloride. Alfuzosin is before the FDA for the treatment of the signs and symptoms of benign prostatic hyperplasia, but today we will be presenting electrocardiographic studies that we have performed to assess the effect of alfuzosin on cardiac repolarization.

In this presentation, we'll provide evidence to demonstrate that the studies we have performed are adequate to make an assessment of the effect of alfuzosin on cardiac repolarization; that the effect size that we see, as measured by the QT interval length, is small, even at supratherapeutic doses; and that these increases are not clinically significant.

The reason we have made that conclusion is the following.

First, the increase the we see at the maximum studied dose is likely to be the maximum that will be achieved because the drug is pharmacokinetically very well behaved.

Two, we have used a control agent that produces a modest increase in QT interval length in a reliable manner, and our effect size at supratherapeutic doses was well below that level.

Further, drugs that have represented a ventricular arrhythmogenic risk produce effect sizes that are much larger.

And in addition to that, we have something that many sponsors don't have at the time of initial approval, and that is we have a large post-marketing database, and in our surveillance of the post-marketing use of alfuzosin, there is absolutely no signal of ventricular arrhythmogenic risk.

Now, our presentation is divided into four parts.

First, I will present background on alfuzosin and discuss some of the issues that bring us here today.

After that, Dr. Jim Oppermann of Sanofi-Synthelabo will discuss pharmacokinetics as they relate to the evaluation of the adequacy of the design of the studies that we have undertaken and will describe today.

Following that, Dr. Wojciech Zareba, who is associate professor of cardiology at the University of Rochester, will describe the study design and present the results of our electrocardiographic studies.

Following that, Dr. Jeremy Ruskin of the Massachusetts General Hospital will provide his perspective on our data.

We also have a number of consultants to aid us in answering questions from the panel. They include Dr. Pierre Maison-Blanche from Hopital Lariboisiere in Paris. Dr. Maison-Blanche was a principal reviewing cardiologist on the studies that we performed. Dr. Craig Pratt from the Methodist Hospital in Texas is also available to answer questions. Dr. Claus Roehrborn of the University of Texas was the principal investigator on our large U.S. BPH study, and Dr. Roehrborn is an authority on BPH. And finally, we have Joel Verter of the Statistics Collaborative to address analytical issues. We also have additional members of Sanofi-Synthelabo who will also be available to answer questions.

Alfuzosin was first approved for this indication in 1987. It's now approved in 108 countries, including all of Europe and Canada and Australia, but it has never been marketed for any indication other than BPH.

We filed an NDA for a once daily dosage form in

December of 2001, and that NDA demonstrated that there was an improvement in the symptoms of BPH and it also increased urinary flow. In those studies we identified 10 milligrams once daily as the therapeutic dose and that no dose titration was necessary. This dose is important because it will become a benchmark dose in the studies that we're discussing today.

Finally, the drug was very well tolerated in these studies.

Now, our NDA also contained a number of additional sources of information that are very relevant to the assessment of ventricular arrhythmogenic risk, besides the ECG studies.

First, we provided results of assay in the hERG potassium channel, and we provide results here, all conducted in the same system, first of a number of drugs that are associated with ventricular arrhythmogenic risk, astemizole, cisapride, and terfenadine. And then we have an assessment of all of the approved alpha blockers.

We present first the IC50 for each of these drugs in this particular assay and then provide the IC50 relative to the Cmax at the therapeutic dose of each of these drugs. You can see, at least for alfuzosin, there is a wide separation between the Cmax at therapeutic dose and the concentration necessary to provide inhibition in this

particular assay, and this is contrasted to the ratios that are obtained with the drugs that are known to be associated with ventricular arrhythmogenic risk.

Next we have a number of clinical sources of information. In the NDA, we provided a high dose ECG study and that was study 4532, with the highest dose of 40 milligrams per day. We'll be presenting that briefly later. That showed no clinically significant increase in the QT interval length at supratherapeutic dose.

As I mentioned before, since the drug has been on the market since 1988, primarily in Europe, we have a large experience base from post-marketing use, accounting for 3.7 million patient-years of use, and we've identified no signal of ventricular arrhythmogenic risk. Very importantly, there has never been reported to us, either in any of the clinical studies or ever in post-marketing use, a single case of the signature adverse event for drug-induced ventricular arrhythmia, and that is a torsade de pointes type of arrhythmia.

Now, in October 2001, we received an approvable letter from the FDA, and that approvable letter did not identify any issues related to the efficacy of the drug. The only issue that was raised related to the assessment of the effect on cardiac repolarization. Based on the approvable letter that we received and then subsequent

discussions with the FDA, it became apparent that they felt they could not evaluate whether alfuzosin did or did not have an effect on cardiac repolarization because the method that we had employed in our ECG studies was novel and had not been used extensively to evaluate drugs known to have an effect on cardiac repolarization. Therefore, the study needed to be validated.

The second issue was that we had not performed an interaction study with ketoconazole at the maximum allowable dose.

To address those issues, we had several discussions with the FDA and obtained their recommendations on the studies that we should perform and developed a plan, and that plan included study 5105 that compared single doses of 10 and 40 milligrams of alfuzosin to placebo. It was very similar in design to the previous study, 4532, except that now we have added to the study a positive control and that control was moxifloxacin, an approved antiarrhythmic, as I said, that has been known to reliably produce a modest increase in the QT interval at the therapeutic dose.

We also provided the protocol for a study to assess the interaction with the maximum allowable dose of ketoconazole.

With that, I will turn the podium over to Dr.

Jim Oppermann who is responsible for clinical pharmacokinetics at Sanofi-Synthelabo, and Dr. Oppermann will discuss the pharmacokinetics of the drug as it relates to the design of the studies that we will be showing today.

DR. OPPERMANN: Thanks, Jon, and good morning.

Today I'd like to talk about the pharmacokinetic properties of alfuzosin that demonstrate that the QT interval evaluation that we did after a single dose is appropriate. And secondly, I'd like to talk about the intrinsic and extrinsic factors that may alter or increase the exposure to alfuzosin and compare those factors relative to the exposure that we had in the 40 milligram ECG study and demonstrate that in fact at this dose, we basically exceeded those exposures that would be expected to be achieved in the clinical situation, even at the extremes of certain exposures.

Now, when considering single-dose versus repeated-dose designs, there are three major factors to worry about. The first is the time to reach steady state. The second, what is in fact the exposure after repeated administration versus single administration, and then thirdly, what's happening to the metabolites?

With respect to time to reach steady state, on this graph I've plotted the trough levels of alfuzosin, that is, 24-hour samples that were obtained after the first

dose, second dose, third dose, fourth, fifth dose of a once-a-day regimen. 24 subjects were in this study. As you can see graphically, basically there was no difference in the mean values across the 5 sampling days. Statistically they say the same thing. There's no day effect. So based on this analysis, we can conclude that steady state is essentially reached after the first dose.

Now, let's look at a 24-hour plasma profile comparing single and repeated administration. So this particular slide represents the plasma concentration time profile in 58 subjects receiving a single dose of an alfuzosin tablet. As you can see, there's a nice prolonged plateau, basically plateauing from around 6 hours to 14 hours. And if we now overlay that graph with the plasma concentration time profile that occurs after 5 days of repeated administration in 42 subjects, you can see that there are very small differences from a single dose to repeated dose in these two curves.

And if you then look at the pharmacokinetic parameters, single dose versus repeated dose, for Cmax, a very small increase. For AUC, approximately a 15 percent increase was observed, single versus repeated dose, and essentially no difference for Cmax. This base value basically agrees with the exposure increase you would expect for a drug that's got a half-life of 9 hours, which

alfuzosin does.

Now, what's happening to the metabolites? This is a radiochromatogram of a plasma sample taken from a subject who received C14-alfuzosin. The first thing to note is that alfuzosin is in fact the major radioactive component in this sample. The metabolites that occur are in the background. They're very low level. There are two major peaks here which represent the glucuronides of alfuzosin itself and the glucuronides of its two O-desmethyl metabolites.

Now, what is the time course for this appearance and disappearance of these metabolites in plasma? Again, this is a graph from a radioactive study conducted in 3 human subjects given 10 milligrams of the C14-alfuzosin. The top curve represents total radioactivity, which then would be the sum of alfuzosin and its metabolites, and the bottom curve represents alfuzosin itself.

First of all, you can see from this curve that the metabolites, which are the differences here, are rapidly produced. So, therefore, they would be expected to be present at the time you're doing a single dose evaluation of the QT interval. And secondly, the metabolite disappearance mirrors the disappearance rate of alfuzosin. So they're formed and rapidly eliminated.

They're probably formation rate-limited because they're glucuronides and they are rapidly excreted. So under these conditions, there would be no expected accumulation of metabolites after repeated administration.

Therefore, based on the steady state, the results after repeated administration, and the fact that metabolites don't accumulate, we feel that the single dose design to evaluate QT effects is in fact appropriate.

Now, what other factors might increase exposure to alfuzosin, factors that might impact on the choice of the top dose or the design of the QT interval study?

First of all, metabolism is the primary elimination pathway of alfuzosin, and in that regard, CYP3A4, cytochrome P450 3A4, is the primary isozyme responsible for metabolism of alfuzosin. In vitro, in human hepatocytes, ketoconazole inhibits 90 percent of alfuzosin's metabolism.

We had done a study with 200 milligrams, the recommended dose of ketoconazole, and the agency asked us to go back and do a study with 400, the maximum allowable dose, and we did that. This study was conducted in 12 healthy male volunteers, and the study design was alfuzosin alone, then treatment with ketoconazole for 8 days, and on the 7th day of that 8-day treatment, alfuzosin was given again.

These profiles represent the results from that study. The bottom curve is alfuzosin when given alone. The top curve is alfuzosin when given in the presence of ketoconazole at steady state, and the parameter changes, as a function of the high dose of ketoconazole, were for Cmax, 2.3 times increase, and for AUC, 3 times increase.

Now, the 40 milligram dose was the dose chosen for the ECG study based on those results, but we also looked at the exposure that we got with the 40 milligram dose relative to other factors that might increase exposure. So we had conducted a study in hepatic impairment and basically in moderate and severe hepatic impairment. The clearance changes are roughly 3- to 3.5-fold difference. Age has a slight effect in subjects that are greater than 75 years old. There's a slight increase in AUC and Cmax in the order of 1.3-fold. Renal impairment has about a 1.5-fold effect on the plasma concentrations. This is as expected because renal clearance is only a minor pathway. Less than 10 percent of the dose is excreted in urine, as alfuzosin itself. Here's the ketoconazole results, which I showed you. Diltiazem, which is a moderate 3A4 inhibitor, as expected, gave lesser effect than ketoconazole, about 1.5-fold, and then basically this is the small increase in AUC that we saw with a repeated dose versus a single dose.

So the bottom line is that 40 milligrams covers all these situations, and it should be noted at the 40 milligram dose in both of the ECG studies, that there was a significant percentage of postural hypotension that was achieved. 20 percent of the subjects had an issue with postural hypotension indicating that we're getting close to the top tolerated dose.

We also compared the exposure that we got in the 40 milligram QT study with data that we had generated during our phase III trials. In this particular slide, we have plotted the actual peak concentrations. These were determined in this 10- to 14-hour window after alfuzosin dosing in our phase III trials, and basically you can see at the sampling times of days 28, 56, and 84, there's very little change. There was no accumulation in these subjects, with the n's listed here. Basically if you go back to one of my initial slides where I showed the peak levels that were achieved in the two pharmacokinetic studies, they're in the same range there too. So there's no accumulation from day 5 to day 28.

So under these conditions -- and these are, again, real-time situations. People here are on 3A4 inhibitors. The subjects are old. Some of them have renal impairment. You can see we greatly exceeded that exposure.

We actually did a little simulation where we

said, okay, what would happen if you had renal impairment than then you, on top of that, took ketoconazole, or what about age and, on top of that, ketoconazole?

This is what this graph shows. So here are the estimated Cmaxs, simulated Cmaxs, and AUCs that you would predict would occur in subjects, for example, who are greater than 75 years old and who had taken ketoconazole or subjects who had moderate or severe renal impairment and had taken ketoconazole, and then I compared this to the exposure that we got. For example, here's the Cmax in the 40 milligram ECG study. So you can see that even in the simulated conditions, the dose that we used seems to cover the exposure.

So what I tried to show today, first of all, is that evaluation of the QT interval after a single dose is in fact appropriate for alfuzosin because the steady state is reached very rapidly, exposure after repeated administration is very similar to single dose, and that the metabolites which are formed are rapidly formed and eliminated with similar half-lives as alfuzosin itself. Secondly, the exposure that we got on the 40 milligram dose covers the clinical situation even in the real-world, worst-case scenarios.

Thank you.

DR. BORER: Dr. Oppermann, before we continue,

I want to take some time for any questions that have to do with clarification of what you've presented. I'd like to begin with two, and then we'll see if there are any others.

First, a minor one. The postural hypotension you mentioned, my recollection is -- and I just want a confirmation of this -- that to account for this, when you did your studies, you had people reclining for, I think it was, 12 hours before you did the measurements. Is that correct?

DR. OPPERMANN: Yes.

DR. BORER: More importantly, you showed us time to peak plasma level and justified the 1-day dosing on the basis of that. That seems reasonable except that in theory it's conceivable that the time to peak QT effect is not the same as the time of peak plasma concentration. Do you have any information that would allow us to be confident that the time to peak QT effect, whatever that may be, is reasonably captured by the time to peak plasma concentration that you gave us?

DR. OPPERMANN: Can I go to my backup slides, or do you want to hold that? I have a backup slide that might address it.

First of all, we are not aware of any situation actually where the QT changes were at a time point significantly different than at Cmax, or saying it in other

words, that there were QT changes that occurred at later times than Tmax. We're not aware of any situation like that.

Slide 21 please. Obviously, we don't have tissue concentration data in humans, although actually we have prostate values in humans. But we don't have heart concentrations.

So in trying to evaluate what's happening in other tissues, specifically the heart, this is a graph showing heart concentrations of total radioactivity and plasma concentrations of total radioactivity after administration of the radioactive alfuzosin to rats, 8 rats in the study. So this curve again represents alfuzosin itself, and alfuzosin and its metabolites, the combination of that.

I have a similar curve, if you just wanted to measure alfuzosin here, but this represents both metabolites and alfuzosin.

So, first of all, you can see, as I mentioned before, in plasma the radioactivity levels are rapidly reached in the heart, but then they decline at approximately the same levels as plasma. So if we can extrapolate rat to human -- and we can because the metabolic profile is very similar -- measuring it at times of Cmax is probably appropriate.

DR. BORER: Okay. I don't want to take any more time with this. Now, I appreciate those data. We may want to come back to this topic later, but that's fine for now.

I'd like to ask if anyone else has any issues of clarification here, and I'd like to specifically ask Dr. Pritchett, since I can't see when you press your red button here, if you have any questions you want to ask Dr. Oppermann right now.

DR. PRITCHETT: I do not, Jeff. Can you hear me?

DR. BORER: Yes, fine. Thank you.

DR. PRITCHETT: Jeff, the only mikes that I can hear are the mikes at the committee members' desks. I cannot hear the speakers from the podium or from the audience. So if you can get someone working on the audio there, it would help me here.

DR. BORER: Okay. We will try and do that right away.

DR. PRITCHETT: Thank you.

DR. BORER: So that would account for you have no questions or comments.

(Laughter.)

DR. BORER: Steve Nissen has to leave at about 10:30. So, Steve, do you have any questions you need to

raise at this time?

DR. NISSEN: No.

DR. BORER: Anybody else? Dan?

DR. RODEN: I'd like a little clarification about the metabolites. You haven't shown us where the C14 was inserted on the molecule, so I'm not 100 percent confident that measuring C14 activity is a measure of actual metabolite accumulation. And since you know the pathway is 3A4 and yet you show us glucuronides as the major product at 1 hour, I wonder if you know the identity of these major metabolites, and do you have any information on their cardioactivity?

DR. OPPERMANN: No, we don't have any information on the cardioactivity of the metabolites.

Can I have slide 14 please? This is the metabolic profile of alfuzosin. The metabolites that I showed you in plasma were the glucuronide conjugate of this, which is the O-desmethyl and its corresponding O-desmethyl compound there. So these were the two metabolites, together with conjugation of alfuzosin itself, which are the major metabolites appearing in plasma. They're also major metabolites in urine.

Another metabolite which appears in the feces is this one, but it doesn't appear to any great extent in urine.

I have a slide where we measured the urinary rate of elimination of this metabolite as its glucuronide, and this one as its glucuronide, which basically shows that the half-lives are in the 4- to 6-hour range or less.

DR. RODEN: It seems to me that the most straightforward way of addressing what you want to address is to get some concentration data at steady states or after somebody has been on it for a week or 2 or something that nobody is going to argue about and tell us what the metabolite concentrations in plasma are. And do you have those data?

DR. OPPERMANN: No, we don't. We actually elected not to measure metabolites because they were glucuronide conjugates and it would be very unlikely that they would be pharmacologically active. So at that point there was a decision not to measure metabolites.

But I think the urinary data do demonstrate that these have relatively fast half-lives and would not be expected to accumulate.

DR. BORER: Are there any other issues that require clarification before we move on?

(No response.)

DR. BORER: You can hear now, Dr. Pritchett.

DR. PRITCHETT: I can. Thank you very much.

DR. BORER: Way to go.

Why don't we move ahead then?

DR. OPPERMANN: Then I'd like to introduce Dr. Zareba who will talk about the methodology and the results of the ECG trials that we did.

DR. ZAREBA: Ladies and gentlemen, it is my pleasure to present for you data in regards to methodological aspects and findings of the study focus on the effect of alfuzosin on ventricular repolarization.

This presentation will emphasize how increased heart rate may influence QT interval and eventually how we can adjust for heart rate and correct for heart rate in such conditions. We will demonstrate relatively new so-called Holter based RR bin method which tries to control for heart rate but not correcting for heart rate. We will speak about design and results of two studies which were specifically conducted by the company to evaluate effect of alfuzosin on QT interval.

Alfuzosin is an alpha-1 blocker, and as such, may increase heart rate. This slide shows data from the study that was mentioned by Dr. Villaume, study 5105, during which we had subjects administered 10 milligrams and 40 milligrams of alfuzosin, in addition to a positive control of moxifloxacin 400 milligrams.

As you may notice, on average, there is an increase in heart rate in therapeutic dose, moderate, about

1.5 beats per minute, which increases to 3.7 beats per minute with the higher, supratherapeutic dose of 40 milligrams of alfuzosin. It is worth emphasizing that 33 percent of patients at the supratherapeutic dose showed a heart rate increase which exceeded 15 beats per minute, and as we know, 15 beats per minute is a very usual observation we have on an everyday basis in any subject.

This particular change in heart rate, of course, prompts us to determine methods to adjust the analysis of QT for heart rate, especially since QT is associated with heart rate, a very strong relationship.

Over decades, we had several methods developed to adjust for heart rate, and of course, there are traditional QT correction formulae, including Bazett and Fridericia, which try to compare QT to the standard heart rate of 60 beats per minute or RR interval 1,000 milliseconds, and they are broadly used clinically.

Recently there is evidence that those two traditional formulae create some under- or over-estimation in some subjects whose exponent is not exactly matching .5 or .33, as it is shown in Bazett and Fridericia. There are two methods of correction which recently have been exercised. One is population-based correction with regression modeling, helping us derive a coefficient which is pertinent for a specific population, and another is

subject-specific. Each individual, having a substantial number of QT and RR points, has the ability to demonstrate specific QT/RR correction with a specific exponent which will be pertinent for the subject.

Let's take a look at an example of another subject from study 5105 who had a 60 beats per minute heart rate which increased to a 75 beats per minute heart rate, and accordingly, the QT shortened, as physiologic response should be.

If we look at the Bazett formula, you all of a sudden see that there is a 24-millisecond over-correction of QT interval with this mathematical correction. Fridericia performed somewhat better, but if we compare these two subject-specific based formulae, which is derived based by the behavior of QT and RR in this particular subject, we can appreciate that this correction practically follows exactly the pattern of 60 beats per minute. This approach should be exercised more and more, but this approach again is based on modeling, modeling which tries to fit the linear or curvilinear line.

There are other methods which could be exercised, and one of the methods which I would like to present to you today is the so-called Holter-based RR bin method.

What is the Holter RR bin method? The ECG

required for this methodology should consist of at least several minutes, but usually it is a 24-hour Holter recording. And if we have such a recording, we first try to identify QRS complexes and sinus beats, measure RR intervals between beats. Subsequently specific beats with a specific range of RR interval every 10 milliseconds are clustered to create so-called RR bins. Like in this example, you have a cluster of beats creating a bin of 1,000 milliseconds and 1,010 milliseconds, and subsequently there is signal averaging implemented to create the final beat which represents this particular beat. This beat serves for further analysis using manual measurement of QT, and this measurement is performed blindly and also as fiducial points which we will see on this slide are kept in digital format.

This method has the following advantages. First of all, it controls rather than corrects for heart rate. There is no need for correction which may eventually incorporate some bias.

On top of it, it provides the ability to explore a wide range of RR interval for each subject and, therefore, we can exercise direct comparison of absolute QT at various heart rates. This could be done on placebo and this could be done on drug.

Another advantage is that we get multiple

points to develop even better fitting of a QT/RR regression model. And the next slide is showing this kind of example of individual QT/RR relationship. So if we have a wide spectrum of RR interval and we have behavior of QT through this wide spectrum of interval on placebo, one could imagine that if the drug had not any QT effect, we would have superimposed lines. Whereas, where we have drug, which potentially contributes to some QT prolongation, we will see an upward shift of this regression line.

This method also allows us to look at specific RR interval. Whether 800, 1,000, or 1,200, we can just simply look at absolute QT on placebo and on drug and compare it. This has the advantage of avoiding any QT correction formula.

This method has been applied in two studies which I will be presenting. The first study is a study Dr. Villaume already mentioned, study 4532, which was included in the original NDA. And the study, which is the primary topic of my presentation, is study 5105, was specifically designed based on the recommendations of FDA, and this study compared single doses of 10 and 40 milligrams of alfuzosin with a positive control in the form of 400 milligrams of moxifloxacin, an antibiotic known to increase QT prolongation, and of course, placebo.

Speaking about the first of these two studies,

study 4532 was a single-center, randomized, double-blind, four-way crossover study involving 24 healthy male subjects who were administered 10, 20, and 40 milligrams of alfuzosin and placebo. This study included Holter recordings done at screening, at four periods of single-dose administration.

As was already reported in the original NDA, this study showed that there was a 2-millisecond increase in QT1000 which reflects QT measured at 60 beats per minute with an upper confidence interval of just 3 milliseconds. There was no evidence for dose dependency in this particular study.

Because this method of the Holter bin approach was relatively novel, FDA requested that we provide additional evidence that this method is useful and is sensitive enough to identify any signal on ECG. Therefore, the study 5105 was designed with the following objectives: to validate the Holter bin method by using both a positive control and QT corrections from 12-lead ECG recordings. Again, a positive control using moxifloxacin at therapeutic approved dose of 400 milligrams. And to reassess the effect of alfuzosin given at two different doses, a therapeutic dose of 10 milligrams and a supratherapeutic dose of 40 milligrams, on QT interval using the Holter bin method.

Again, this study was a single-center, randomized, double-dummy, four-way crossover study involving 45 subjects who are given alfuzosin 10 and 40 milligrams as well as placebo and moxifloxacin 400 milligrams as a positive control. Each period consisted of a run-in placebo, followed by a single-dose administration, and there was a washout of 5 days between successive periods.

The primary endpoint was QT measured using this novel Holter bin method. Change in QT1000 was of primary interest because it is similar to other formulae which try to correct for heart rate exactly at 60 beats per minute. On top of it, the other primary endpoints included change in QT at RR bin with the largest number of complexes, as well as change in QT averaged over all RR bins.

On top of this primary endpoint, we wanted to exercise other measurements of QT utilizing standard 12-lead ECGs. They included individual-based corrected QTcNi. We used also population-based correction based on the population of interest, as well as traditional formulae I mentioned before, Fridericia and Bazett.

On top of it, we also explored some measurement of QT interval at other heart rates spanning throughout quite a wide range of RR intervals.

It's important to emphasize that we tried to

make sure that those measurements are performed in the time window which matches the highest concentration of the drug. In light blue, we can see concentration of the drug given at 10 milligrams; in dark blue, given at 40 milligrams; and in red, the concentration of the moxifloxacin which was used as a positive control.

As you may notice, the administration of moxifloxacin was on purpose shifted 6 hours later after the administration of alfuzosin to accomplish matched peaks of plasma concentration. The period between 7 and 11 hours was of particular focus to make sure that we will be able to evaluate QT at maximal action of these drugs.

The study was powered to detect a 5-millisecond change caused by moxifloxacin in Bazett corrected QTc. This 80 percent of power required 45 subjects and simultaneously, these 45 subjects were sufficient to provide more than 80 percent of power to detect just a 3-millisecond difference using the Holter bin QT1000 method for any treatment group.

Moving to the results, I will first show you moxifloxacin data. The Holter bin method with QT1000 demonstrated a 7-millisecond increase in repolarization duration after therapeutic and approved dose of 400 milligrams of moxifloxacin. This was confirmed by individual correction, population correction, and

traditional formulae. This particular exercise led us to believe that in fact the Holter bin method is successfully able to identify a potential signal if it exists.

Data for the therapeutic dose of alfuzosin at 10 milligrams did not show any significant difference in QT duration. If we look at QT1000, the upper limit is 2.6 milliseconds. The other correction formulae show similar effect. There is a slight trend toward significance for Bazett correction, but let's remember what I showed you at the beginning. The Bazett correction has this huge tendency of over-correcting for increased heart rate.

When we look at 4 times the therapeutic dose, which means 40 milligrams, which was tested on purpose, as was discussed a moment ago, we observed a change in QT1000 in the range of 2.9 milliseconds with the upper limit around 5.5 milliseconds. This was further confirmed by both individual and population-based formulae. And of course, as expected, traditional formulae, whether Fridericia or Bazett, showed higher prolongation, which is not surprising since one-third of the patients in this cohort showed a substantial increase of heart rate.

We also analyzed two other secondary endpoints on top of QT1000. We looked at QT change at the largest sample size RR bin, as well as QT change over all RR bins. As you may appreciate on this slide, the results were

identical, that alfuzosin at 10 milligrams didn't show an effect. At 40 milligrams there is less than a 3 millisecond change in QT which is less than half of what is seen for moxifloxacin.

We also were interested whether there is any evidence for rate dependency. Rate dependency shows that for alfuzosin 10 milligrams in white, we do not see again any significant signal. If we go to 40 milligrams of alfuzosin, at heart rates faster than 60 beats per minute, again there is no signal. At lower heart rates, below 60 beats per minute, there is some increase, as I mentioned, and on average we had this 2.9 in 1000, but as you may appreciate, this does not exceed 4 milliseconds and importantly doesn't grow with increased bradycardia. To compare, we show you the data for moxifloxacin which shows, of course, some modest QT prolongation along all heart rates we exercised.

The average QT is one important piece of the story, but we also have to look at outliers. We found that no subject had outliers defined as above 450 milliseconds in absolute terms or change over 60 milliseconds when we used Fridericia, normalized by population-based or subject-specific formulae. We found a couple of subjects who had outliers using Bazett, and further investigation of those subjects revealed that in fact those subjects had those

outlier values because they have increased heart rate which contributed to over-correction by the Bazett formula.

We tried to further explore the outliers by investigating the subjects who had higher plasma concentration of the drug. This was above 70 nanograms per milliliter. There were few such subjects analyzed. As you may appreciate in this table, QTcNi, which is the subject-specific method, showed that none of those cases demonstrated QT prolongation exceeding 30 milliseconds when compared to placebo.

Let me, therefore, summarize. Study 5105 using the Holter bin approach had the required assay sensitivity. With a therapeutic dose of 400 moxifloxacin, the Holter bin method documented a 7-millisecond increase in QT1000 which was compared with QTc measured using classical correction methods in the order of a 9- to 12-millisecond increase.

We also demonstrated that at a therapeutic dose of 10 milligrams, alfuzosin did not produce significant changes in QT1000. At four times the therapeutic dose, alfuzosin produced a mean QT1000 change of 2.9 milliseconds, less than half of what is observed with moxifloxacin administered at the therapeutic dose which is approved for clinical use. We believe that whatever the dose we exercise, there is no clinically relevant change in

QT/QTc which should be of major concern.

Thank you very much, and I will ask Dr. Jeremy Ruskin to continue with additional summary and conclusions.

DR. BORER: Thank you, Dr. Zareba. Before we go on to Jeremy, or while you're both up there, again I want to make sure there are no issues that require clarification. Blase?

DR. CARABELLO: Yes. Could you go back to your slide number 35?

DR. ZAREBA: Yes.

DR. CARABELLO: I presume that patient was taking placebo?

DR. ZAREBA: Yes. It's just taken from the placebo arm. Correct.

DR. CARABELLO: Okay, thank you.

DR. BORER: Paul and then Steve.

DR. ARMSTRONG: I have two questions. The first relates to providing a better understanding of the heart rate changes at the different doses, and the time course of the increase in heart rate relative to the plasma concentrations you demonstrated, and to what extent those heart rate changes tracked a blood pressure lowering as opposed to another effect of the drug of interest. Could you clarify those points for me please?

DR. ZAREBA: There is evidence for heart rate

increase by alfuzosin. In terms of plasma concentration, there is some slight trend. I'll be able to use one of my backup slides.

DR. ARMSTRONG: I'm especially interested, Mr. Chairman, in knowing whether the window of Holter interrogation tracked the maximal changes in heart rate and to what extent those were paralleled by changes in blood pressure. That's what I'm trying to get at here.

DR. ZAREBA: May I have slide 57 from the backup? We do not have simultaneous analysis of blood pressure in these patients, so I cannot comment on this particular aspect of the story.

When we look at heart rate, as you see from this slide, there is some upward-going regression showing concentration and change in heart rate in comparison to placebo. So there is confirmed evidence that, apart from a stepwise effect, which I showed you, with 33 percent of subjects having a heart rate increase by at least 15 beats per minute at the higher dose, there is in a continuous fashion some increase with heart rate.

Unfortunately, as I said, we don't have simultaneously acquired Holter data for blood pressure.

DR. ARMSTRONG: Is there someone within the company that can address now or later the issue of blood pressure tracking heart rate since I think that's quite

germane?

DR. VILLAUME: Can we hold that for later?

DR. ARMSTRONG: Sure.

And my second question, if I may, is in the backup documentation references, Drs. Malek and Camm comment on an unreliability or a disconnect between the relationship of the QT interval and the heart rate changes because of the autonomic modulation of this relationship and other factors that might mediate it. I don't know whether you or Dr. Ruskin are in the best position to help me understand then the legitimacy of these measurements through a broad cross section of circumstances where disconnect between the QT and the heart rate would be affected.

DR. ZAREBA: There is definitely association of cause between QT and RR and this is primarily driven by the autonomic nervous system. If we analyze QT behavior and QT variability and when we analyze separately heart rate variability, they follow each other in more than 80 percent. Studies utilizing coherence function, which were done independently of this study, demonstrated that about 15 to 20 percent of variability of QT could be eventually coming from a direct effect on the ventricle without simultaneous influence of sinus node by the autonomic nervous system. So there is intrinsic ventricular

component driving QT. There is no doubt but this component is relatively small.

DR. BORER: Can I just follow up on that before we get to Steve's question? That there is a relation between RR and QT seems incontrovertible. But in line with Paul's question, I'd wonder a little bit about what you did to account for the possibility that the temporal relationship between the change in heart rate and the change in QT may not be immediate. I mean, I don't know if it is or it isn't, but it may not be. It may take a while -- I don't know how long -- for the QT to respond to the heart rate.

And it seems to me that if you're looking at bins of RR1000 and people getting 40 milligrams of a drug that causes some modest degree of hypotension -- or some modest fall in blood pressure I would say, not hypotension -- some modest fall in blood pressure clearly is associated with an increase in heart rate. The fact that people had beats at a heart rate of 60 while that drug was on board is unusual. It's certainly conceivable, but you have to wonder what beats those were.

For example, I could conceive -- and I'm certainly not suggesting that this is what the data showed, but I could conceive of finding a group of post premature beat beats that had RR intervals greater than or equal to

1000 that might not really be representative of the normal beats or a few beats interspersed with a lot of others where the RR was 1000 that might somehow not be representative, and they might have occurred early in the measurement interval as opposed to later.

So I'm just wondering what can we say about the temporal relation of the RR interval change and the QT interval change, and did you do you something to account for that like, for example, only looking at the 50th beat with an RR interval or after the 50th beat with an RR interval of 1000 or something like that? I think you understand what I mean. I just need some reassurance about that.

DR. ZAREBA: There are a couple of points you raised.

Regarding the behavior of QT, of course, this a dynamic phenomenon, which comes usually from several preceding beats. As it was discussed with FDA over a year ago, for this particular study there was a recommendation that we use all beats in the set without eliminating beats which eventually would be coming from a very long RR or a very short RR interval. So we accounted for those. If we accounted for the phenomenon of hysteresis, we tested that we would need to reject 75 percent of beats.

Another approach which could be exercised here,

and was exercised by Dr. Pierre Maison-Blanche several times before, was a selective signal averaging method, trying to look at QT with preceding heart rate encompassing 1 minute or even up to 3 minutes prior to measured QT. This method seemed to be more robust than classical measurement of just one preceding RR but altogether, generally speaking, results are similar.

Again, based on the recommendation of FDA, we exercised over here all beats without implementing hysteresis.

DR. BORER: Steve?

DR. NISSEN: Yes. I want to focus on the population in study 5105. I noticed that these were men with an average age of 27 years of age. Now, fortunate for me, 27-year-olds don't generally have BPH. Even people my age in their early 30's --

(Laughter.)

DR. NISSEN: -- rarely have BPH. So the population that's likely to get this drug is going to be an elderly population with a fairly high incidence of concomitant heart disease. If I look at the people that I see in my clinic with BPH, they're men in their 70s, 80s, and older.

So one of my questions is, why didn't you do this study in elderly men, the population that's going to

get the drug? Do we know that the fact that there's not so much effect in a young 27-year-old population -- what does that mean for a group of people that may have concomitant heart disease? That's the first question and I have a follow-on after that. So reassure me that this population isn't any different in their characteristics of what the drug does to the QT from a population with heart disease in their 70s and 80s.

DR. ZAREBA: There are a couple of points which we need to address. I'm not sure whether Dr. Ruskin would like to start, or I would be happy to start.

DR. VILLAUME: Dr. Ruskin will comment on this in his presentation. So if you'll hold that question because it obviously is a pivotal question.

DR. NISSEN: Yes. But you certainly could have found 45 old men to do this study in. I mean, they're out there. So I guess this is for the FDA more than anybody else. I mean, the question is if we're going to do these sorts of studies, shouldn't we do them in the population for which the drug is intended to be administered?

And the second question, which I think might be similar, is that my concern about drugs that affect repolarization is what will happen to patients who may have ischemia. Imagine an older man who is on a drug like this has an acute myocardial infarction. Will the presence of

an agent that alters the QT have an effect on the likelihood of such a patient having ventricular fibrillation or torsade or some lethal arrhythmia? So maybe Jeremy also can comment on that.

But obviously, you can't test that very easily, but I'd like to know if anybody on the panel or if anyone else can help me understand that because some of the men that get this drug are going to have acute ischemic events, and the question is, what does the drug do to the QTc in the setting of concomitant ischemia compared to not having the drug on board? I don't know that I understand the answer to that question, not being an electrophysiologist.

DR. ZAREBA: Let me just briefly comment before Dr. Ruskin covers this to a greater extent. In this particular study, we on purpose exercised a dose of 40 milligrams which is four times the therapeutic dose. At the therapeutic dose, we didn't have any increase of QT. Therefore, if you have a patient who has ischemic heart disease and taking the recommended 10 milligrams per day, I do not expect any deleterious effect even in the presence of an ischemic condition in such patient. The data from 40 milligrams showing just a 2.9-millisecond increase is also reassuring that we do not expect more.

I'm not aware of any systematically analyzed data of risk of ventricular fibrillation and acute MI while

on specific drugs. Maybe somebody else.

DR. KOWEY: Steve, can I just comment?

I'm not as worried about ischemic disease as I might be theoretically with, for example, hypertrophic disease where repolarization clearly is legend. The reassurance that I have -- and again, Jeremy may address this -- is that this class of drug has been used in patients with hypertension, and although there are some warts in those data, one thing that I think has not emerged is a clear signal that there has been proarrhythmia with those drugs using it in a very, very large number of patients who have hypertrophic disease. I mean, if you're going to pick a target population that's going to get this drug that I would worry about more, it would be hypertrophic disease than ischemic disease. As I said and in the documents that we received, there's a fairly reasonable amount of reassurance from what we've seen with these drugs that we haven't seen a clear signal of proarrhythmia. So that's as best I think that we might be able to do to help you with that question.

But I think it would also be reasonable -- this is not a question you have to answer right away, but it's one of my questions. I'll preface this by saying that I realize that there is a strong limitation on preclinical information, but it would also be reassuring if you could

show us some information preclinically in relevant models that in fact there are no signals that animals with ischemia or hypertrophic disease are at higher risk of developing changes, for example, in transmural dispersion. Those data certainly could be garnered from a basic model.

DR. NISSEN: Peter, just to follow up, that was exactly where I was going with that, and I was sort of saying it would have been reassuring to know that in, say, a dog in whom you produce ischemia that you can give this drug and not lower the threshold for ventricular fibrillation or torsade.

DR. ZAREBA: What Dr. Kowey said is, in fact, 15 years of experience in Europe, Australia, and Canada. As you said, these are patients who are usually probably 70 years old having several ischemic, hypertensive, and other comorbidities. Therefore, we do not have any post-marketing evidence for any increased risk in these patients, as well as other alpha blockers.

DR. BORER: Jeremy, are you going to be discussing this whole area to some extent?

DR. RUSKIN: I'll make a comment --

DR. BORER: Okay. Maybe we can wait until you do that because I see there are some other questions here, rather than getting bogged down in this one issue, which is an important one, but if you're going to come back to it.

John?

DR. NEYLAN: Thanks. I had a question about the Holter methodology. It's certainly very clear why such a relatively novel strategy to evaluate QT interval effect might be used in drugs that have a chronotropic effect. And you listed some of the advantages of this methodology over a traditional surface EKG. I wonder if you could also give us a few comments about the potential disadvantages. And I'm speaking of two at least major areas -- but my colleagues on the committee may also raise other points -- that speak to some of the challenges of validating this method in the future study of QT.

One is the potential for motion artifact, and I'm wondering if these subjects were, in fact, at bed rest or largely confined to bed rest when you did the period of Holter evaluation because motion artifact obviously can have an effect on the wave form.

And the second is the wave form itself. Given the limitation of leads used, are you, in fact, optimizing the best capture of wave form to optimize the measurement? And is there reliability within the subject as to the lead placements over several periods of study?

So those are two general thought areas or questions.

DR. ZAREBA: Good questions. Regarding your

last point about the design of the study, the patients were, in fact, in the supine position during the study, so we eliminated motion artifact in these particular conditions.

Secondly, the electrodes were positioned in the same identical position based on simply markers put on the skin, and this allowed us to repeat this successfully.

Regarding the quality of the recordings and also acquisition of the data, as well as processing of the data, I didn't have time to elaborate more, but each class there, each bin, for every 10 milliseconds, should consist of at least 50 beats. And this was certain quality assurance which we implemented, and these clusters in fact ranged between 50 up to 800 beats depending on the variability of specific RR intervals. The clusters which were extremely noisy were excluded either automatically or manually. This, of course, adds to the labor intensity of this method.

But we believe that this particular method, allowing us to evaluate QT, at heart rate, whichever you like, it's not just correcting with the risk with one or the other formula we under- or over-correct at high or low heart rate. Here we have the ability to look at every heart rate and look at the absolute QT, and this allows us to really answer the question whether there is any rate

dependency as I showed. The QT1000 was chosen because of comparative data for Bazett correction and Fridericia, but as you may appreciate, there is vast opportunity to look at other rates and therefore conduct a thorough evaluation of QT.

DR. NEYLAN: Mr. Chairman, could I have one follow- up question?

DR. BORER: Yes, sure.

DR. NEYLAN: And that is given that these subjects were supine, I'm curious as to your opinion as to whether this methodology might be useful in the ambulatory setting for this purpose.

DR. ZAREBA: I think yes. It is exercised in Dr. Maison-Blanche's lab and a few other labs, and it is exercised in conditions of, of course, everyday clinical conditions which are not associated with a supine position. This brings, of course, a number of beats which need to be rejected due to changes either in position or motion artifact, but the method could be still analyzed. In fact, the recorder which we have been using, so-called ELA Medical recorder, is a recorder which we are using in a clinical setting and every day in my class at the University of Rochester, and we have this RR bin method implemented and it works. We can do it again with a number of beats requiring rejection higher than when you have it

done in the supine position, but it could be done.

DR. BORER: JoAnn?

DR. LINDENFELD: Just a clarification. The leads in the Holter monitor and the different position than usual 12-lead ECG. Can you reassure me that the QT changes that you see in the Holter monitor exactly those we see on the 12-lead EKG which is sort of our point of reference in the past? In other words, is a 2-millisecond difference in the 12-lead -- do we see a 2-millisecond difference in the Holter?

DR. ZAREBA: May I have slide 83 please?

The position used in this particular setting were mimicking lead II. This is based on the international standard for Holter monitoring. We're using CMV5 as the primary lead which reflects exactly lead II. This particular methodology has been used not only in these studies but several other studies which are used for drug evaluation. This was our primary measure.

DR. BORER: Mike and then Toby and then Peter.

DR. ARTMAN: Yes. I had some similar questions about the Holter technique that Dr. Neylan had.

But to expand on that a little bit, again trying to translate to clinical practice in the real world -- and one of the things we've been struggling with are these heart rate changes in response to the drug. So I

think the fact that the subjects were supine help explain perhaps why, with a decrease in blood pressure, their heart rates were not more elevated.

So I'm wondering if you have data on ambulatory patients, patients who are up and about and may have even greater heart rate changes than this third of patients who had a heart rate increase above 15. Do you have data on those subjects and do you have data in other patients who are ambulatory? That's one question.

Then another question to the technical aspects. Were the Holter tracings screened in any way prior to being sent to the blinded cardiologists for review?

DR. ZAREBA: Regarding ambulatory data, for this study we didn't have ambulatory data in particular. As I mentioned before, unrelated to this project, we clinically and research-wise are using the Holter bin method in our laboratory facility and it works. But again, I don't have data for ambulatory specifically for alfuzosin data.

In terms of question -- sorry. What was the second one?

DR. ARTMAN: So those patients that did have a significant increase in heart rate. There was a third of patients on the higher dose and a few patients on the lower dose.

DR. ZAREBA: We all together had a quite surprising range of heart rates. We had RR intervals in these subjects ranging from 700 milliseconds to 1400 milliseconds despite the fact that they were supine. So there was natural variation plus probably some other factors contributing to it, and because of this relatively wide range, which ranges from 45 beats per minute up to almost 90 beats per minute, we had the ability to evaluate a wide range. I focused mostly on 800 to 1200 milliseconds because this was the main representation of our data, but we have a limited number of beats also recorded below 800 milliseconds and above 1200.

I only wanted to say that in this particular setting we still did not have the ability to see any signal whether at lower heart rate or higher heart rate, and the same in terms of looking at the patients who presented specifically increased heart rate. Those patients showed outliers using the Bazett method, but when we look at them using the Holter bin or the subject-specific normalized method, we did not see any increase of QT.

DR. ARTMAN: And then the other question was were the Holter tracings data for individual patients screened before being sent to the cardiologists?

DR. ZAREBA: Routinely these patients were screened for usual arrhythmias, as it is done, to make sure

that -- as I mentioned in the introductory slide for the Holter bin method, we were concerned of having only sinus beats. So, therefore, annotation had to be performed to eliminate all artifacts, eventually non-sinus beats, but this was the only type of prescreening which was done. Otherwise, all beats were qualified.

DR. BORER: Toby.

DR. BARBEY: Just a very simple question. Your cartoon suggests that the averaged beats were derived from one single lead?

DR. ZAREBA: From one single lead.

DR. BARBEY: So, not better or worse, but as opposed to the 12-lead approach where increasingly there's a tendency to measure all 12 leads simultaneously, this technique focuses on the quill of lead II and does a single lead.

DR. ZAREBA: These techniques allows us to look at other leads, but in this particular study, we focused on one lead II, which seems to be -- let's say, a modified lead II which seems to be representative usually in ECG.

DR. BORER: Peter, then Alan, and then JoAnn.

DR. KOWEY: Actually, if you could put of slide 54. This is just a comment, Jeff, and then I have just a very brief question. But we all get very hung up on correction formulae and trying to understand exactly what

is happening with repolarization, whereas in real life, it seems to me that we should be more worried about what's happening to the QT interval.

I want to just tell you that I really like this information. I think this is not only scientifically sound, but it's also clinically reasonable because if you anticipate any change in heart rate in an older individual taking this drug, the heart rate would go up, and as the heart rate goes up, this slide clearly shows that the liability of the agent is going away.

The other thing that's very interesting about these data -- and I don't think you're going to be able to tell us the explanation for this, but we've seen it in other data sets -- is that there's seems to be -- as you get up into even slower heart rates, the QT change actually gets less. It does a little bit for moxi, but it certainly does it for your drug. That may be due to other effects the drug is having on repolarization not measurable by just its effect on IKr.

The question I had was related back to Steve's question about target populations. How well do old men tolerate large doses of this drug? I would think that the limitation of doing these studies in old men would be that it would be very difficult to get up to a 40 milligram dose. Is that true or are we just making that assumption?

Is it true that this study would be very difficult to do in older men? Do you have any information on what happens if you give a 65- or a 70-year-old man, who is twice the age of Steve, to see what would happen?

(Laughter.)

DR. ZAREBA: Let me comment further on your comment. I was extremely attracted to these data too, but I was also intrigued and, to tell you the truth, happy to see that if you have an older patient who has a tendency to bradycardia, which also happens quite frequently, and as we know, bradycardia is a condition which has the ability to prompt torsade in such situations, that we do not have further increase of QT. This I think was reassuring clinically for me that we have safety also over here, especially at night when you have the patient asleep and you may have, let's say, 50 or 45 beats per minute, and we do not have further prolongation which eventually could prompt torsade. So this was definitely reassuring.

In terms of age, again, I'm not sure whether I should really step in Jeremy Raskin's comments which will be coming very soon. So my proposition is that let's go over the issue of age and adequacy of the patient population after his presentation.

DR. BORER: Let's see. Who was next? Alan, JoAnn, and then Tom.

DR. HIRSCH: Well, let me continue the discussion regarding methodology from my naive age of 20.

Did torsade and sudden death and dysarrhythmias occur suddenly, spontaneously, occasionally without great predictability? So I want to methodologically talk about things beyond heart rate change and QT prolongation in steady state. I'm going to ignore the safety database and just talk about methods and say that I'm concerned, naively perhaps, whether or not we miss signals of QT change, again in the supine position, without looking at adrenergic and vagal stimuli that occur in real life. I don't know if the previous EP database has evaluated this, but again, although the heart rate may increase with a drug like this, what goes up, must come down. There are going to be changes in both directions that are transient.

Again, for both of these drug classes where there's going to be occasionally Valsalva maneuvers, straining to urinate, sleep -- you get the idea -- post-exercise responses, in real life, whether it's a 25-year-old or a 40-year-old, has the bin method with the Holter been applied in a more ambulatory setting or in these transients whereby a bin after these perturbations, these normal physiologic perturbations, might find a signal of danger that would be completely missed in a supine steady state condition?

DR. ZAREBA: Yes. First, regarding this concern about various heart rates, as it was already stated. As I mentioned, the RR interval in observed healthy subjects ranged between 700 and 1400, which is already, to a certain extent, a high range. If you speak about 700, we are close to 90 beats per minute. So, therefore, despite the fact that these subjects were lying down, they were probably stressed because 12 hours in bed is kind of a difficult situation to handle. So I think that they had some range of heart rates which were of interest.

Regarding potential stimulation of the adrenergic system, of course, we could be concerned, but as was mentioned a moment ago, if you look at these data which show shorter values of RR interval which potentially may reflect eventually a higher heart rate with or without adrenergic stimulation, we do not see any signal. We even see the white bars going down. So I think there is not a big concern regarding this.

You mentioned also the vagal tone which speaks about low heart rate. Again, we do not see at the therapeutic dose any signal, and even in the supratherapeutic dose, it goes down, whether we speak about the Valsalva maneuver or night. This is why I think we have not that much concern about this part.

DR. HIRSCH: But to follow up, I'm going to ignore those particular safety data, which I agree are somewhat reassuring. It's more of a methodologic question as we look at future drugs. When a drug is being administered for a certain indication where certain physiologic parameters may be known to change, straining at stool, coitus, straining for urination, I was wondering if this method should be actually evaluated in the clinical condition in which we know the drug is going to be used. I just raise that for future regulatory questions.

DR. ZAREBA: Let me tell you that there are data -- and I'm just trying to pull out the appropriate slide -- showing the use of this method in other conditions. May I have, please, slide number 43?

This particular slide shows the data for exactly the same approach, with QT1000 using something like adrenergic stress produced by tilt test, using nocturnal recordings, and using dofetilide, which is another drug which may eventually not cause adrenergic problems but simply cause QT prolongation. So in these studies, this method was also shown to be useful in identifying a potential signal.

May I also have slide number 49 for a moment?

Just recently in December of 2002, Dr. Pentti Rautaharju analyzed almost 12,000 healthy subjects trying

to look at this phenomenon, looking at heart rate and looking at QT in absolute value and trying to identify normal confidence intervals. So we already have substantial data to learn what we should consider as the upper limit of normal without any correction.

So the evidence is growing for this new method. I fully agree with you that we do not have yet sufficient data in the literature, but I truly believe that this method will be slowly, slowly more often presented at these meetings because of their particular advantages.

DR. BORER: JoAnn and Tom.

DR. LINDENFELD: Drugs like this sometimes change the T wave, and I'm interested in just understanding your technique. If you know by the Holter bin method how many beats are counted, how many actually are able to be counted. And then if you know that, I wonder if that changes between placebo and drug, and if it changes based on the RR interval. So I'm wondering if the drug were to change the T wave, if you would measure less beats that might be altered with drug or at different RR intervals. Just so I understand the technique better.

DR. ZAREBA: It's a very good question. Let me start with slide number 45 from the backup set.

On this slide, you see the number of complexes at each RR bin during the four run-in placebo periods for

all subjects. As you may see over here, despite the fact that we are repeating this four times in the same subjects, there is pretty much overlap, confirming that we have evidence for a wide range of RR intervals.

Simultaneously, when we look at slide number 46, we look right now at treatment periods, and of course, as you see in this blue line, for 40 milligrams of alfuzosin, there is some shift in number of complexes which are eligible for analysis, naturally because the drug increases heart rate, so we have shorter RR intervals dominating this. However, the overlap throughout the entire recording is so substantial that we can easily correct.

You also mentioned T waves, so I will ask you to show me slide number 30. We, in fact, were concerned that a drug like alfuzosin could eventually change the morphology of T waves. As we know, some drugs which affect the HR channel may lower amplitude of the T wave, and we tried to look whether in this setting we have any evidence for flat, notched, T wave or unusual U waves, which may eventually be of concern regarding safety.

As you see on this table, we have no cases of flat T wave. We have just very infrequent cases, single cases, of notched T wave, but there was absolutely no difference between four arms of the study, and in terms of

unusual U waves, it's also very infrequent. So all together the findings were very infrequent and it was not in any way associated with drug.

Secondly, of course, a very flat T wave will compromise analysis of QT. Therefore, in the rejection system, some of those T waves had to be rejected because of the inability of measuring QT.

DR. LINDENFELD: Can we just go then back to the last slide just so I understand this? I apologize. The one you just showed. Yes.

So that at higher heart rates, there are far fewer beats that can be counted. Is that what this demonstrates?

DR. ZAREBA: I would not say far fewer because we speak about 300 beats, 300 beats over here, 150, 150 here.

DR. LINDENFELD: Well, but there are far more beats at higher heart rates.

DR. ZAREBA: So 150 beats to analyze QT I think is sufficient.

DR. LINDENFELD: But at higher heart rates, that means you're throwing out a lot more beats.

DR. ZAREBA: Yes.

DR. LINDENFELD: So fewer of the total numbers of beats can be counted.

So I guess I wonder if you've thought about whether or not that introduces any artifact into the measurement. In other words, at an RR interval of 500, that's twice as many beats at a heart rate of 60 and you have way fewer complexes.

DR. ZAREBA: Again, we are looking at the comparison of QT at specific RR intervals, and if we look at, let's say, fewer beats versus higher beats, of course, we may have some little bit different results, but all together this will provide an overall good representation of behavior every 10 milliseconds.

So I understand your point that it might be that if we have one bin dominated by 3000 beats and another will just have 50 or 60 beats, this other one might be not fully representative. But still this lower threshold of 50 beats provides me with some comfort of why I'm saying that if we speak about 10-second standard 12 ECG, we usually have no more than 10, 12 beats, and we rely all clinical decisions on this small strip with 10 seconds, and we are comforted. Over here, we put a requirement of having at least 50 beats for each bin, which is I think pretty stringent.

DR. BORER: Can I just ask in follow-up? I'm not sure that JoAnn's total question was answered. I'm given confidence by what you say. But, JoAnn, I thought

you were suggesting that in these RR interval regions where there are fewer beats because the heart rate is, in fact, faster, it's more likely that they will be rejected beats, and therefore that the beats your actually sampling, even if there are 50, will be less representative of the totality of what happened at that RR interval than at slower rates where a smaller percentage and a smaller number of beats would be rejected, and there might be some distortion in the results occurring because of this differential rejection. I don't think you specifically responded to that. Is that an issue?

DR. ZAREBA: Again, I generally agree with you that, of course, if we have a smaller number of beats, especially if there are more of them rejected, they will be less representative. The rejection rate over here was very small. Why? Because of supine position. I agree with what was commented before. In ambulatory conditions, this will contribute to more rejection. But in the supine position, we had really a very limited number of rejected beats.

DR. LINDENFELD: Again, it will be math off the back of the envelope here, but it seems like six times as many beats were rejected. If you look at an RR interval of 500, you only have 100 beats there.

DR. ZAREBA: It doesn't mean they're rejected.

They simply were limited. So you may not have patients reaching specific RR. This graph doesn't mean that you have all of them rejected. We have simply the number limited at specific heart rates. If you speak, for example, at 100 beats per minute, we had more or less 100 or 120 beats because these subjects didn't present much more.

DR. KOWEY: Can I just put this in some perspective? We're talking about measuring hundreds of beats, which is a standard -- we rarely have seen that number of beats being measured. Granted, there's a differential between the numbers you're measuring at high and low heart rates, but we're still talking about an incredibly large sample size, which is not anything like what we usually see.

And I just had a follow-up question. Your T wave question was very, very important. If you could just clarify some of the methodology. Who looked at the T wave morphology? Were they blinded? Did they have criteria for calling what they called abnormal T waves? And was it done from a 12-lead ECG or just from a single lead from the Holter?

DR. ZAREBA: I think I will ask Dr. Pierre Maison-Blanche who performed this work to comment on it because this will be probably the best source of

information. T waves were screened and he performed this analysis, so I will ask him eventually to comment on it.

DR. MAISON-BLANCHE: Thank you, Dr. Zareba.

The T wave morphology analysis was based on 12-lead ECG analysis. A slide which has been shown to you is coming from a 12-lead ECG analysis. So the T wave categorization was made on all 12-lead data. That is my first answer. And that has been done by a central lab service. Only the Holter data has been analyzed by an academic core lab.

So how deep the persons were trained in the core lab is as follows. I was personally in charge of training the physicians in charge of T wave categorizations. So that was done with predefined menu and people were trained to identify notched T wave, flat T wave, and U wave.

DR. KOWEY: And that was blinded analysis, blinded to the treatment?

DR. MAISON-BLANCHE: Both the Holter data analysis and, of course, the 12-lead ECG analysis was totally blinded.

DR. FLEMING: A couple of issues. First, if we could go to slide 51, I'd like to understand your results relative to what's in the FDA briefing document and also what's repeated in the questions to the committee in

question 5 of the FDA.

These are the results from 5105, and they seem to differ from the results that are presented to us in the FDA briefing document and the questions. For example, if we look at these 10 milligram results for Bazett, it's 3.3. I think FDA has 10.2. Fridericia, you have 1.6; FDA has 4.9. Could you clarify?

DR. ZAREBA: Yes. I will ask Dr. Sylvain to clarify these differences.

DR. DURRELMAN: I'm Sylvain Durrelman from biostatistics in Sanofi-Synthelabo.

I would just like to clarify this point. The 12-lead ECG analysis was a secondary analysis in these studies. Actually two analyses of these 12-lead ECG data were performed, one at the time of Cmax, and this is the one that the FDA has selected in their briefing document. We have also performed an analysis which covers the same time period as the Holter period, that is time T7 to T11. That covers the time of maximum plasma exposure with five ECG data points. This is what we have selected in our main presentation as it is a good reference to compare with the Holter bin method that is evaluated along the same period.

However, in our company's briefing document that was submitted to you, we have provided, of course, the two analyses. And on page 54 of Sanofi-Synthelabo's

briefing document, you will find the time of Cmax analysis for the 12-lead ECG, and the numbers are exactly consistent with the FDA analysis. Overall, the numbers do not change by a great deal, and the ordering is always the same with the effect at the top dose of alfuzosin 40 milligrams being about half of what is observed with moxifloxacin, with some minor numerical differences.

DR. FLEMING: Actually it looks like the numbers are, in fact, somewhat different.

Let me go on to another question because the time is short, and the essence of my question is on page 54. Could you go to slide 54? I'd like to make sure I understand the methodology you're using here.

Suppose you have a patient who has at baseline a heart rate of 55 and on alfuzosin their heart rate is 60, and let's say they're on alfuzosin 40 milligrams. Their data point would be represented under the 60. Is that correct?

DR. ZAREBA: It's every 10-millisecond bin. So it depends. In this particular graph, we just selected bins which are representative. They are not overlapping over here. So, of course, you will have five bins between 950 and 1000. So for clarity, we didn't present them all.

DR. FLEMING: Well, let me just be specific. Suppose a patient had at baseline a heart rate of 55, so

they're at 1100. And suppose on 40 milligrams of alfuzosin their heart rate is 60. Then with their heart rate at 60 on alfuzosin, you measure the QT. Correct? And so they would enter into the column there that corresponds to 60.

DR. ZAREBA: Correct.

DR. BORER: Can I just interrupt one second? Maybe I've completely misunderstood, but any individual has a variation of heart rate from second to second, minute to minute, hour to hour. If heart rate was measured at 60 at the measurement moment and you actually did multiple measurements over time or did a Holter, which is what you did for this list mode bin method, then although the measured rate at the instant of measurement for profiling here might have been 60, 2 minutes later on the Holter, it might have been 57 or 56.

DR. ZAREBA: That's correct.

DR. BORER: And that patient's information would be categorized at 57 when it was 57, at 60 when it was 60, at 63 when it was 63. Is that correct?

DR. ZAREBA: That's correct. It's the Holter bin method. It tries to look at QT and specific heart rate. Whether it's 5 beats apart or 3 beats apart, we only establish this 10-millisecond range of overlap. Otherwise, they are considered separately because of the dynamic nature of QT.

DR. FLEMING: So you've got a patient now that has a heart rate of 60, and what we're computing here is the QT change is approximately, if I can eyeball this, 2.5 seconds for those with a heart rate of 60. That is precisely computed in what way? We're looking at the QT for this particular patient at this point with a heart rate of 60 and we're adjusting that regarding the placebo in what fashion?

DR. ZAREBA: I have this methodological slide from the main presentation which shows the method.

DR. FLEMING: While you're pulling up the slide, my understanding is you are, in fact, with this analysis adjusting for the fact that there is, as you showed in that one slide, a definite relationship between QT and heart rate.

DR. ZAREBA: Yes, slide 37 please.

As it was mentioned, there is this process of combining QT -- the QRS complexes are generally beats from specific 10-millisecond bins. They are combined and they may come from neighboring RR intervals, but they may come from distant RR intervals, just to create a bin of 1000 milliseconds or 1010 milliseconds. They are averaged to represent specific heart rates. On this average beat, we have measured QT manually and blinded. So we speak right now not about just single beats which represent a moment or

an instantaneous change, but we speak about a group of beats which is transferred into some average complex which is representative for the entire class there.

Why is that? Because of potential influence of noisy beats or some outliers, this signal averaging allows us to really demonstrate the good reproducibility of the method.

DR. FLEMING: You still haven't gotten to my question. Essentially what you're trying to do, going back to slide 54 -- what is intended here is to understand what the change in QT is that is influenced by alfuzosin beyond the element of what change should be if you simply looked at the change in the heart rate. Is that correct?

Essentially what we realize is alfuzosin is changing the heart rate.

DR. ZAREBA: Yes.

DR. FLEMING: That intrinsically could change the QT.

DR. ZAREBA: That's correct.

DR. FLEMING: But we also know in untreated patients, if the heart rate changes, the QT changes, and we're attempting to adjust that out.

DR. ZAREBA: That's correct.

DR. FLEMING: So if we look at the 60 data, for example, patients on alfuzosin at 40 milligrams who, in

fact, have a heart rate of 60 will have a given QT or a given QT change. Is there, in fact, a subtraction here when you compute this blue bar that is factoring out -- if somebody started at 55 and went to 60 in their heart rate, you realize that their QT, in fact, would have changed on the placebo. And you're subtracting that out. So this represents the excess change in QT beyond that that you would ascribe to a placebo change in QT or a natural population change in heart rate.

DR. VILLAUME: Maybe Dr. Durrelman can clarify the method a little bit along with, if necessary, Dr. Maison-Blanche who was the reading cardiologist.

DR. DURRELMAN: Yes. Let me try to clarify from the statistical standpoint first.

I would like to make the point that in the slide 54 that we have here, you must understand that the subjects contribute to several of the batches. Right?

DR. FLEMING: Sure. Not a problem.

DR. DURRELMAN: So if we can have the backup slide 44.

You have in this slide the distribution of subjects by RR bins. So depending on the bins you are at, you have a sample size that is more or less larger or smaller. Around the interval from 800 to 1200 that we have decided, we have about all the sample size equals all

subjects' experiences RR bins.

Now, when we go back to the main slide I think 54, what we do is to classify the various bins during the run-in placebo period, time 7 to 11 hours at day 2, and on the other hand, classified the RR bins for all subjects also during the treatment period at day 3. And for a given RR bin corresponding to a certain heart rate, we do the comparison, and then between this run-in placebo period and the treatment period. And we do that then for all of the four treatment groups: placebo, two arms of alfuzosin, and moxifloxacin 400 milligrams. Then we would be able to plot this, adjusting for placebo.

DR. FLEMING: So am I correctly interpreting this, that if we focus on the 60 heart rate column, what we're saying here is a patient that is at 60 on alfuzosin would have about a 2.5-millisecond higher increase in QT than you would expect from natural history adjustment for the relationship that exists between heart rate and QT. Is that correct?

DR. ZAREBA: That's correct, using this placebo run-in method exactly at 7 to 11 hours.

DR. FLEMING: And then your overall reported summary for the increase at 40 is a weighted average of all of these blue bars. You're coming up with an average of --

DR. DURRELMAN: 2.9 milliseconds.

DR. FLEMING: 2.9 and that's a weighted average.

DR. DURRELMAN: 2.9 milliseconds in the prospectively defined QT1000 parameter, which corresponds to the heart rate of 60, and that's a weighted average. Right.

DR. FLEMING: A weighted average of the blue. So what we realize is that the actual increase in QT relative to what you would expect it to be, adjusting for heart rate, is in fact specific to heart rate, and you're taking a weighted average of these.

I guess the last point in interpreting this, though, is if, for example, somebody came in with a heart rate of 55 -- and that's the people over here to my left -- and on alfuzosin those people would become a heart rate of 60, the people here on my right, then essentially what this is doing is it is looking at the alfuzosin person here that was on my left and they're putting them in the bin over here on my right, with all of these placebos who are now like them at 60, and it's making the fundamental assumption that you're no longer comparing this person to their true colleagues, their true randomized colleagues. You're putting them in a systematically different bin under the assumption that the only thing that really matters on QT is heart rate. It's the right thing to do if the only thing

that matters is heart rate. But if there are other things that influence QT, this person who really belongs on my left is not being compared to the comparable to people.

So that's a fundamental assumption to this approach that has to be recognized that this approach is not pristine. It's in fact violating the assumptions that we would typically look for of keeping people with their colleagues with whom they're truly intrinsically the same, and it's only valid if the only thing that matters about QT is heart rate.

DR. MAISON-BLANCHE: You're absolutely right, sir. But there is a "but," and my answer is a "but." We have some time match. We compared T7, T11 on the treatment to T7, T11 placebo, which means that we tried -- at least we do our best -- to compensate for circadian variations. I am not aware of such big efforts to do that in the past. So we try to compensate for also the night influences. So first we try to get rid of circadian influences. Then all the patients are in supine positions on the run-in placebo and on the treatment. So in addition to the circadian variations, which are non-negligible, we tried to compensate for daily activities. We cannot compensate for multi-stress. We cannot compensate for respiratory sinus arrhythmia. That's true. But we did our best to compensate for the other influences.

Do I answer clearly your question?

DR. FLEMING: I understand but the concerns that I have which I think are intrinsically unavoidable is that you're having to make assumptions here, and I just want to make clear what those assumptions are.

DR. ZAREBA: I think we are in agreement with only this additional piece of information. As we showed, on drug and off drug, there was substantial overlap of RR intervals, allowing us to have, as I mentioned before, at least 50 beats for each class, which allows us to really demonstrate the representative QT interval for a specific heart rate.

DR. BORER: Tom Pickering and then Dan.

DR. PICKERING: Yes. I wanted to bring up the issue of respiratory sinus arrhythmia that you just mentioned. These are young people who were supine and probably breathing relatively slowly, and vagal tone tends to be high in younger people I think. So one of my questions is, to what extent is the RR variation due to sinus arrhythmia where you would just have one very long RR interval per breath, whereas in an older population taking the drug for therapeutic reasons where upright vagal tone is probably going to be much lower and sinus arrhythmia are also much less?

DR. MAISON-BLANCHE: Thank you for your

question. Yes, it's true. So back to my previous answer. We are dealing in this population with a relatively high respiratory sinus arrhythmia. As far as I know, I (unknown words) to get rid of that is that we are basing which is an invasive technique which we usually cannot apply in this setting. So we have to do something with respiratory sinus arrhythmia.

Among the two techniques which we investigated to compensate for hysteresis, we manipulated the heart rate variability analysis to select those beats which may be affected by the hysteresis phenomenon related to respiratory sinus arrhythmia. In that population, what Dr. Zareba said is true. We found that the rejection rate was 75 percent because they have a significant respiratory sinus arrhythmia. Not only do you expect but our findings in the elderly population, the rejection rate will be smaller because they will have less respiratory sinus arrhythmia.

So if we try to compensate for hysteresis, we will eliminate 75 percent of beats. If we do not, if we put into the bins all the data, and I analyze the presence of sinus (unknown word) phenomenon by the way in the setting of 10 seconds of ECG strips, who knows what happens before and after. At least from continuous ECG monitoring -- that may be part of the discussion later on, but at

least continuous ECG monitoring has potential solutions. 10-second snapshots do not.

DR. BORER: Dan?

DR. RODEN: I don't know if I have a question or just a comment. Could you put up your slide 39?

Tom, as a statistician, has come up with the fundamental problem that the relationship between QT and RR is I think inevitably or terminally confounded. You can't possibly sort out a true relationship. If you have a drug that affects only QT, you might. If you have a drug that affects RR through multiple mechanisms, QT through multiple potential mechanisms, then trying to come up with a number is not going to work. So I like this approach with the caveat that as long as it's being analyzed in a way that's not rejecting systematically beats.

So I wonder, Wojciech, whether the bar that you show on the slide that Dr. Fleming didn't like --

(Laughter.)

DR. RODEN: No, no. I can't remember what number that was.

DR. ZAREBA: Slide 54.

DR. RODEN: Don't go back to 54 yet.

But each individual has one line on drug and one line on placebo. So there's a delta at any given QT that you want to select. Then you can go on and you should

be able to show us the delta QT with a standard deviation or with a confidence interval, each derived from an individual subject. Maybe that's what was bothering Tom.

DR. ZAREBA: These data are just mean change, and you may remember from the main presentation I mentioned that the upper confidence interval was 5.5 milliseconds. So, of course, there is some range.

DR. RODEN: If it's not on the slide, I don't remember.

DR. ZAREBA: Yes, I understand. But if you go in the main presentation to slide -- I don't have it here in front of me, but I am speaking about the slide showing data for 40 milligrams, the table for 40 milligrams.

DR. RODEN: 53 I think actually.

DR. ZAREBA: Slide 52 please.

If you look here, we speak about QT1000. I understand that slide 54 showed different other heart rates, but if you look at this particular situation, if you look at the confidence interval, the upper limit is 5.5 milliseconds. This is what we are aware of, that of course, there will be patients who will show 4 milliseconds, some others 1 millisecond, and some of them even 5 and higher milliseconds, which is still very modest prolongation.

DR. BORER: Ed Pritchett, do you have anything

to ask of this speaker?

(No response.)

DR. BORER: I think we've totally lost the hookup now.

DR. PRITCHETT: Can you hear me, Jeff?

DR. BORER: Now I can hear you.

DR. PRITCHETT: No. I'm actually able to follow this remarkably well, given the technology I've got here. I have enjoyed this.

I like this Holter bin method. I just would have one comment, though, as we try and struggle with how to use it, and that is, why do we think that the QT interval is something to worry about? And it's because historically we have learned that drugs that prolong the QT interval are associated with a higher risk of this arrhythmia that we call torsade de pointes. Most of what we know about the QT interval for those drugs was measured with 12-lead ECGs. It's what we know from studies of quinidine and sotalol and more recently dofetilide and drugs like that.

What we've got here is a very interesting assay for QT interval effects, but we don't know what predictive value it has because we haven't done lots of drugs to see if they're studied with the Holter bin method, whether it predicts the occurrence of QT. But as an assay for QT

interval, I find this to be quite an interesting idea and quite attractive. End of my comment.

DR. BORER: Thank you.

DR. ZAREBA: Just in reply to this comment, I want to emphasize that, of course, as I mentioned, we analyze our data not only using the Holter bin method, but we use traditional 12-lead with very recently proposed subject-specific correction. So we try to address this from both angles.

DR. PRITCHETT: Yes, I agree.

DR. BORER: Jeremy, how many minutes is your presentation approximately?

(Laughter.)

DR. RUSKIN: I'll try to stay under 10.

DR. BORER: Okay. The reason I'm asking is that I want Steve to have the opportunity to comment after you present. Well, do you have any comments you want to make before Jeremy?

DR. NISSEN: I just had one. Could I see that slide 54 again?

(Laughter.)

DR. ZAREBA: It's a popular slide.

DR. NISSEN: Yes, it's a popular slide.

I guess the question I would ask the panel more than you is, is the relevant number the average change

across all heart rates, or is the most relevant number for this analysis what the worst case scenario is?

Given the fact that what we're really trying to do is to determine whether a drug that's used for a nonlethal condition has the potential for a lethal side effect, my argument would be that if we're going to use this method, we might want to look at what is the worst case. At what heart rate is the change the greatest as a security blanket, if you will, to make certain that we're not in a range where there's a lot of risk because clearly heart rate does change from moment to moment. What we really want to know is what is the risk that this drug is going to cause harm.

And so when I look at the data, it looks to me like people that are around 60, 57, 55, if they get a lot of exposure, will be in the range of 4 or so milliseconds prolongation. Now, what does that mean? That's another question entirely.

But in terms of the analysis, I think one could make a case here that it's not really quite fair to average this across every imaginable heart rate and then sort of throw it into a great big gemisch because that's not really what an individual patient experiences in terms of risk. So that's a comment before I exit.

DR. ZAREBA: I think it's a very valid point

that we have to take into account that variation and possibilities that the response will be different. But to my knowledge, we don't know of a drug that produces arrhythmia and has QT increase properties at any given heart rate at the 5-millisecond range.

DR. NISSEN: And that will be discussed later, but in terms of what number we actually use as we think this through, my argument might be that we use the worst case number if we're going to use this kind of bin method.

DR. KOWEY: Just since you addressed it to the committee, I'll take a shot at this. But I think we're looking obviously, at central tendency here, and you did present data on outliers. When you said the word "worst case scenario," the thing that always comes to my mind is an outlier analysis. They did two kinds of outlier analyses. They did one looking at the worst QTs and then they also did the one with the worst plasma concentrations. In both of those, "what's the worst thing that could happen" scenarios, we didn't really see a strong signal of a problem.

So I agree with you. I think that we were getting riveted on central tendency measurements, and obviously they're very important. But in real life what we want to know is what could happen in the worst case, and I think that question is very germane. But I think that the

information at least has been presented. We can debate whether we like it or whether we don't like it, whether we find it reliable, but it's there.

DR. BORER: Tom.

DR. FLEMING: I'd just like to reinforce two points that I think Steve has made. One is, as we look at these results, it's very important to know whether there is an interaction between heart rate and age, for example, or another way of saying this is if these tables were generated in a younger population, are these exact same associations seen in an older population, which is a very fundamentally important assumption we're having to make.

The second point that comes to mind on what Steve's saying is if, in fact, you had 1 percent of the population in whom the increase was, in fact, 20 and the rest of the population, the increase is 0, and you're looking at the weighted average, you're going to see something that's trivially small that wouldn't concern us.

But if it's 20 in 1 percent of the population and it would induce a high rate of torsade in that subgroup, the challenge we're running into here is if we're dealing with efficacy that's in a life-threatening setting, then you accept a small risk of life-threatening adverse events.

On the other hand, if you're not looking at

that for benefit, then you have a very low threshold and it does become critically important not to look at averages, but to, in fact, look at outliers because it's unacceptable to have 1 percent of the population that in fact would be a very high level.

DR. ZAREBA: In this study, there was no evidence for outliers which would be of major concern using both classical methods and using even Bazett correction method. Again, I think that there are no data in post-marketing studies indicating any increased risk. I understand that we do not have a heart rate for this post-marketing data, but across the board there is no signal indicating this drug or other drugs of alpha blockers are associated with increased proarrhythmia.

DR. BORER: Now we can move on to Jeremy.

I'd like to make one point -- two points actually as you're coming up here. This doesn't presuppose any final comments that this committee will make.

While we're all concerned about outliers, et cetera and all the points that have been made, I think it's important to reinforce what comes across in the book that you gave us and in that slide which is that you had a positive control. We're focusing on the blue bar, but look at the red bar, a positive control, a drug that affects QT but doesn't seem to cause arrhythmias, and it caused more

of an effect on QT than this drug did. And I think that's important for us to remember as we go forward.

The final comment is that Sanofi-Synthelabo has its headquarters, I think, somewhere outside the United States, so I have to make the point that Massachusetts in the United States has 4 S's not 5.

(Laughter.)

DR. BORER: Thank you.

DR. RUSKIN: Thank you, Jeff.

Mr. Chairman, ladies and gentlemen, I'll try to keep my comments very brief. I'm just going to offer a couple of summary statements about the limitations of correction formulae, the adequacy of the study design in 5105, the results of that study, one comment about pharmacovigilance and one about safety margin.

This slide shows you four different correction formulae used in the 5105 data. These are data points from the population in study 5105 showing you the relationship between the corrected QT interval and the RR interval, that is, the heart rate. These are data that are familiar to all of you by this point, both prior to and during this discussion, and that is, that the goal of a correction formula is to eliminate any correlation between heart rate and QTc.

A number of comments have been made, important

ones, by panel members about other influences on the QTc, but by far the most important, the most potent influence on QT is the heart rate. So the goal in any development program is to correct for heart rate, to achieve a 0 correlation between heart rate and the QTc. In general, what's done is to try to correct the QT for what it would be at a heart rate of 60.

When these data are corrected using the Bazett correction, you can see that as the cycle length decreases, that is, as the heart rate increases, there is a rather dramatic over-correction of the corrected QT interval. So there's a correlation here between heart rate and QTc that should be there.

This is somewhat mitigated by use of the Fridericia formula which brings the slope of that regression line a little closer to the optimum of 0.

Much better corrections are achieved using either a population or an individual subject-based correction in which the correlation becomes close to 0. That is, the QTc becomes a near constant interval.

The Holter bin method, about which you've heard and about which there's been a lot of discussion already, avoids entirely the need for rate correction by using the bin method and by comparing QT intervals at comparable heart rates before and after the drug.

Importantly, the results in this trial, which you've just heard, correlate very closely both with the group and subject-specific individual corrections using standard 12-lead ECGs. What you've also heard from Dr. Pritchett and others is that there's limited experience with this technique in drug trials.

With regard to the study design of 5105, I want to make just a couple of points. The first is that the study covered a 4-fold dosage range, 10 milligrams and 40 milligrams, and at the 40 milligram dose, exposures exceeded those seen with maximum metabolic inhibition with 400 milligrams of ketoconazole, as well as exposures seen in patients with renal impairment.

In addition, a substantial percentage of healthy volunteers experienced postural hypotension at the dose of 40 milligrams.

The study also used a well-studied positive control, moxifloxacin, for which an effect size has been determined in many other drug studies, to demonstrate the ability of this design to detect small changes in QT intervals induced by a drug.

And finally, using 12-lead ECG measures known to everybody here, there is internal validation within this study of the Holter bin method.

Just to reiterate what you heard from Dr.

Oppermann about exposures, the 40 milligram dose of alfuzosin provides exposures that are roughly 4-fold those seen with the standard therapeutic dose of 10 milligrams, and these exposures exceed what is seen with maximum metabolic inhibition with 400 milligrams of ketoconazole.

These are the QT and QTc results in 5105 for alfuzosin 10 and 40 milligrams and a standard therapeutic dose of moxifloxacin, 400 milligrams. As you can see, the QT1000 correlates very closely with what was observed using both individual or subject-specific and group correction formulae with standard 12-lead electrocardiograms. And this effect size at the standard therapeutic dose is, at least to my interpretation, essentially undetectable.

At four times that exposure, again exceeding exposures achieved with maximum metabolic inhibition, the effect size, regardless of the correction formula on the 12-lead ECG or using the QT1000 method, is below 5 milliseconds and it is half that seen with a standard therapeutic dose of moxifloxacin, a drug in wide use.

This slide compares for you the effect sizes seen in the two studies that used the Holter bin method, 4532 and 5105, and despite very small numerical differences in the effect size at 10 and 40 milligrams, I can see no statistically detectable difference in the effect size at these two doses between the two studies.

With regard to outliers defined as a QTc greater than 450 milliseconds or a change in QTc of greater than 60 milliseconds, there were none with any correction formula other than the Bazett formula. And all the QTc Bazett outliers occurred in association with significant increases in heart rate, that is, in patients who had changes in heart rate ranging from 18 to 49 beats per minute.

There were no outliers defined as a QTc greater than 500 milliseconds in any study with any method used, and there was no QT or QTc greater than 440 milliseconds by any correction method in subjects with concentrations exceeding five times dose therapeutic, that is, in the PK outliers. And these outlier analyses were alluded to by several members of the committee earlier with regard to their significance in detecting some signal of risk.

In 15 years of use and an estimated 3.7 million patient-years, there has not been a single case of torsade de pointes reported with alfuzosin.

This slide summarizes for you, as you saw earlier, the IC50s for hERG and the IC50 to Cmax therapeutic concentrations for drugs known to cause torsade de pointes compared to alpha 1 blockers. Specifically with regard to alfuzosin, you can see that the IC50 for hERG is three to four orders of magnitude higher than with these

drugs, and the ratio of IC50 to Cmax is two to four orders of magnitude higher than with drugs known to cause torsade de pointes.

Shown graphically, if one plots the IC50 on a linear concentration scale shown here and compares it to exposures seen with alfuzosin 10 milligrams, 40 milligrams, and in a number of clinical scenarios, including renal impairment, elderly age, and a combination thereof, you can see that in fact you simply can't detect the exposures here in relation to the IC50 for hERG on a linear scale. If you plot this on a log scale, these concentrations or these exposures do become evident and you can see again that alfuzosin 40, which produces the largest exposure of any of these scenarios, is at least two or more orders of magnitude below the IC50 for hERG.

Just a couple of comments about drug known to cause trouble, the paradigm for difficulty with a drug that has a small effect size at a standard therapeutic dose, terfenadine, an agent which is well known to everybody on this committee.

Terfenadine, when taken at standard therapeutic doses, at peak has a QTcB effect of about 18 milliseconds, and it's a lot lower than that at non-peak, probably about 8 milliseconds. However, when exposed to a metabolic inhibitor at standard therapeutic doses, a non-peak

increase in QTcB exceeding 80 milliseconds is observed, and we don't know what that effect size is at peak.

It's important to contrast this with the observations on alfuzosin which at standard therapeutic concentrations has a virtually undetectable effect on QTc using an appropriate correction formula, and at an exposure four times that of the 10 milligram dose and exceeding what is seen with maximum metabolic inhibition, the effect size remains under 5 milliseconds. So there's no way to get from here to here with this drug.

Questions have been raised about other patient populations, high risk subsets. With regard to age, the primary issue that arises in that circumstance is one of increased exposure, and we've seen from the data presented by Dr. Oppermann that increased age is associated with an exposure that goes up about 1.3-fold. So it's not comparable to the 4-fold increase that's seen at the 40 milligram dose, data for which there is QTc information, and that change remains under 5 milliseconds.

With regard to patients with heart disease, particularly advanced heart disease, hypertrophy, congestive heart failure, issues raised by Drs. Kowey and Nissen, those substrates are clearly inherently unstable, high risk substrates, and they can be viewed as effect amplifiers. But I know of no situation in which a drug

with a very small effect size, even under conditions of maximum metabolic inhibition or maximum exposures exceeding those achieved with maximum metabolic inhibition, in normal volunteers has been unmasked to exhibit a huge effect when given to patients with underlying heart disease. I'm not aware of a single situation in which that has occurred. So there's no question that risk will be increased for anything related to arrhythmias in patients with advanced heart disease, advanced hypertrophy, congestive heart failure, but we're talking here about an effect size that is so small that even a multiple of that would not, based on any experience we have to date, be associated with risk for torsade de pointes, very different from the kind of situation we see here. Again, this was unmasked in healthy volunteers.

So in conclusion, the QT effects of alfuzosin are very well characterized. Even at exposures four times those seen at the standard therapeutic dose and exceeding exposures achieved with maximum metabolic inhibition, the effect size is less than 5 milliseconds, and this occurs at a dose associated with postural hypotension in 20 percent of normal volunteers. The effect size at this 4-fold exposure is about half that seen with a standard therapeutic dose of moxifloxacin. There are no outliers using appropriate correction methods, and in 15 years of

clinical use and experience exceeding 3.5 million patient-years, there has been no case of torsade de pointes reported.

Thank you.

DR. BORER: Thank you very much, Jeremy.

We're going to take a break in a moment. Before we do, if there are any questions that have to do with clarification of what's been presented, let's raise them now. Otherwise, if we're going to get into the philosophy and judgments about what we've seen, let's hold it until a little bit later.

Dan and then Blase.

DR. RODEN: Just two tiny questions. Jeremy, I don't think you're the one to answer this, but maybe you are.

Does the agency or anyone know or can they provide information on the safety of moxifloxacin, number one?

And number two, is there overdose experience with alfuzosin?

DR. RUSKIN: With regard to the first answer, I think I would defer to FDA for that information because I'm sure they have more than we do.

There is some overdose experience with alfuzosin. It's small but the company can provide that.

DR. RODEN: And 3.5 million patient-years is 1 patient for 3.5 million years or?

(Laughter.)

DR. RODEN: How many patients?

DR. RUSKIN: Actually it's 2 for half that.

(Laughter.)

DR. RODEN: How many patients?

DR. SALLIERE: Good morning. I'm Dominique Salliere. I'm the head of pharmacovigilance in Sanofi-Synthelabo.

To answer your questions concerning overdosage, maybe I can have slide number 2. We received during the last 15 years only 5 cases of overdosage, but it is interesting to note that the patient had taken between nearly 40 milligrams up to 100 milligrams, and 4 out of these 5 patients were over 75 milligrams. And no cases of arrhythmia, ventricular arrhythmia were reported. And one severe hypotension was reported. This is expected with the ingested dose, and in all cases, the outcome was favorable. So I think that up to 10 times the recommended therapeutic dose, no ventricular arrhythmias were reported.

DR. CARABELLO: The 3.5 million patient-years safety data are, if robust, to my mind very compelling because they would account for all the vagaries that we discussed here this morning between age and the presence of

heart disease, changes in barometric pressure, and so forth. How robust are these data? Is it simply that dead men don't talk?

(Laughter.)

DR. CARABELLO: Or is the reporting structure in the countries from which the data come robust?

DR. SALLIERE: To calculate this number, we have taken the number of tablets sold with the mean recommended dose. So we determined the total number of patients exposed at this for 1 year.

Alfuzosin is marketed in Europe and pharmacovigilance has been set up for a long time, and there is active pharmacovigilance in all countries where alfuzosin is marketed. Periodic reports are submitted to the health authorities and no questions related to ventricular arrhythmia were raised by any health authorities and no variation of the labeling was requested.

DR. BORER: Doug, I assume that in the FDA presentation, you'll be covering the issue that was raised by Dan about the data about a positive control. Is that right?

DR. THROCKMORTON: Well, I don't want to speak for the other speakers. I'm not sure or not. It's true that we monitor the reports of torsade for moxi, and without getting into specifics of those, I think it's safe

to say that we see no clear signal for a --

DR. MacCARTHY: This is Paul MacCarthy from Bayer Medical Lab. We will cover some of the moxifloxacin safety data in our presentation.

DR. BORER: Okay, great. Thank you.

Then we'll take a 15 minute break. I'm sorry. We have a question before we take a break. Tom.

DR. FLEMING: A question for Jeremy, and while he's getting up to the microphone, just a curiosity on slide 17. I have no question terfenadine has a higher effect. It's curious that you presented the Bazett having just been lectured on the fact that that's an overestimate.

(Laughter.)

DR. FLEMING: I want to understand. I thought you were saying something to the effect that, yes, as Steve was mentioning, there is in fact some particular concern that people could be at high risk, people with ischemia, heart disease, whatever. Did I understand that what you were saying was that, however, for other interventions that would induce the level of QTc change that we're seeing here, there's no evidence that it has induced adverse effects in such patients? Could you repeat the essence of your message there?

DR. RUSKIN: Let me try to answer the first question or the first comment first. With regard to

presenting the data for QTcB, I presented it because that's the data that's available for terfenadine. That's how it was analyzed and published, and there's no way to present it with any other analysis.

In addition, terfenadine, while it has a small effect on heart rate, is not close to what you see with alfuzosin, but I certainly agree that Bazett is not the optimal formula for any drug.

With regard to what I was saying, which was simply a comment, because nobody has data in tens of thousands of patients with heart failure to know exactly what magnitude of increased risk one may see with a QT-prolonging drug in that population. The comment I was trying to make was that we know that that is an effect amplifier, but there's no evidence with any drug that it has the kind of impact that you see with drugs that have metabolic liability, the drugs that can have a very small or modest effect size at standard doses that can then go up by an order of magnitude when their metabolism is inhibited. And that's the commonest paradigm for getting into trouble. It's true of cisapride. It's true of terfenadine. It's true in a number of situations.

DR. FLEMING: I had thought what you were addressing was the setting of where we would have people who are at intrinsically higher risk with ischemia, heart

disease, et cetera in whom there may be, in fact, other drugs such that you can have drug-drug interactions that would exacerbate the problem because of their effects on metabolism, and that in essence you were saying for such settings with other agents that would have modest increases in QTc, there's no evidence that that in fact translates into substantial higher risk.

If that's what you were saying, it just sounds like potentially an absence of evidence doesn't mean evidence of absence type of scenario here. Do we really know? And I'm not criticizing. I'm just recognizing the intrinsic limitations of really getting reliable data as to what the effects would be in such people.

DR. RUSKIN: No, I hear you and I agree with what you're saying. There is no way to get a scientific answer to that, particularly the interaction problem, the pharmacodynamic interaction problem, which is very difficult to study and hard to get a handle on in any population.

I think the best that you can end up with is pharmacovigilance which we know has very significant limitations, but the fact is that this drug has been marketed for 15 years in many millions of patients with no labeling restrictions whatsoever in a population that has a prevalence of heart disease of around 50 percent. They're

older people with heart disease. And there have been no signals, not a single case of TdP reported, and no sense of a proarrhythmia signal that has come to light in any of the countries in which it's been marketed. Now, that is highly imperfect data. I would be the first to admit that, but I think it's about the best that one gets in this kind of situation.

DR. FLEMING: But where I would expect under-reporting would be precisely the setting where the kinds of outcomes that I would care about are, in fact, not rare due to natural causes in those populations.

DR. RUSKIN: That's exactly correct.

DR. FLEMING: So if in fact we're increasing by 5 percent, we may not see that reported at all because this is a setting where those events should occur even in the absence of an intervention.

DR. RUSKIN: You can't exclude that possibility. Absolutely.

DR. BORER: With those comments well in hand, we'll take a 14-and-a-half minute break, and we'll begin exactly at 11 o'clock.

(Recess.)

DR. BORER: We're now 6-and-a-half minutes behind schedule. So if we can reconvene please.

We will go on to the presentation from Bayer,

and we'll deal with any residual questions about either product when we get to our discussion in the afternoon. The presentation with regard to Levitra will be introduced by Mary Taylor, who is the Vice President for Regulatory Affairs in North America of Bayer.

MS. TAYLOR: Good morning, ladies and gentlemen, Dr. Borer, members of the advisory committee, and FDA. We are pleased to present to you today our product, Levitra, vardenafil hydrochloride, NDA 21-400. This product has been co-developed and will be co-promoted by Bayer Pharmaceuticals Corporation and GlaxoSmithKline.

I'm Mary Taylor, Vice President of Regulatory Affairs for North America for Bayer Pharmaceuticals Corporation.

The agenda for today is I will provide a brief introduction to the product.

This will be followed by an assessment of QT, QTc, effect of vardenafil by Dr. Tom Segerson. Tom has been with our program for a long time and is now Vice President of Medical and Scientific Affairs for Bayer Canada.

Dr. Joel Morganroth will follow that with an assessment of QT study designs, heart rate correction factors, and arrhythmias associated with QT-prolonging drugs.

We have with us a distinguished panel of consultants. Dr. Joel Morganroth is from the University of Pennsylvania and eResearch Technology. He has been an advisor for FDA and HPB.

Dr. John Camm is a professor of clinical cardiology at St. George's Hospital in London, also a well-known cardiologist and an expert in QT assessment.

Dr. Gerald Faich from Pharmaceutical Safety Assessments is an expert in epidemiology and post-marketing risk assessment and former head of drug safety at FDA.

We have Dr. Gary Koch, a professor of biostatistics from the University of North Carolina, and Dr. Udho Thadani, Professor of Medicine from the University of Oklahoma, an expert in ischemic heart disease.

These individuals will be available for questions, as well as people from Glaxo and from Bayer.

Our proposed indication for Levitra is for erectile dysfunction. The starting dose is 10 milligrams which may be titrated up or down as necessary.

The NDA was submitted in 2001. This was followed by an approvable letter in July of 2002. The application is currently under review at FDA.

It is approved in 34 countries: UK, Germany, and 13 other European countries, as well as Australia, New Zealand, and several Latin American countries. The product

has been on the market since March of this year.

You can see here we started our phase III development program in approximately the year 2000. There were numerous changes in the methodologies to assess QT prolongation during that time. As you can see here, as mentioned earlier, there were several guidances and proposals issued post the development of our phase III program. Health Canada, the ICH, and as Dr. Throckmorton mentioned, the FDA issued their draft concept paper in November 2002.

This brings us to the current topic of today. In our clinical pharmacology program, we showed an equivocal effect on the corrected QT interval. FDA was concerned about what could potentially be observed with supratherapeutic doses and asked us, therefore, to conduct a definitive QT study. We are here today to talk about our clinical trial design, approaches to correction factors, and the risk of cardiac arrhythmia.

We have worked very closely with FDA on this clinical trial, and we would like to take this opportunity to thank them for the excellent collaboration.

We would also like to take this opportunity to thank the entire GlaxoSmithKline team for the conduct of this study.

Next I would like to introduce Dr. Tom Segerson

who will present the QT/QTc effect of vardenafil. In conclusion, we hope you agree that we have conducted a definitive study which shows no clinical concern.

DR. SEGERSON: Thank you, Mary.

Good morning. In my presentation I'd like to present some background information on vardenafil. Specifically I'll talk about the pharmacology and mechanism of action, the efficacy and adverse event profile, and some pharmacokinetic data from humans.

In addition, I'll provide some information that is specifically relevant to evaluation of the QT interval from our preclinical studies, clinical pharmacology studies, and also from the phase III clinical studies.

And finally, I'll discuss the results from a study which was specifically and rigorously designed to evaluate the effect of vardenafil on the QT interval.

Vardenafil is a potent inhibitor of phosphodiesterase type 5 with an IC50 of approximately 1 nanomolar. Vardenafil is also highly specific for the subtype of PDE which, when inhibited, leads to the accumulation of cyclic GMP in smooth muscle cells of the corpus cavernosum of the penis and potentiates thereby the erectile response.

PDEs of several types are also distributed throughout the vascular tissue and thus effects on blood

pressure and heart rate are expected with these compounds. In fact, we have observed in our clinical pharmacology studies transient effects on both blood pressure and heart rate after a dose of vardenafil which peak around the Cmax, or maximal concentration, and have a duration of approximately 1 half-life. The magnitude of the effect we've observed is up to about 7 millimeters of mercury reduction in systolic and diastolic blood pressure and about a mean increase in the heart rate of approximately 4 beats per minute.

Vardenafil has also been shown to be efficacious in the treatment of erectile dysfunction in our clinical studies, and shown here are data from studies from the general erectile dysfunction population. In addition, we have demonstrated efficacy in populations that are typically more resistant to treatment. Shown in these figures are data from this pivotal study in the general population where doses of 5, 10, and 20 milligrams of vardenafil were both clinically and statistically superior to placebo as measured by the Erectile Function Domain of the International Index of Erectile Function. This is a validated questionnaire which is a standard and accepted endpoint for the establishment of efficacy in these compounds.

In addition in a study in diabetics, doses of

20 and 10 milligrams were also superior to placebo.

The next slide shows a summary of the safety data from our clinical program. This is looking at the incidence of adverse events in placebo-controlled trials. Shown here are the adverse events of vardenafil compared to placebo. In the vardenafil group, approximately half of patients reported an adverse event compared to approximately one-third of patients in the placebo group. And if we look at the most common adverse events that occurred more commonly in vardenafil, those were headache, flushing, rhinitis, and dyspepsia, which are adverse events that are commonly observed in trials of PDE5 inhibitors.

The pharmacokinetics of vardenafil demonstrate that it's rapidly absorbed and eliminated from plasma as shown here in the pharmacokinetic profile in a clinical pharmacology study in men after a single dose of 20 milligrams. The maximal concentration is achieved at approximately 1 hour, half-life is approximately 4 to 5 hours, and at 24 hours, there is only about 1 to 2 percent of the maximal concentration present in plasma. This, therefore, indicates that with a minimal interval of 1 day, of exactly 1 day, the chance for accumulation of vardenafil is small. Moreover, these data suggest that to evaluate any effect on the QT, a single-dose study is appropriate.

The elimination of vardenafil from plasma

occurs by hepatic metabolism principally and to a lesser degree by renal excretion.

The next slide shows the result of hepatic metabolism which results in a series of metabolites, and here showing the pharmacokinetic profile of those metabolites compared to vardenafil, the parent enzyme, in a logarithmic scale to demonstrate the similarity in both the time to maximal concentration and also the elimination profile of these metabolites. This, therefore, suggests that also for evaluation of potential effects of the metabolites on the QT interval, a single-dose study is appropriate and also that the potential for accumulation of metabolites is approximately the same as with the parent enzyme.

The metabolites themselves are formed by hepatic metabolism through largely cytochrome P450 CYP3A4 as well as CYP2C9 and thus the pharmacokinetics of vardenafil are susceptible to inhibitors of CYP3A4. We, therefore, evaluated a number of such inhibitors and the most potent effect or the greatest magnitude of effect that we observed was with ritonavir, an HIV protease inhibitor, which is both a very potent inhibitor of CYP3A4 but also an inhibitor of CYP2C9. Thus, we concluded that the co-administration of ritonavir would represent the scenario of maximal metabolic inhibition.

The next slide shows data from a study where we sought to determine a single dose of vardenafil that would achieve levels in plasma that match or exceed those under maximal metabolic inhibition. The parameter we evaluated was Cmax, with the assumption that the maximal effect on QT, if present, would vary instantaneously with the concentration of vardenafil and thus maximally occur at Cmax.

Moreover, we studied a dose of 5 milligrams in combination with ritonavir, with the agreement of the FDA, as this is the highest dose recommended for concomitant use with potent CYP3A4 inhibitors and thus covers the proposed labeling for concomitant use of these compounds.

These data are crossover data from the same subjects showing the mean Cmax and individual Cmax data after a single dose of vardenafil 5 milligrams, after a dose of vardenafil 5 milligrams plus ritonavir at a maximal clinical dose, and after a single dose of vardenafil 80 milligrams. And the mean Cmax after the single dose of 80 milligrams exceeds both the individual as well as the mean values observed after a dose of 5 milligrams of vardenafil on the background of ritonavir at steady state. Thus, the dose of 80 milligrams of vardenafil would represent and cover the scenario of maximal metabolic inhibition.

In addition, I should mention that we did study

doses higher than the 80 milligrams, specifically 120 milligrams, and this dose was not well tolerated in normal volunteers.

Also, I should mention that ultimately when we studied the single dose in the QT study that I will present subsequently, the distribution of Cmax values mirrors that we saw in this study.

Next, I'd like to cover some of the data that we developed during development to assess the potential for effects on the QT interval for vardenafil. These include preclinical data. In vitro we evaluated the effect of vardenafil on the hERG potassium channel which encodes the IKr potassium current, a component of the late repolarization phase of the myocardial action potential and also the target for all known drugs to affect QT and produce torsade de pointes.

We compared the results of vardenafil and sildenafil in vitro, and the IC50s for both of these compounds were relatively similar, 30 micromolar for vardenafil, 47 micromolar for sildenafil, and compared to the free concentration after maximum clinical dose, which we would consider the relevant comparison to in vitro conditions in the absence of protein, both compounds had IC50s for hERG which were at least 1,000-fold above the free concentration after maximum clinical doses, 100

milligrams of sildenafil and 20 milligrams of vardenafil.

In vivo we also evaluated the effect of vardenafil on the QT interval in beagle dogs, which is a recommended preclinical model for this evaluation, and moreover, in the case of vardenafil, the metabolic pattern of vardenafil in the beagle dog is very similar to humans.

In our safety pharmacology studies in both anesthetized and conscious beagle dogs at doses up to 10 milligrams per kilogram, we observed no effect on the QTc interval, and the concentrations that we achieved with these doses were with respect to the maximal clinical dose at levels achieved after 20 milligrams in humans, 100-fold greater, and with respect to the concentrations of metabolites after a 20 milligram dose, at least 10-fold greater.

In our clinical pharmacology program, although we did not have a study that was specifically designed to evaluate the QT, we did have in six placebo-controlled studies paired electrocardiograms pre and 1 to 2 hours post dose that were part of the standard clinical safety assessment. They included studies evaluating doses up to 80 milligrams. If we looked across the results from these studies, which as I said, were not specifically designed to evaluate the QT, we saw what we would interpret as equivocal changes on the QT and QTc intervals with no

obvious dose-response relationship.

In our phase III program, we also did not have specific design in those studies to evaluate QT pre and post dose because of the interval use. We had very little electrocardiographic data that correlated with a recent dose of vardenafil. But even in examining those limited data, we did not observe any consistent effect on the QT interval.

We could, however, evaluate the incidence of adverse events which may signal an occult ventricular arrhythmia in the sample size from our clinical trials at least, and these specifically are syncope, dizziness, palpitation, and seizures. In the case of syncope, dizziness, and seizures, these events were not very common, but we didn't observe any difference between placebo and active. In the case of dizziness, there was a greater incidence than in placebo, but given the vasoactive effects of vardenafil, we would not consider this a very sensitive or specific adverse event for occult ventricular arrhythmia. We did not observe torsade de pointes in our clinical trials with vardenafil.

If we examine the circumstances of death that occurred in our clinical trials with vardenafil, I should say up front that we had 9 deaths that have occurred in patients after enrollment in the study but before receiving

treatment. 7 of these deaths were actually cardiovascular in origin, and that underscores the risk for death in the population that we studied in our clinical trials.

In our completed clinical trials, we have observed 7 deaths. This shows the treatments under which those deaths occurred: 1 on placebo, 1 on sildenafil, a total of 4 on vardenafil, and 1 in a patient who was randomized to vardenafil but then was diagnosed very soon thereafter with bronchogenic carcinoma and had a massive hemoptysis and apparently did not take drug.

In all of the cases of death on vardenafil, there was either no temporal relationship to the dose with respect to the event that led to death or the death itself or information that suggested an alternative cause for the death. That correlates with the assessment of the investigators, as well as their own drug safety group, that none of these deaths was related to vardenafil treatment.

So we then embarked on a study to evaluate specifically the QT effects of vardenafil and the scenarios that we chose to evaluate were both the effects at therapeutic doses, at supratherapeutic doses, and at plasma concentrations following maximal potential interaction with CYP3A4 inhibitors. This approach and design was discussed with and agreed with the FDA, and it was performed by the clinical pharmacology and statistical groups at

GlaxoSmithKline.

The primary objective of this study was to exclude a greater than 10-millisecond effect in the Fridericia corrected QT at the 1-hour post-dose time point after a dose of 80 milligrams of vardenafil.

Secondarily we evaluated the uncorrected QT, as well as both the corrected and uncorrected QT, at Tmax for the evaluated compounds, as well as the maximal change from baseline for QT and QTc over the 4-hour period of evaluation.

The study was a six-way crossover study, single-dose evaluation, controlled by placebo. The doses that we evaluated, the period of evaluation, the choice of a positive control, and the statistical analysis were all discussed with and agreed with FDA.

These are the treatments that were included in the study. They started with a vardenafil 80 milligram dose, which as I've demonstrated, achieves concentrations of vardenafil in plasma which exceed those of strong metabolic inhibition. We also studied the recommended starting dose of vardenafil 10 milligrams, and this therefore represents an 8-fold difference in these doses evaluated for vardenafil, and in fact, in terms of plasma concentration, a 12-fold difference.

We correspondingly compared with the

recommended starting dose for sildenafil, 50 milligrams, and an 8-fold multiple of that dose, 400 milligrams of sildenafil.

Moxifloxacin 400 milligrams was chosen as the positive control and this is because of the well-described effect of moxifloxacin on the QT interval and also the extensive post-marketing and safety database. And all of these active treatments were compared to placebo.

We derived data for evaluation of the QT from a total of 59 healthy subjects that ranged in age from 45 to 60 years of age. The QT interval was determined by a validated central laboratory which was blinded to the treatment assignment. The QT interval itself was determined by manual digital measurement of an average of 3 beats in a single lead, lead II. The end of the T wave was identified by the return to baseline or, if this was not possible, by tangent method. Subjects were maintained non-ambulatory, supine, and fasting during the study to reduce variability in the QT interval measurements.

This shows a schematic of the study design. We had three time points that were evaluated before dosing, ranging from a half an hour up to the time point immediately before dosing. At each of these time points, there were a total of 6 electrocardiograms taken and they were taken 1 minute apart over a time period of

approximately 6 to 10 minutes which would be expected to cover a range constant concentration of the compounds evaluated.

Immediately before dose and after the electrocardiograms, a pharmacokinetic sample was obtained. And then post-dose time points from one-half hour out to 4 hours post dose were evaluated again with 6 electrocardiograms at each time point 1 minute apart, and a pharmacokinetic sample at each time point taken after the electrocardiograms were performed.

Shown here are the data for change from baseline after placebo treatment looking at the raw or uncorrected QT interval, the heart rate, and the QT interval corrected for heart rate with the Fridericia formula. We observed a mean increase in the raw QT of 6 milliseconds and a corresponding reduction in the heart rate of 3 beats per minute. When we correct for that change in heart rate, we observed after placebo a QTc of 0 milliseconds at the mean.

And if we then did a comparison of the active treatments to the placebo change, showing here the placebo-subtracted mean change from baseline and 90 confidence intervals at 1 hour, again looking at raw QT, heart rate, and QTcF, we can see that for the doses of vardenafil 10 and 80 milligrams, as well as for both doses of sildenafil,

there was a mean reduction in the raw QT interval of 1 to 2 milliseconds, and that contrasts with moxifloxacin where there was a mean increase of 3 milliseconds. This corresponds to a differential effect on heart rate of the PDE5 inhibitors and moxifloxacin showing, in the case of vardenafil and sildenafil, a 4 to 6 average increase in the heart rate compared to a lesser magnitude of effect for moxifloxacin of 2 beats per minute.

The corrected QT interval using Fridericia for the primary analysis of 80 milligrams showed a mean difference from placebo of 10 milliseconds at 1 hour, with an upper limit of the confidence interval of 11 milliseconds. These confidence intervals are very similar to what was observed with the high dose of sildenafil, 400 milligrams.

In both the case of vardenafil and sildenafil, the difference in the effect from 80 milligrams to 10 milligrams and 400 milligrams and 50 milligrams was very small, that is, a 2- to 3-millisecond difference in the effect on the QT interval despite an 8-fold difference in dose.

And with respect to moxifloxacin, we observed a mean difference from placebo of 8 milliseconds prolongation of the QT interval which is very comparable to the effects seen in previous studies in the range of 5 to 10

milliseconds.

As I said, primarily we used an evaluation of the Fridericia corrected QT, and this sort of evaluation assumes a constant relationship of the heart rate and QT interval across the population, but as has been stated, typically we observe a lot of variation in this relationship from individual to individual. And thus, it has been suggested that one also apply an individual correction to the heart rate or RR-to-QT relationship.

In our study, we used off-of-treatment data from both the baseline evaluation, as well as from data during placebo treatment, which in this case covers the time frame of the active treatments, and with those data, had electrocardiograms, 138 in number, for each subject.

We used two approaches in this evaluation, one a linear relationship where we derive the slope of the linear regression for each individual and use that for correction of the QT, as well as a nonlinear relationship which uses an exponential formula similar to what's used for Fridericia and Bazett, but instead of a square or cube root, the individual exponent is derived and used to correct for heart rate. And for both of these approaches, we performed the same analysis as we had for Fridericia corrected QT.

Shown here graphically are the results of the

QTci, or individual correction, using the linear relationship, compared to the data I've just shown you for the changes at 1 hour for QTcF. What we can see is that the magnitude of the effect, in the case of vardenafil and sildenafil, is reduced compared to what we observed in the Fridericia correction, down to the lower end of the 5- to 10-millisecond range or even below that range. That's in contrast to the effect on moxifloxacin where there's very little change in the magnitude of the effect from the two correction formulae.

I should also note that there's very similar effects still, as we saw for QTcF, for sildenafil and vardenafil and, again, a very narrow dose-response range. We can see that numerically in the next slide. We show these data that I just showed you graphically, and here we observe again the linear relationship for QTci and we see a magnitude of effect in the range of 4 to 6 milliseconds for both vardenafil and sildenafil, both doses, a very shallow dose-response of 1 to 2 milliseconds, and again not as great a change in the magnitude of the effect of moxifloxacin between the two correction formulae.

These are the data, as I said, from the linear relationship, and Dr. Morganroth will discuss and present the data that we have from the exponential relationship or nonlinear relationship, and they are very similar to these

data.

We also evaluated, in addition to the QTcF at 1 hour, the QTcF at Tmax, or time of maximal concentration, for each of the active treatments compared to the matched time in placebo, as well as the maximum QTcF change that occurred over the 4-hour evaluation period, compared to the maximum QTcF change after placebo. And that was not time-matched, whereas the change after placebo would not necessarily occur in the same time after active.

But if we look across these different approaches to the evaluation, the magnitudes of effect for each of the tested active compounds, this is very similar regardless of the evaluation, with largely overlapping confidence intervals, and again, a very shallow dose response for all of these evaluations, very similar effects for vardenafil and sildenafil.

In our outlier analysis, we saw no uncorrected QT values that were 500 milliseconds or greater, no value that was corrected for QT heart rate with the Fridericia formula that was 450 milliseconds or greater, no change from baseline in the QTcF that was 60 milliseconds or greater. And in the case of change from baseline of 30 milliseconds or greater, we observed only 1 subject, as it happens, after sildenafil 400 milligrams with a mean QTcF change of this magnitude at any time point, and this was

based on an average, as I said, of 6 electrocardiograms over a period of 6 to 10 minutes, a range of time that we'd expect constant concentration of both of these compounds.

We also modeled the effect of the QT interval, in this case QTcF, to the concentration of vardenafil, sildenafil, and moxifloxacin. Shown here are the observed data plotting the QTcF against the vardenafil plasma concentration, and what we can see is there's a lot of scatter in the observed data. And this is from the large intra-subject variability, as well as day-to-day variability.

We did, however, observe that in the majority of subjects the maximal effect on QT did occur at the time of maximal concentration, and thus a direct effect model was appropriate for testing. A number of such effect models were tested, and an Emax model best described the relationship. That's shown by this red line where we can see that the QTcF, across a very broad range of concentrations out to the far end of the data points here, shows essentially a constant relationship for QTcF.

And if we look at the inset, the concentrations at lower concentrations, which would represent concentrations observed after the 10 milligram dose, we again see a relatively constant relationship of QTcF to vardenafil plasma concentration. Thus, this very shallow

or even flat concentration-response relationship mirrors the shallow dose-response relationship that we saw from the primary analysis.

So in summary, in clinical trials, we have shown vardenafil to be both safe and effective in the treatment of male erectile dysfunction. Our preclinical studies that were performed to evaluate potential for effects on the QT interval would not have predicted an effect on the QT interval at clinically relevant concentrations, and we did not see evidence for torsade de pointes in our clinical development program.

A study that was performed to specifically evaluate the effect on QT with 10 and 80 milligrams had the following results. The primary analysis did not rule out an effect greater than 10 milliseconds, at the upper confidence interval, 11 milliseconds, but overall the data for 10 and 20 milligrams in this study, performed in accordance with current regulatory guidance, showed an effect in the range of 4 to 10 milliseconds of mean maximum change in the QT corrected for heart rate.

After vardenafil, we observed actually a shortening in the uncorrected QT, and this is in contrast to moxifloxacin which lengthened the uncorrected QT.

The concentrations that we achieved in this study cover the range that would be observed with strong

metabolic inhibition.

The relationship of the effect on QT at both vardenafil doses and concentrations was very shallow, specifically a 2-millisecond increment with an 8-fold increase in dose, 12-fold increase in concentration.

Finally, the effect that we observed for vardenafil was very similar to the effect that we observed after sildenafil, an approved drug in the same class.

It is the opinion of Bayer and GSK that the magnitude of effect that we have observed in this study is of no clinical consequence. We are, however, committed to ensuring the safe use of this product and have a large pharmacovigilance program planned for the post-marketing period, which we'll be happy to share the details of that with the committee if they so desire.

In terms of the relevance of this effect to clinical risk, Dr. Morganroth will now discuss that, as well as critical evaluation of the design of this study and approaches to correction of the heart rate. Dr. Morganroth?

DR. BORER: I think there will probably be a number of questions about how these things were done, but maybe we should defer those until after Joel has presented because he's going to talk about them, as I understand.

However, at this point we've seen a big

presentation book and we've heard a summary of it. Does anyone have any questions specifically about the factual evidence, not how it was obtained, but about the data themselves? Dan?

DR. RODEN: The QTci measurement relies on generating a graph of RR intervals versus QT intervals over some range of RR intervals generated by this series of 18 electrocardiograms at baseline. Can you give us a sense of how much RR variability there really was? I would imagine these guys are lying around. They've been lying around for a long time, and the RR intervals can't possibly vary all that much.

DR. SEGERSON: Dr. Morganroth will address that.

DR. RODEN: Joel, if you're going to address it later, then that's fine.

DR. MORGANROTH: I'm going to address it.

DR. PICKERING: Could you tell us in what substantial ways vardenafil differs from sildenafil in its general actions? It seems to be very similar.

DR. SEGERSON: Well, they're both PDE5 inhibitors. Vardenafil in vitro shows greater potency and greater selectivity of the PDE5 enzyme. In terms of other comparative data, that's all we can say.

DR. BORER: Peter.

DR. KOWEY: You showed us Cmax for 5 milligrams, 5 milligrams plus ketoconazole, and 80 milligrams, but 5 milligrams isn't the dose that you're giving. Do you have Cmax for 10 milligrams plus ketoconazole?

DR. SEGERSON: As I said, the 5 milligram dose is the maximum dose that we have recommended for use in combination with strong CYP3A4 inhibitors, and thus, in agreement with the FDA, that was the dose that we chose to evaluate in the study.

DR. KOWEY: But you know that's not going to work. Okay. You know that somebody is going to be on a regular dose of the drug and get ketoconazole. So that isn't going to flush.

DR. SEGERSON: I'll ask my colleague, Dr. Sundaresan, to address that.

DR. SUNDARESAN: The left half of this graph shows the data that has already been shown earlier, which is the ritonavir interaction results. As mentioned earlier, what they're showing is the effect on Cmax, and what was studied was vardenafil alone, the 5 milligrams, vardenafil plus ritonavir, and then compared to that is the 80 milligrams alone of vardenafil. As was pointed out, the 80 milligrams very well covers the ranges that are reached with the 5 milligrams of vardenafil plus ritonavir, which

as indicated, is the maximal recommended dose for use with potent CYP3A4 inhibitors.

Now, what we have shown on the right side is we have done simulations of 1,000 patients on what's likely to happen if the dose was 10 milligrams or if the dose is 20 milligrams and the ritonavir is given under those circumstances. As you can see, this is the results with the 10 milligrams plus ritonavir, and these concentrations are also well covered by the 80 milligram dose. The 20 milligrams plus ritonavir is less well covered, but as you can see, there were concentrations that reasonably at least -- 10 percent of the concentrations still cover not the median as well as expected, 10 to 90 percent range.

DR. KOWEY: I misspoke in my question. I meant ritonavir, and that answers the question. Fine. Thank you.

DR. RODEN: Wait a second. Those are simulation data. To get to 20 and R, you multiply 5 and R by 4 I guess.

DR. SUNDARESAN: No. Sorry.

DR. RODEN: That's certainly what it looks like from here.

DR. SUNDARESAN: No. See, what happens is what you do is you have the population results from these and you simulate for 1,000 patients and you get the median and

the range.

DR. RODEN: You're making an assumption about linearity of disposition which is not justified by anything that you're showing us. It may be true, but you can't just multiply by 4 and say that's the way it's going to work.

DR. SUNDARESAN: I agree with that limitation.

DR. BORER: Any other issues of fact here? Tom?

DR. FLEMING: I'd like to understand the active control. Moxifloxacin is here basically, as I would say, just to get a sense of sensitivity of this assay, of this approach. It's interesting. If I look on page 31, you've indicated that basically, as the briefing document says, there aren't any subjects that had a QTc measured by the Fridericia method that had more than a 30-millisecond increase. We saw another report earlier this morning that indicated that with moxifloxacin, you would expect 10 percent to have that level of increase. That would have meant I should have expected 4, 5, 6 people. Any comment on why we shouldn't be surprised that there weren't any increases of 30 milliseconds?

DR. SEGERSON: I'll ask Dr. Morganroth to address that question.

DR. MORGANROTH: The ability to detect outliers depends on all the parameters in the design of the trial,

the number of ECGs obtained, the precision of the ECG measurements, the sample size, et cetera. I believe that the vardenafil trial had short of 17,000 ECGs in a sample size of 59 subjects, as you saw, 6 replicates at each time point with very accurate digital manually derived determination in a very powered study at 59 subjects.

Probably that accounts for the fact that the moxifloxacin central tendency effect was exactly -- well, within a millisecond or 2 of what was seen in the moxifloxacin NDA in their clinical pharmacology trials that were designed to look for QTc versus when one uses, let's say, less robust designs, the moxifloxacin would expect to be perhaps larger, as was seen in the earlier trial. I think that accounts for the differences in outliers. The central tendency is, I believe, the most reliable method of determining assay sensitivity.

The percentage of outliers is, again, determined by numbers of ECGs done at baseline and on therapy and time courses. I'm going to discuss that by showing the percent of observations as a method of looking at the definition of outliers as the FDA has in the briefing book versus the percent of patients that have definition of outlier. And those numbers become very confusing depending on the approach that you use.

DR. FLEMING: So are you saying then that you

would expect there should have been no increases of 30 milliseconds using the Fridericia method when we look at moxifloxacin?

DR. MORGANROTH: The answer is yes, and the basis for my guess that that's what should have been found is on the fact that in the trials previously that have looked at the clinical pharmacologic effect on QT of moxifloxacin, the magnitude of the ECG numbers and sample sizes were far smaller than that that was used in the vardenafil trial, and therefore one would expect more noise, more variability to be detected, more people that will randomly on placebo go to 30 to 60.

In fact, if you look at most phase III trials that have one baseline and one ECG here are there on treatment and you look at the percent of subjects who go 30 to 60 milliseconds on placebo, it's usually at least 10 percent and it can be as high as 60 or 70 percent. The 30 to 60 is very non-specific. It's too sensitive almost, a too-sensitive cut point for outliers if in fact you have infrequent ECGs.

Now, if you have a lot of ECGs on drug and only one baseline, which sometimes people design trials that way -- they only get one baseline and have an ECG every week and month during a clinical trial. And your variability of the QTc is about, on average, 75 milliseconds a day. So if

your single ECG at baseline happened to have been taken towards the 365 versus the 440 part of the cycle, 440, the upper limit of normal, and you do many measurements on drug, what's the likelihood that one of them might be 30 milliseconds higher than that single baseline? Obviously, the more ECGs you obtain, the more that likelihood is, and it can be as high, as I said, on data sets that I've seen, over 50 percent to 75 percent of patients that might even meet that kind of criteria.

In this trial with 18 at baseline, 30 on drug, in 58 subjects, I couldn't predict. I had expected it to be very low. Actually, as you remember from the briefing document, the percent of actual ECGs out of placebo and baseline -- there were about 10,400 ECGs.

DR. FLEMING: Correct.

DR. MORGANROTH: And of that number, there were only 30. Well, it depends on the correction formula and the approach you take. But using the individual correction formula, QTci, as I recall the data, there were only 30 subjects that had -- excuse me -- 30 EKGs out of 10,400 ECGs that had 30 milliseconds more.

I think that attests to the fact that moxifloxacin is not a very potent QTc prolonger. We will show you in a moment that the post-marketing surveillance is pretty clean, if you will, in terms of incidence of

torsade on moxifloxacin, a point that Dr. Borer made earlier. Therefore, one wouldn't expect a lot of outliers because one would expect more of a signal in the marketplace of a lot more torsade.

DR. FLEMING: Let me pick up on the point you're just making. I can't help but contrast a little bit from what we've seen with alfuzosin where it looked there that the effect on QTc there was less than moxifloxacin. It looked like, if I follow, on slide 22, your intention was essentially to be able to show a similar pattern in this trial. You were designing the trial to rule out a 10-millisecond change. In fact, not only rule it out, your data suggests a 10-millisecond change using your primary endpoint specified Fridericia method.

If we then go on to slide 26, your point estimates for the average change are in that right-hand column basically the same or higher than moxifloxacin, again clearly consistent with the hypothesis you were trying to rule out, that you would have less than a 10-millisecond increase.

Finally, if I go to those 10,440 measurements that you were talking about and use your Fridericia method, there are 62 that were outliers, and the two arms that had the highest number were moxifloxacin and your 80 milligram dose, both of which had 16.

So you designed the trial to rule out 10, trying to establish it was much less. You actually have data suggesting it's 10 by your primary specified endpoint, data that suggests it's the same as moxifloxacin, and outlier data that suggests that you have greater than 30 milliseconds with the same frequency of moxifloxacin. Am I misinterpreting anything?

DR. MORGANROTH: I think everything you said is correct in terms of the numbers that you just went over, and what I'd like to do in the next 10 or 15 minutes is sort of put that in a clinical perspective to try to answer the question which correction formula gives you the more accurate estimate.

DR. FLEMING: Of course, that's a little bit post hoc. You, in fact, did prespecify the Fridericia method was your --

DR. MORGANROTH: Well, one of the questions this panel will be addressing this afternoon is exactly that issue. Should, in fact, sponsors when they do definitive QT trials, prespecify a correction formula and a plan --

DR. FLEMING: So in helping to understand that, can you give us the rationale that you used for choosing this prior to seeing the data?

DR. MORGANROTH: I wasn't involved but I

understand that the FDA at that point requested this objective to be specified in the protocol despite the company wanting to, in fact, say that our objective is like the alfuzosin this morning, to evaluate the QTc effect of the drug without trying to prespecify a magnitude of an effect or a correction formula.

Again, one of the questions you all will be addressing is whether or not for definitive trials should such prespecified correction factors and limits be part of the definitive trial or should one take the approach to do as adequate a design as possible with placebo and positive controls and have the ability to look at various correction factors and find the one that provides the best correction for heart rate, a major influence as you talked about this morning, and then use a statistical plan that is appropriately looking for not only central tendency but outliers, and then, after looking at the totality of the data, determine what the magnitude of the effect is, what the magnitude of outliers is, and what the potential clinical risk is from that trial. That's a question the FDA has posed to you because obviously there isn't a uniform consensus in the world as to how one should go.

My personal opinion is that in our level of what I'll call misunderstanding about the relationship of QT to QTc to clinical outcomes, as you all were inferring

this morning correctly, that I do not believe one should have a prespecified correction formula in trying to rule out 10 milliseconds. I think you have to look at the dose effect. 5 milliseconds at 3 times the dose, going up to 15 milliseconds may be a very different kettle of fish than 5 milliseconds 8 times the dose and 12 times the concentration going up only by 2 milliseconds. Because that really addresses what may happen in the clinic when you get the drug used in a patient as discussed this morning by Dr. Kowey and others, the patients with hypertrophy and ischemic heart disease, et cetera. That's my opinion.

You all have to make your opinion and answer the question regarding this issue, but I think this is what the issue is, whether one should prespecify or not.

DR. FLEMING: Well, we'll discuss this later on, although just briefly to follow up, clearly, yes, you would look at all data. Generally, though, we would hope that sufficient forethought is put into designing a trial that what we target as the primary endpoint is at least as, if not more, representative of what we really care about than the other measures. So it's a little perplexing when we define a primary endpoint, don't see what we want to see, and then we move away to other measures, wondering how much that's driven by the true, legitimate science versus

the interest in being able to get a conclusion we wanted to reach.

DR. MORGANROTH: Yes, I think that's a generally good principle; that is, you should not stray away from your primary objective in a clinical trial in post hoc analysis. I 100 percent agree with that in general. The only problem is when you're trying to determine the QTc effect of a drug, because of all the problems that were discussed this morning, which correction is the factor is the better, has the assay sensitivity performed correctly, your control groups performed correctly, et cetera, I'm not so sure we know enough about this field to be able to say a priori prospectively what a correction factor, what limits, et cetera should be applied to any particular drug. Even this issue about single-dose versus multiple-dose studies and pharmacological coverage is not easy to grapple with, as obviously the comments have alluded to.

DR. BORER: Susanna and then Paul.

DR. CUNNINGHAM: I noticed on slide 23 you said you used the tangent method to determine the end of the T wave, and yet there was an article that we were given by the other company written by Drs. Malek and Camm which specifically says that the tangent method wasn't necessarily the best one for estimating the end of the T

wave. So could you comment on your choice?

DR. SEGERSON: I'll leave that to Dr. Morganroth as well.

DR. MORGANROTH: Yes. The standard, as Dr. Segerson pointed out in the slide, is not to use the tangent method, to use the end of the T wave and try to distinguish a QT and note very critically abnormal U waves or notched T waves as another -- we'll call that a morphologic phenomenon rather than a quantitative effect.

There are some cases, however, in which the U wave obscures the end of the T wave, and that is very uncommon, in fact, did not occur in this trial. So in this trial, it's a 0 incidence because there were only 4 patients who had any T wave abnormalities and those T waves were a slight flattening. Frankly, that's because of the way the study was conducted, as I'll point out.

I always expect at least 1 or 2 patients who are going to have inversions, even though they're healthy people, relatively healthy. This was a mean age population of 53, so I would have expected some more T waves. But I think the conduct of the study tried to eliminate --

DR. BORER: We're not going to call that old now, are we, Joel?

(Laughter.)

DR. MORGANROTH: Yes. I've got to be careful,

don't I? Very careful. I'm not 30. I'd like to claim I am, though.

DR. ARMSTRONG: In the positive control, moxifloxacin, as depicted in the tables 1 and 2 with the questions to the committee, coming back to Tom's point, if we're going to use that as the reference point to establish the two drugs of interest, the QT data for the same dose of moxifloxacin is quite different. It's unclear to me how much of that represents the sample size or other issues. But if we're going to reference this to a positive control, the positive control between the two studies is substantially different, and I was just looking for insight as to why that was.

DR. MORGANROTH: I commented on that a moment ago, but let me expand on it just a bit. I think that the purpose of the positive control is assay sensitivity. The magnitude of that positive control, according to the FDA concept paper, is to be in the 5- to 10-millisecond range, not therefore to use a drug like sotalol that might give you 30 milliseconds. It's too easy to see that because you want to make sure that if the placebo and the new drug under consideration look identical, that in fact, in that assay in the whole trial all the design features were such that your positive control hit a 5- to 10-millisecond effect, which is sort of the threshold that the concept

paper suggests is something that's desirable to know about.

I believe that -- at least I didn't hear this morning the numbers of 12-lead ECGs that were done by the first moxifloxacin data set that you're referring to because the vardenafil data set does not have Holter monitoring, which is a very intriguing and very interesting method and I think deserves more attention. But we don't have that in both trials. We only have standard ECGs in the vardenafil trial to compare to the standard ECGs that were done in the alfuzosin trial.

So I don't know if they had a magnitude of ECGs that were comparable to the magnitude in this trial, which was 17,000 in 59 subjects. If they had 45 subjects and had far fewer ECGs, my guess would be that's a reason for why there was a difference in the magnitude.

Number two, another reason might be the differences between the measurement techniques. They were both done digitally but in different laboratories, and there are differences between laboratories, even between people within a laboratory. So one might expect a difference there, the conditions of the study, in terms of how well people were really kept from having effects on heart rate, et cetera.

So to answer which is the right number, I think one has to go to the biggest set of data, and that biggest

set of data comes from Bayer's NDA and post-marketing clinical pharmacology program. I think if one looks to the label of moxifloxacin, I believe the number is 6 milliseconds. So I think that as long as you're between 5 and 10 milliseconds, that you've hit the gold standard of the method which is all of their data put together.

As we do more and more of these phase I definitive QT trials with moxifloxacin, we'll see how they come out in terms of whether it makes it identical to the NDA. I've been involved in about a dozen such trials in the last year and I've seen all of them come between 5 and 10 milliseconds. So I would think that the differences we're seeing here are probably solely design issues.

DR. KOWEY: Paul, when we had this discussion at DIA about positive comparators, it specifically was for this problem that you point, which is extremely important, which is because of differences in patient population and methodology and just the way you do the studies and how you make the measurements and given all the vagaries of all that you've heard about the measurement, that having a positive comparator group, which is difficult to do in these kinds of trials, as you can imagine, to tell somebody in a clinical trial we're going to give you a drug that we know prolongs QT interval as a positive comparator -- even though it's difficult, we thought that it was probably a

reasonable thing to do so that we wouldn't have difficulty interpreting any individual study. In other words, if you just looked at the moxifloxacin label and said, well, 6 milliseconds, you wouldn't have predicted in the first study that we saw that the QTc change was really much greater.

But it's the assay sensitivity issue that is important here, and I think these two studies actually point out exactly why having a positive comparator is so very, very important. I think the point that you raise is germane to that argument.

DR. BORER: If there are no other questions of fact -- oh, I'm sorry. Tom.

DR. PICKERING: I just wanted to ask, was this study done only in men? I don't think you specified. And I ask because I could see that it might be used in women unlike alfuzosin.

DR. SEGERSON: The study was performed only in men.

DR. BORER: Joel?

DR. MORGANROTH: Thank you very much.

I've been asked by the sponsor to comment on, in a critique manner, the design features of the trial that they did in terms of what was good, what wasn't good, what the interpretation of the correction factor data provide us

in terms of recommending one correction factor approach over another in definitive QT trials, and finally to give you some comments if I were asked the question, well, how do you determine what the risk of 5 to 10 milliseconds is? What are the methods and the data that we have in order to judge whether that's an issue or not an issue for approvability or for labeling or what have you.

Most of my comments and I think most of the concepts that we've been talking about today really come from the November 2002 concept paper in which the principal message, I believe, is that it's very important to get this right. We need to understand for non-cardiac drugs whether they have a QTc effect or not, and to do that, we need to use careful consideration not just in this definitive phase I trial, but in all of the trials with specific design recommendations using central validated methods as a way of determining the QT effect in the pharmacology studies, phase I, as well as in the clinical trials.

I think the important issue for today is the comment in that document that goes to say that all bioactive compounds should undergo a definitive phase I trial, irrespective of what the preclinical data are. Even if you think you have a negative preclinical, a phase I definitive trial is needed.

Therefore, the real question is how does one

determine whether the design is adequate enough to be definitive, that is, so that you can really believe in this trial that you have answered the question of have you ruled out a false negative or a false positive due to this huge spontaneous variability in the QTc duration, not QT. The QT has huge variations with heart rate, as we all know, but how do you deal with the QTc.

Well, these principles that I believe are fairly straightforward are mostly detailed in the concept document. I want to just give you my sort of experience and viewpoints about each of them very quickly in terms of what are the sources of QTc variability and how do you design a trial in order to eliminate those sources as much as possible so that you can get a drug effect, a treatment effect and not be subject to a false result.

Well, the first is, obviously, that the study is adequately powered in order to detect a small QTc effect. The definition of small is given in the document, which is, as we've talked about, 5 to 10 milliseconds. And the sample size usually to do that, because of the variance is so high of the QTc measurement, is at least 30 to 50. In the trial you've seen today in yellow, which is my comment about the vardenafil QT trial, it was 59, so it was adequately powered. It was very well powered in fact. Usually 30 to 50 subjects will do that.

Now, clinical pharmacologists are not real happy about that or used to that because most of the trials run 6 or 12 or 20 people, and those are ones that are not going to be very definitive.

The next thing is how often you measure the parameter under consideration; i.e., how many EKGs do you do?

DR. BORER: Excuse me, Joel. I'm sorry to interrupt you in the middle here, but I don't understand that statement that 30 per arm provides the power to detect a modest QTc change. I would think that that would have to be coupled with and would be a function of the number of observations per patient, and I know that that is not in that document. On what basis do you say that?

DR. MORGANROTH: Well, that's a good statistical question. Maybe I'll ask Tom to answer it.

It's my understanding -- and I'm not a biostatistician, as you know -- that the principal determination of power to detect 5 milliseconds is based on the variance of the QTc measurement in a population. That variance tends to be somewhere between 8 and 20 milliseconds depending on the number of ECGs that you obtain. Unfortunately, I believe most statisticians -- and maybe Tom could answer this -- generally don't have enough data regarding numbers of ECGs to variances so that they

assume an average variance and then calculate a power of usually 80 at least, if not 90, with an .05, which usually drives a sample size in the 30 to 50 range.

But you're right. To be precise about it, you'd like to know in the population you've selected to study, whether it's 53-year-old men, as in this trial, or whether it's men and women with a mean age of 27 in a typical trial of this nature, you need to sort of know in that population if there are a lot of vagotonic patients. And if they're athletic, they're going to have a different heart rate spectrum, and probably because of their autonomic tone being different in people who aren't as athletic -- in other words, the variance of the QTc in the measurement, which laboratory you use, which method you use. You're right, but it's very complicated in terms of getting very precise about that.

Therefore, in my experience, which is all I'm trying to suggest here, is that it usually takes 30 to 50 patients versus the 8 on drug and 4 on placebo or 6 and 2 that most phase I trials are generally conducted by. And that's the only point I mean to make.

DR. BORER: Okay. We've seen the data from the 59 patients. There were a large number of measurements made. The data looked pretty good.

Tom, can you comment on that please?

DR. FLEMING: I'll just make one brief comment. Certainly it depends on what measure you consider to be adequate to judge whether or not there's an increase in QTc. If you're looking at the average increase in QTc, measured by the approaches that we've seen today using population or individual adjustments or Bazett or Fridericia, basically with this sample size, you're going to be able to estimate changes where basically it's 2 standard errors or plus or minus 2. So I think this statement is in fact proper if that's the measure you consider to be sufficient to make your judgment.

If you consider outliers to be important, what are the fraction of people that have values above 450 or values above 500 or changes of at least 30 or 60, these sample sizes are strikingly inadequate to be able to understand those issues.

DR. MORGANROTH: Yes. Let me just say I totally agree with that, but again, it becomes practicality. To do these trials with 250 subjects in an arm, when most people are used to doing it with 8 in an arm, is mind boggling.

I think Jeremy Ruskin made this point -- and I think I agree with him -- that you don't really get outliers isolated from a central tendency, meaning that if you don't have some evidence that you affect the QTc

duration in a mean change from baseline, placebo corrected with a positive assay, and if you had 0 milliseconds or 1 millisecond and you have a big outlier frequency, you've got something funny going on that isn't in the experience that most people have.

Again, that may be because of the small sample size, and that's the point you're making. I think that's another answer I should have given you before. The sample size being small, you get sort of spurious data for outliers. It's not very robust.

The frequency is important and I need to dwell on this just a little bit because the typical phase I trial often has, well, I'm going to do 3 EKGs, which the guidance document says, at baseline. I think that's wholly inadequate because what you need to do is be able to cover the concentration of parent metabolites, diurnal variation, et cetera. You need to do a lot of ECGs at baseline and you need to do a lot of ECGs on drug. My general experience is you need to do them about the frequency you do a PK analysis, which means about 10 to 15 to 20 ECGs, over the period that you would want to look at a PK as an analogy, might be the right number to do a QT assay.

You need to have measurement precision. The document says, digital process, manual method, core laboratory, 3 beats in lead II. The attraction to the

Holter method is you get a lot more beats, and Peter made that point and I agree with him. That's what's attractive about it.

The other issue is, of course, the digital process allows for the potential of using new methods. As was pointed out over here, one could take all 12 leads and put them on top of each other, and maybe that gives you a better measurement than only looking at 3 beats in lead II. There is some data that I've seen from Pharmacia that suggests that doesn't actually work, to my surprise, because I would have thought intuitively it would be better. But right now since the CPMP document in 1996 and through all subsequent documents, 3 beats in lead II seems to be what we've all, sort of out of pragmatism more than out of any other reason, settled on.

Now, population is a very important thing. You've already noted that in your questions or comments. Generally, the tug of war is between wanting to really get the population at risk. You'd like everybody with heart failure that's going to have, as Jeremy pointed out, the maximum magnitude of effect in and of itself because of these issues. But the problem with that is if you use people that are older with heart disease and variations and you're going to have, say, 35-40 subjects in a group, you have so much heterogeneity, even if they all have heart

failure or if they have ischemic heart disease, that you add so much variability into that equation, that you can, in fact, not get a very precise signal.

So these generally should be done, in my opinion, in healthy men and women volunteers with the assumption that if you study a supratherapeutic dose and you don't have a magnitude of central tendency of concern, what's the likelihood that you're going to have one when you have magnifiers of effect? Dr. Ruskin pointed out that if you can cover the supratherapeutic dose and you know that the magnitude at the supratherapeutic dose isn't very much and then you use the clinical dose in someone who's very sick, maybe you'll get up to that supratherapeutic dose. Hopefully, you've picked a supratherapeutic dose that will cover that possibility.

Now, in this particular vardenafil trial, all men were chosen and they used the target population, the same mean age versus what was in their phase III program.

The conditions of the ECG recording we've already talked about. I'll skip for the sake of time. But the subjects need to be controlled from heart rate changes because hysteresis and looking at heart rate differences, as people go up and down, can have an important magnitude.

The supratherapeutic dose we've talked about. That's a very important issue. You need to make sure you

cover the maximum range. In my experience, that's usually 3 to 5X the clinical dose, if you want a ball park, but it really needs to be done the way it was done in both of these trials we've heard about, that is, by careful consideration of what the metabolic pathways are and sort of figuring it out pharmacologically. Though, if you for some reason can't or don't, 3 to 5 tends to be a good thing.

We've talked about the need and importance of the positive control to interpret the data and placebo.

The correction factor, of course, is very important, and the statistical plan, being able to look at not just central tendency but also outliers.

The other thing that was specific to the vardenafil trial is to ask the question was the 4-hour sampling time appropriate and was, in fact, a single dose versus the more natural multiple dose to steady state, which I think most of definitives trials will be done by -- I think that in this particular drug, vardenafil used as a single dose intermittently and with the PK that showed that its metabolites and its parent -- you have a 1-hour Cmax and fairly rapidly go away with nothing at the end of 24 hours so that a 3-day washout period would work very well -- I think that that's all appropriate.

Now, if one is going to do a crossover trial

versus a parallel trial, it's my opinion that unless you're certain that the parent and metabolites are really not going to be present and you know the metabolites and you know their time course, then the risk of a crossover study is you're going to have the potential of carryover. And then how do you deal with the baselines? Well, that often says, well, use only the first baseline before any treatment and we'll apply that to all the groups, or I'll average them, or you get lots of different cuts at the data that gets very complicated. So a crossover trial for vardenafil was fine because of the PK, but PK needs to be known if you're going to do that.

Finally, if you know drug affects heart rate from other studies, your earlier phase I trials, it's very important to consider the special procedures known for heart rate correction, for all the reasons that were talked about this morning and I won't reiterate them.

I think I want to make a couple of comments. The Fridericia formula I think was first used at the Cardio-Renal Advisory Committee about five years ago on the drug cilostazol. Prior to that, no one ever thought but to use Bazett's and that's why the terfenadine data that Jeremy showed was by Bazett's. It was a trial in which we didn't even think of using anything else but that. Now, since the last really five years, because of that precedent

in which this committee agreed with the Fridericia approach, seemingly better than the Bazett's approach, that has become sort of, I think, by consensus the best factor, which is why I think the FDA and the sponsors of vardenafil chose QTcF because of very little experience with QTci, even population formulas.

The population formula is recommended in the guidance document to be done at the time of an ISS, when you have enough patients that you've studied on baseline and placebo to actually calculate that parameter. I think it was first done by Dr. Burkhardt who was at Neuropharm at the time when he did it for the schizophrenic population for the atypical antipsychotics. His factor at that point was .37. Many people in neuropharm go to the QTcN, N for neuropharm, which equals an exponent of .37. It's just a historical note.

Clearly the individual corrections, as in the guidance document, which is the first one that actually suggests using that, has some important limitations that have to be considered. The question asked a moment ago is important. What is the heart rate range at baseline you're studying? Is it appropriate in order to look at the effect of heart rate? Really what that drives is the common experience that you need at least 50 to 100 ECGs in order to make this assessment of an individual correction. So if

you're doing a parallel trial, that means you've got to do 50 to 100 ECGs at baseline, not 7 or 10. You've got to do 50. If you can afford pharmacologically to do a crossover trial so you can use all those baselines because you're using the same patient over and over, then obviously you can get up to 50 to 100 pretty easily.

In this particular trial, they had 138 ECGs in each patient because they went through 6 times 18. Right? Plus, they had 108. Plus, they had 30 when they were on the placebo arm. Because you have 108, the FDA very cleverly said, well, what if you don't use the placebo and just use the baseline and how does that compare to using the baseline and placebo? That's that whole part of the document about QTci.2 I think it's called, which is trying to answer the question does it matter whether you use the placebo and how does it affect it or not.

Now, what happens here in this trial is that we have the ability to look at the relationship of QTcF to QTci based on a very powerful trial with lots of samples. With QTcF versus QTci, you see that the pattern is pretty much the same. The relationship of the two drugs, vardenafil and sildenafil, and the doses are not very different. A flat dose response remains. Moxi, which doesn't affect heart rate, pretty much was within 1 millisecond by the two different approaches. Whereas the

difference for the PDE5 inhibitors that increase heart rate is a clear reduction in the QTc duration, closer to this sort of 5-millisecond rather than vardenafil which is closer to the 10-millisecond when you use the QTcF.

That's, of course, a critical question. Which is believable? Which is the one you should use if you then want to apply some recommendations as to what magnitudes relate to risk?

Well, the way I think you approach that is statistically. You ask the question which of these correction factors gave the best fit so that no heart rate influenced the QT? Let's look at the clouds.

I'm sorry. I'm one ahead of myself. But I did want to make the point that there are two ways of doing this QTci measurement. One is using linear regression and the other is using exponential techniques. It doesn't matter. They come up with the same data, in this data set at least with this design.

Now, here are the clouds. If you look at the Bazett formula -- and you didn't even see data on Bazett for sake of time -- you see exactly what was shown to you this morning. Now, I've used heart rate here because most people presumably in the audience do not think about RR. What you see is, as you increase your heart rate, you get the over-correction. So in this data set, like this

morning, you have exactly the poor performance of Bazett which is why generally it doesn't help very much.

But look at Fridericia's. That looks pretty good. That's a pretty flat cloud.

Now, if you look at the QTcF and the QTci, I'm choosing X instead of linear. They really come out identical. It's exponential and this is exponential. At first blush, it would appear that the QTci is not good. It's not the best correction formula to use. It looks like the QTcF would be the one you would want to believe. That I think is principally driven by these points right out here because if you can mask them from your eye, you will see that these curves look pretty identical. So I'm a little suspicious as to whether, really, the QTcF is better than the QTci, and it wasn't worth all that extra ECG frequency to bother with the QTci.

What you're really, however, trying to do in this analysis is you want to look at each individual and you want to find out if in fact for every individual in the trial the relationship of the heart rate to the QTc stays constant.

And the next slide shows you what I call, instead of a cloud performance, a pick-up stick equivalent. This is what the pick-up stick model looks like for the QTcF. What you see is here is the individual lines. Now,

this tells you the range of heart rates. The range of heart rates, like this morning, went from 40 to 90 or so, the same rate you saw this morning. And that's what happens when you take a mixture of healthy people, older or younger, maybe more likely in the older I suspect because they're more likely less athletic, and you put them in a supine position and their heart rates are going to vary. Now, some people don't vary much at all, where others vary a lot.

In the QTcF, a lot of people aren't very well corrected. They're over-corrected. Some are under-corrected. Some are pretty flat. And the overall cloud looks flat. So maybe the cloud isn't the best way of looking at it. Maybe what you really want to do is the individual regression lines.

And the FDA has done that very nicely in their briefing book. Instead of using pick-up sticks, they use dots, about how you vary from 0, but it's exactly the same analysis.

Of course, this is going to be much more flat because every patient is designed to make them flat, so by definition they're flat.

Next slide.

DR. FLEMING: Just before we leave that point, though, obviously if you fit a model for how the adjustment

should be and then you apply it to individuals, there's going to be some randomness so that the model doesn't predict the individual person perfectly; whereas, if you use the individual person to fit the model, of course you're going to fit that individual person perfectly. But are you overfitting the data? So the right looks great, but I can always get the perfect model by using an enriched model and fitting it to the data.

The essence of what makes me choose one or the other is which one of these particular approaches more accurately reflects people who are at increased risk of what I clinically care about. Obviously, we don't have that data.

DR. MORGANROTH: Yes, we don't have that data, nor do I think we'll ever get that data because to do that, you need a prospective trial looking at torsade as the endpoint, frankly, because you can't use a surrogate, and that's an infeasible study.

So the concept on the table is that the reason you have to correct for QT and you cannot use QT -- take an antibiotic. A person has a fever. Their heart rate is fast. The QT is short. You give them an antibiotic. It cures the pneumonia. Their heart rates come down to normal. Their QTs are going to be long. So you absolutely have to correct the QT for the QTc for any drug or

condition treated by a drug that changes heart rate, which turns out to be an awful lot. You saw the difference in moxi, even though it technically doesn't. There could be a couple beats per minute that could influence the data.

So if you agree with the assumption that the correction formula should try to correct best so that at any heart rate you have the same QTc -- I mean, that is the assumption. If you buy that assumption, then this is the model that by definition should be the best. That's what we've all thought. And the real question is do you gain enough for all the extra resources.

Now, that doesn't answer the clinical question. It doesn't answer the question if in fact by doing a good correction like this, the heart rate doesn't affect it, that you can predict the events that occur in the high-risk patient population. That was your point I thought, and I agree with you. It doesn't mean this is the right way to go. Absolutely. We just don't know the clinical impact of that. But in an ignorant state, when we have no way of going, I think it's intuitively more obvious to use this approach than it is to use Fridericia's or clearly Bazett's.

But one could argue that maybe Bazett's is fine because we've learned about terfenadine with Bazett's, but I have a reason to disagree with that concept, that

Bazett's is the only thing we should be using.

DR. FLEMING: Let me make one more attempt. I'm not saying the right or the left is better. I'm saying the fact that the right looks perfectly horizontal does not mean it's better. There could be many factors. Clearly one of them that's very important is heart rate that affects QT. There could be others, and I'm allowing the full richness of my data set to factor in a lot of other factors to get parallelism on the right-hand side. Some of that may be noise. I may be overfitting the data. The truth may be the left, and then other unrelated things are coming in, are influencing creating that noise on the left.

DR. MORGANROTH: On the other hand, we have a lot of sources that affect the QTc, the power of the study, the frequency of the measurements, the quality of the measurements, the population that's selected, the ability to correct QT to QTc best. So you're right. We're only looking at 1 of 10 or 20 features that are important to consider in a clinical design, and I think to make the judgment of which correction factor to use I still think the one that produces the least effect on heart rate seems intuitively -- all it is is intuitively -- better to me.

But as you point out, you have all kind of other factors that may be influencing this model. I think heart rate is the very predominant effect of that model and

it's not the only thing.

DR. RODEN: I'm sorry. I want to hear Tom and Joel talk about -- you talked about the cloud and you sort of said this cloud looks better than that cloud, but this other cloud doesn't look so nice, but you're being distracted by these 14 points up here in the corner. Are there any measures of goodness of fit for any of these things?

So the pick-up sticks on the left there are shown as lines, but those are lines through 18 or 138 or some number of data points. It's entirely possible to me that each one of those pick-up sticks represents a little cloud that contributes to your big cloud. It wouldn't surprise me if your regression line through that big cloud was vertical instead of horizontal.

(Laughter.)

DR. RODEN: You just can't say that stuff.

And the Bazett thing looks bad because of 14 points in the upper left-hand quadrant.

My biggest concern about all this is this is all baseline data, and when you get a drug on board that affects the heart rate, you'll get one effect. If you get a drug on board that affects QT, you'll get a second effect. If you have a drug that affects both QT and RR, I think this is inevitably confounded. You will make no

conclusion. And the only conclusion that counts is what predicts torsade.

DR. MORGANROTH: I don't disagree with you. I think what you're saying is very much what Dr. Fleming said, that the statistical method, whether it's one that's going to look at a cloud with a regression line or whether it's one that's going to look at individual regressions, the ability to know by evidence-based, prospective data that that correlates with anything clinically that's better or worse than something else -- we have no data on that. Therefore, it is incorrect to be dogmatic that one method is by definition better. And I agree with you.

DR. RODEN: I don't think we solve the problem by just getting a whole lot more data. I think you can get as much data as you want. When you're faced with drugs that have multiple effects, this kind of extensive analysis at baseline I don't think can possibly make you smarter. It's inevitably doomed. One of the things we're supposed to discuss, Doug, is how to get out of this morass that we've gotten ourselves into, and getting more ECGs at baseline I don't think solves that problem. It's obviously a discussion we can go on to later.

DR. MORGANROTH: It clearly gives you better precision. The question is does it predict any better than getting one EKG at baseline or none. We won't answer that

easily.

Because of time, I want to finish up real quickly with one other concept. Let's skip this issue because it's not important.

(Laughter.)

DR. MORGANROTH: It's important but we're just going to dig ourselves into a deeper hole.

I want to make two points here that I think are important. Central tendency is very important and often people want to do a time match. They want to go Cmax because they think at Cmax is where all the action is. If you know the Cmax of your metabolites and your parent, that might be where all the action is, but you better know about the time course of your metabolites. So often one wants to go to a mean maximum change by picking a point that you have the longest QTc, the worst case analysis, that sort of mechanism by which you define an outlier.

The concern I would have for precision is that if you only have one ECG at hour 2 or hour 7 and you go back to your baseline and take the single ECG at hour 7, you're really having no different than a 1 and 1 comparison. You lose all of the power and the frequency of measurement issues. So often what you want to do is take the mean of your baseline as the best point estimate for that person and look at the time point of interest, and if

you only have one ECG, that's all you have.

The particular study done by the vardenafil definitive had 6 ECGs at each time point, which gave them the ability to go and have more precision at any particular time point. And they showed you the 1 hour to the Cmax, the Tmax, et cetera. And I think those numbers are more valid because they had more measurements at those time points.

There are technologies, the 12-lead continuous Holter, that when you post hoc find the time point of most interest, you can go back and do more ECGs at a time point.

The other point is what's the definition of an outlier. There's a lot in your briefing book about whether one should use observations or patients. I think that conceptually to me an outlier is show me a patient who, because maybe they have forme fruste congenital long QTc syndrome, as Dan Roden calls repolarization reserve, problems -- you want to find that patient. You need a large sample size to really find a lot of them. And that's the outlier.

To look at the number of ECGs above a certain level to me is more of a statistical method of trying to define whether you have a drug effect of a central tendency. You have more changes on various drugs -- suggests they really have a QT effect. It doesn't really

to me tell you the outliers, the real risk of outliers. I think the outlier risk is 60 milliseconds, not 30 to 60. I think that's the specific data. It comes from our terfenadine database of placebo. Clearly people who have new 500s or new T-U waves, these are the three parameters that to me are the ones to look at for outliers. Everything else is sort of difficult.

We've already discussed this, so I'll skip this. I think this is all that we're really looking at there.

So, finally, I think this vardenafil trial in my opinion is valid. I think the results are reliable. I make that statement for two or three simple reasons.

One is placebo came out to 0. That's very unusual because usually there's enough spontaneous variability, and the 0 milliseconds is just very comforting.

Moxifloxacin hit the number it should. It's in the 5- to 10-millisecond range. So that's what I would expect for a positive control. So we have assay sensitivity and a placebo group that really looked like placebo.

No matter how you look at the totality of the data, F, i, 1 hour, Tmax, Cmax, et cetera, all the data hang together within a couple milliseconds.

And the very interesting result of this trial, which is generally not seen for most hERG blockers or drugs that affect the QT, is the extreme shallow dose-response curve with 8X dosing or 12X concentration.

The other thing that was interesting in this trial is the inclusion of not just four arms, but six arms, and two of those arms being a low dose and a supratherapeutic dose of sildenafil, the drug that is on the market that has a lot of clinical experience because here you have a drug, vardenafil, that has only recently been on the market. There's not a great deal of data about it post-marketing, and so I think that's an issue.

Finally, you have vardenafil and sildenafil shortening the uncorrected QT if you believe that the QT is something to look at irrespective of the QTc. Moxi, of course, lengthens it, and I think there's no evidence of any outliers on vardenafil.

Finally, I want to just say a few things about how do you make a decision of whether 5 milliseconds, 10 milliseconds is a good thing, a bad thing, it's a risk, not a risk. How do you make a judgment like that? What's the basis of doing that? Well, clearly the best basis is if we had a prospective trial in which we had torsade as the endpoint with various degrees of QTc duration done by a certain standard method. That's never going to happen in

this field.

So the basis of making a decision is what's been our experience with other drugs that affect the QT like terfenadine, cisapride, ziprasadone, moxifloxacin. What has been this post-marketing surveillance data? This was discussed earlier in terms of what are the signals of risk on moxifloxacin. And in this case, since the vardenafil and sildenafil look so identical in terms of their preclinical hERG, as well as in this definitive QT trial, their QTc central tendency, and outlier analysis, one might be able to say that this PDE5 inhibitor might react similarly because the QT effect is so similar.

And then finally, what do regulators think about this? They have a tremendous amount of experience in all kind of therapeutic drugs and all kinds of decisions over the years, and some of them have published their opinions like Dr. Shah and the FDA concept paper.

You've seen this data and it's meant to point out that a 5- to 10-millisecond effect like vardenafil or sildenafil is not the same as terfenadine, even if you discount the issues of design, et cetera, because of that 18 milliseconds.

The other thing is, is moxifloxacin the same as vardenafil? They both have about the same 5- to 10-millisecond range. So why shouldn't we look at them the

same? Well, there's a big difference. The hERG concentration blockade for IC50 is equal to or very close to the clinical concentration, very different in the 1000X difference on vardenafil.

Number two, if you use 400 milligrams of moxifloxacin, you get the 5- to 10-millisecond range. What if you double the dose? We have data on that. You get doubling of the effect. So you get a very sharp increase in dose-response.

You have minimal effect on heart rate, where you have an increase in heart rate on vardenafil. Therefore, there's a clear difference between moxifloxacin and vardenafil in terms of its QT dynamics.

We now have reasonably good data on moxifloxacin. It's been out long enough. The company did two simple post-marketing observational studies, one in Germany, one in the U.S., about 25,000 subjects each, in which no signal for torsade or risk in a clinical condition of community-acquired pneumonia. Most of these people are sick, elderly, have lots of cardiovascular and pulmonary disease by definition.

And if you look at the post-marketing surveillance data through May 7, 2003, moxifloxacin has been used in 19 million patients, over 400,000 patient-years, and there have been 12 reports to the sponsor of

torsade de pointes. Of those 12, Dr. Faich looked at each one of them very carefully and determined that all of these 12 cases, except for 2, had major confounders, meaning people with fresh infarction, hypokalemia, on sotalol, et cetera. Now, that doesn't mean that moxi didn't contribute to the torsade by any means, but I think it's confounded. You can't really have any idea of how much, if at all, moxi contributed.

There are two cases, however, one of which there was no clinical data and one of which does not appear to have any confounding factors.

If you look at the rate of torsade, using apples to apples, that is, take the rate of the U.S. because that's one reporting system, take the four cases, irrespective of the confounding, take the number of patients who have gotten oral moxifloxacin in the United States, that number is 4 per 7.7 million. And that's about exactly the same rate that Brinker from the Office of Drug Safety reported compared to all kinds of other antibiotics, many of which no one thinks has any QT effect.

Finally, we have the sildenafil database to look at and compare that because of the reference I made. This is from the FDA Adverse Event Reporting System in which there are close to 39 million sildenafil prescriptions from 1998 through December of 2002 and 0

cases of torsade. Obviously, is it under-reported? Are some of the deaths torsade? We don't know, but at least there's no signal in these databases as there was not one, as we saw this morning.

Finally, in my final one or two slides, is what's the regulatory opinion? Well, the regulatory opinion from the Europe and the U.S. is pretty much the same. Dr. Rashmi Shah in the CPMP and the concept paper both have provided what we'll call statements of risk from their experience.

Now, this was provided at the Shady Grove Meeting in January by Dr. Temple. This is the slide he used, which I took off the FDA web site, and he graded 5 to 10 as no clear risk, which is very similar to Dr. Shah's classification. And he points out, however that this is a surrogate, and we know that there is good evidence from antiarrhythmic drugs and terfenadine that the size of the effect relates to the incidence of torsade. But could there be other properties that mitigate this risk or enhance this risk?

So the next slide says what are the factors on vardenafil that might mitigate this no clear risk to make it even less than a no clear risk in terms of concern. I think one is it's going to be used in men, assuming the labeling, which one has to assume for this analysis of

mitigating factors. It's going to be used in men. And clearly the risk of drug-induced torsade de pointes is less in men. Almost two-thirds of the torsades are in women or an even higher percentage.

Number two, you're not giving a drug chronically for months or years. You're giving an intermittent drug.

Number three is -- and this is very important -- this extremely shallow dose-response curve, which even if one wants to argue that the 80 milligram dose -- maybe they could have given a higher dose if the people would tolerate it, which is a question -- could be equivalent to people with all kinds of things going on and they take an overdose of vardenafil, the very flat dose-response curve, instead of having an 8-millisecond, would probably go up, because they've modeled in their slides on this, if you want to see it, to like 8.6 milliseconds or call it 10 milliseconds. It's not going to be an 8 going up to 80 or some major effect.

Finally, the fact that this drug increases heart rate, as has already been mentioned, I think is a mitigating factor versus drugs that don't affect heart rate or particularly those that slow heart rate.

So, in conclusion, I think that we do have a definitive study. We're dealing with the QTci, which I

think is the best measurement for this data set, though not necessarily for all data sets, of 5 milliseconds.

By the way, the QTci exponent is about .20. For the population-based study, it's about .33 which is equivalent to Fridericia's. So the population data, which you haven't seen, is really identical to Fridericia's.

The magnitude is generally considered not a clear risk. There's no clinical outliers, no signal in the post-marketing surveillance. Thus, I think the QTc effect of vardenafil for all these reasons should not pose a cardiac risk.

Thank you very much.

DR. BORER: Thank you very much, Joel.

I'm going to hold any discussion at this point. I think that much of Joel's presentation was, as he said, a critique, and we're going to get into that when we actually do the discussion surrounding the FDA questions.

So at this point, we'll break for lunch. There are tables being held in the restaurant downstairs. We'll get back here and start around 1:35 or 1:36 with the FDA presentation.

(Whereupon, at 12:43 p.m., the committee was recessed, to reconvene at 1:35 p.m., this same day.)

AFTERNOON SESSION

(1:39 p.m.)

DR. BORER: It's now, by my watch, 1:39-and-a-half, and we were supposed to have started at 1:36. So we're 3-and-a-half minutes behind and counting.

We'll begin the afternoon session with public comment before the FDA presentation. We have two requested presentations, one from Pfizer, which will take 10 minutes, and one from Dr. Culley Carson, which will also take 10 minutes. So if we can begin with Pfizer please. It's Dr. Sweeney.

(No response.)

DR. BORER: Well, we'll reverse the order then. Is Dr. Carson here?

MR. CLARK: This is Bob Clark from Pfizer. Dr. Sweeney will be here about a minute.

DR. CARSON: My comments will be considerably less than 10 minutes. I'm Culley Carson. I'm a professor of urology at the University of North Carolina, but I'm here as President of the Sexual Medicine Society which is a society that represents urologists and other clinicians that are interested in investigation and treatment of erectile dysfunction. We've been looking at erectile dysfunction for many years.

Really, one of the reasons I'm here is so that

we don't lose sight of the fact that many patients are well treated for erectile dysfunction by the drugs that are being proposed and the drug that's currently available.

I personally have experience in the clinical trials with all three of the new PDE5s, sildenafil, taldalafil, as well as vardenafil, and have had excellent results with all of these drugs with very little side effects.

I think really one of the issues is that erectile dysfunction is a huge problem in this country. There are an estimated 20 million American men who suffer from erectile dysfunction. Only about 10 percent of them are treated currently. Erectile dysfunction, which may seem trivial to many people who don't have it, is not trivial because it does have an impact on the patient's self-esteem, on couple's problems, on depression, on the compliance that they have with other medications, especially antihypertensives, antidepressants, and even antipsychotics. So clearly there's a major issue with erectile dysfunction, and really the PDE5 drugs are the only ones that are clearly effective and safe for the oral treatment of erectile dysfunction with very minimal invasiveness.

To date, sildenafil has been used for more than 5 years in the United States, more than 7 years in trials.

As you saw earlier today, there are more than 10 million prescriptions written by greater than 600,000 physicians around the world. And the incidence of death has been minimal. Indeed, there are a number of studies looking at a comparison of cardiac events and deaths comparing placebo-treated patients in trials, expected numbers from matched populations, and patients treated with sildenafil, and the numbers are no different in any of those groups. Similar studies have been carried out with taldalafil and vardenafil with very similar results. So clearly the data show that cardiac events and cardiovascular events, indeed, are very few, far between, and certainly with very minimal impact on the total number of patients that are treated for this very difficult condition.

Why do we need newer drugs? Well, we need newer drugs because there are still only 10 percent of patients that are being treated currently, yet many of them have significant distress from their erectile dysfunction. I think newer drugs, in addition to the market, will increase the number of men who can be treated and will be treated, and it will increase the individual's choice by drug profile and type of agent available to them.

And this is important because we know that men's health is a major issue that's not been focused on as much as it should be by our national health system. It has

a limited focus throughout the United States, and this treatment class encourages men to seek medical attention for ED which allows them to see their physician and perhaps be treated for other conditions. Indeed, we know from a number of studies that ED is a harbinger of other more serious vascular events later in patients' lives.

So I would just encourage everyone to remember that there is a large number of patients who have been successfully treated who are enthusiastic participants in the trials and users of these agents to restore their erectile function and, indeed, much of their marriage. Thank you very much.

DR. BORER: Thank you very much, Dr. Carson. I think it's a point well taken that we're talking about consideration of a drug that does have very real benefits that have to be balanced against the --

DR. KOWEY: Jeff, can I just ask one quick question?

DR. BORER: You can. Let me just get one thing done first, if I may.

Dr. Carson, just for the record, though, you need to tell for the recorder if you had any support in coming up here or if this is just for the --

DR. CARSON: No. I came up here as President of the Sexual Medicine Society.

DR. BORER: Okay, great. Thank you.

Peter?

DR. KOWEY: Just a quick question, Dr. Carson. I'm totally naive to this question, so it's not a trick question. Tell us what the benefit of this drug is over current therapy.

DR. CARSON: That's a good question. There are no head-to-head studies, so we really don't know. You've seen what the biochemical profile is in brief today. It's more biochemically potent than sildenafil. Whether that's going to translate into an advantage clinically or not, I don't think anyone really knows, and until either the market determines that or head-to-head studies are available, we really won't know.

DR. BORER: Thank you very much, Dr. Carson.

Now we'll have the planned presentation from Pfizer. Dr. Sweeney.

DR. SWEENEY: Thank you, Mr. Chairman, for the opportunity to discuss Viagra's extensive database, particularly with reference to QTc. We particularly welcome this opportunity because we've been cited in the study conducted by Bayer earlier today and extensively in the FDA document.

As the committee is aware, QTc is a surrogate for the propensity for the causing of ventricular

arrhythmias, particularly torsade de pointes. It's really essentially used with drugs in the investigational phase prior to approval.

A much better estimate of the propensity to cause arrhythmias is real-world clinical experience in millions of patients -- and that's what we have with Viagra -- to exclude a risk for ventricular arrhythmia.

Before I talk about Viagra in particular, I just want to follow up from what Dr. Carson was saying about the context of ED and cardiovascular disease. ED is primarily a vascular condition. In most patients, it's usually arteriole disease. The risk factors for ED are pretty much identical to the risk factors for coronary artery disease: age, hypertension, diabetes, hypercholesterolemia, and the classic lifestyle factors of smoking, obesity, and sedentary lifestyle. If I could paint a picture for everybody, the typical ED patient is a man of over 50 with multiple risk factors and/or overt cardiovascular disease, coupled with multiple concomitant medications.

The other thing to keep in mind is these patients have cardiovascular disease and these patients have cardiovascular events. There are approximately 400,000 sudden cardiac deaths occurring in the United States each year. That's about one every minute, and the

overwhelming majority of these patients have coronary artery disease.

The baseline risk of myocardial infarction in the typical patient of 50 years old, is 1 to 2 percent a year while the ED patient, has approximately twice this risk based on epidemiological evidence. Add on to that the fact that sexual intercourse itself raises the risk of myocardial infarction about twofold in the 2 hours following sexual intercourse. Therefore, cardiovascular events are both expected and do occur in the ED population. So that's the background of the population of patients we're dealing with with this condition.

The Viagra experience. Viagra was approved by the Cardio-Renal Division of the FDA in March 1998 and is currently approved in 120 countries. In 5 years, we've had over 20 million patients treated. More than 1 billion doses of Viagra have been taken. And Viagra has been under clinical research for more than 10 years now. There have been more than 13,000 patients studied, for a total of 13,000 patient-years of exposure. In addition, there are a separate 26,000 patients studied in real-world practice, a cohort followed in the UK. There are 200 independent studies involving up to 10,000 patients in the literature. Overall, Viagra is the most extensively studied drug ever in sexual health.

I want to talk particularly about the post-marketing data first of all. As I have mentioned, we've treated 20 million patients. Most have cardiovascular risk factors. Despite this, we have not had a single report of torsade de pointes anytime in the 5 years, and we have had only two cases reporting QT prolongation, and both are temporally related to concomitant medications known to cause QT.

I'd like to consider them first in detail. The first case is a consumer report of a man who had been taking Viagra for 2 years and cisapride for 7 months who reported that his QT had been prolonged from 205 milliseconds to 235 milliseconds. This was not confirmed by a health care practitioner.

(Laughter.)

DR. SWEENEY: We obviously have patients who are very interested in their health in our population.

(Laughter.)

DR. SWEENEY: The second one referred to in the FDA document is of a health care professional reporting a QT prolongation in association with sotalol in a patient 3 weeks after they had taken their last dose of Viagra. Viagra is essentially cleared from the body in 24 hours. We regarded that cause being excluded because there is not a Viagra molecule left in the body after 3 weeks. Hence,

we feel that there are no cases relating Viagra to QT prolongation.

Post-marketing data analysis, of course, is a highly specialized area and one which has many caveats attached. There are limitations in interpreting this data, but above all, we should keep in mind that the purpose of this data is to generate signals of possible safety issues.

A recent publication of an analysis conducted by Wysowski and colleagues from the FDA Office of Drug Safety had many caveats, but within these caveats, they concluded that reports of death in men prescribed sildenafil that were submitted to the FDA led us to conclude that there did not appear to be an increase in deaths due to MI above expected numbers.

Moving up the hierarchy now of scientific rigor, the cohort observational study in clinical practice completed was a prescription event monitoring study in the UK. The PEM study as conducted by the UK National Health Service sends a copy of every prescription for Viagra written to the unit that conducts these studies, who then send a form to every physician who wrote a prescription and asked them what events occurred in the observation period. And it's done on an ongoing basis. There's normally about a 55 percent response rate and events are sent in irrespective of causality.

We had 26,000 men followed in this study, for a total of 42,000 patient-years of observation. Again, not a single case of torsade de pointes or prolonged QTc was reported in this study, and the rates of cardiovascular events overall, including MI and sudden death, were consistent of those well documented in the UK population, even taking into account any under-reporting in the PEM study.

I'm sure as the panel agrees, the gold standard for the assessment of safety and efficacy of pharmaceutical products is the controlled clinical trial. We have completed over 100 controlled clinical trials to date with 13,000 Viagra patients and 6,000 placebo patients for comparison. The rate of MI and cardiovascular adverse events were comparable between the two. There is no difference. There is no evidence that in controlled studies Viagra in any way precipitates cardiovascular events. The number of sudden death cases was well within the epidemiological prediction. There are so few that we were unable to do valid statistical comparisons, but well within what would be expected from epidemiological evidence.

I now want to talk briefly about study 10929 that was presented this morning, firstly to state that Pfizer had no input into the design of the study and we

only saw the results when it was posted in public on the FDA web site. As such, our comments are from the last 24 hours when we have reviewed this data.

The first thing to note is that sildenafil has an absolute bioavailability of 40 percent. It's about 3 times the bioavailability of vardenafil. It's the most potent 3A4 inhibitors because of the high bioavailability, increased Cmax less than 4-fold. So the 400 milligram sildenafil dose which you saw, 4 times recommended dose, leads to peak plasma levels that exceed those encountered in normal clinical practice.

Despite this, there's no evidence of a clinically significant QTc effect. The mean change was less than 10 milliseconds for a dose well above what would be encountered in clinical practice and is consistent with no preclinical signal and no reports of torsade de pointes being received.

To summarize the Viagra experience, there are no cases of torsade de pointes in 20 million patients, no clinically relevant change in QT or QTc in clinical studies, an incidence of cardiovascular events very similar to placebo in 13,000 patients. There is no evidence in Viagra's extensive clinical trial program and post-marketing of a relevant effect on cardiac repolarization.

Viagra has a wide margin of safety. It has a

relatively high bioavailability, and the differences between the drugs are all in pharmacokinetics. It has high bioavailability and a short half-life. In addition, the extent of 3A4 inhibitor interaction is less with Viagra than some other PDE5 inhibitors, and it does not compromise its overall safety.

As such, the safety and efficacy profile of Viagra may not be applicable across compounds with different PK and structural characteristics. Further data would be required to make that extrapolation.

Viagra is the only PDE5 inhibitor with extensive real-world data in millions of patients showing a lack of proarrhythmic effect through 5 years following FDA approval.

Just some final thoughts now. By necessity, I've talked essentially on safety, but we have to keep in mind that the benefit-risk ratio for Viagra in patients with cardiovascular disease is very positive. It's being used extensively for the treatment of ED in patients with cardiovascular disease, even patients with heart transplant. In addition, it's now being investigated for patients with heart failure and other serious cardiac diseases, and we've had encouraging efficacy data in adult and pediatric pulmonary hypertension with no new safety signals, and that is an ongoing research program that we

hope to file with the agency in future years.

So, again, thank you, on behalf of Pfizer, for this opportunity to discuss our safety and also to keep in mind that Viagra has improved the lives of millions of men with ED and their partners, and this is particularly prevalent in cardiovascular disease. Thank you.

DR. BORER: Thank you very much, Dr. Sweeney. Do you have another presentation from Dr. Falk?

DR. SWEENEY: Yes, Dr. Falk is just going to make a few comments.

DR. BORER: Okay.

DR. KOWEY: Dr. Sweeney, before you leave the podium, experience in women with sildenafil?

DR. SWEENEY: We have conducted an extensive clinical trial program with female sexual arousal disorder and the safety profile is essentially the same as men. We conducted a drug interaction study with oral contraceptives in healthy female volunteers, and although the study wasn't specifically set up to investigate QTc, there was no QTc effect seen.

DR. KOWEY: Can you give us some ball park idea of how many women have been exposed to sildenafil?

DR. SWEENEY: It's around about 800 to 1,000, but that program is ongoing and there's an ongoing discussion with the agency.

DR. BORER: JoAnn?

DR. LINDENFELD: You have a lot of impressive data. I wonder if you could just tell me what the risk profile is of men with coronary disease who take Viagra compared to those who don't?

DR. SWEENEY: As far as we can see, it's exactly the same. The only additional risk is the additional epidemiological risk for erectile dysfunction patients because they seem to have about twice the risk of myocardial infarction than patients without erectile dysfunction largely because ED is a visible manifestation of covert coronary artery disease.

DR. LINDENFELD: You might just wonder if slightly healthier patients choose to use Viagra and whether or not you could be missing a signal there. You have lots of impressive data, so I don't want to emphasize that too much.

DR. SWEENEY: I think Dr. Falk is going to address that particular question about missing signals.

DR. BORER: Thank you very much.

DR. FALK: Members of the committee, ladies and gentlemen, I have no slides and I will be brief since the hour is late.

I've been asked by Pfizer to give my opinion on some of the data that is in the FDA document regarding the

adverse events reported in patients who have been taking Viagra and who either died suddenly or who have had seizures or loss of consciousness, and I will limit my comments to that.

I'm a clinical cardiologist at Boston University School of Medicine and I'm also affiliated there as their cardiology consultant to the Boston University Sexual Health Program run by Dr. Irwin Goldstein.

Looking this over, I wanted to put it into perspective or my perspective, and that is, in the United States it is estimated that there are approximately 11 million people, men and women, with coronary artery disease. There are about 1.3 million to 1.5 million myocardial infarctions per year in the United States, and somewhere between 300,000 and 350,000 cases of sudden death, some of whom will be associated with myocardial infarction, the majority of whom will be associated with coronary artery disease.

It has been estimated in epidemiological studies both from the United States and from Europe that somewhere between 1 and 3 percent of patients who sustain a myocardial infarction do so shortly after having sexual intercourse. So out of 1.3 million per year in U.S., that's about 1,300 people per year, up to 5,000 a year. And in the period that has been surveyed, which is a four-

year period, we're talking between 5,000 and 12,000 myocardial infarctions, some of whom, as I said, will die related to sexual intercourse.

The cases that the FDA has raised their eyebrows at are approximately 192. Less than 80 of these have died and they're reported between 1998 and 2002. There are no reported cases of torsade. These are all patients, of course, who at some time have taken Viagra, not all temporally related. There are two QT prolongations, which we've heard are of dubious association.

There are 88 patients who had either syncope or a seizure, and we are told in the FDA review that patients with normal electrocardiograms recorded were excluded.

So the question is, could these 88 and could these sudden deaths in patients who have taken Viagra be related to torsade? Could some of them? If they were, then I would suggest that one might find QT interval prolonged in patients who had had syncope. We don't know precisely how many patients had syncope. There were 88 with syncope and seizures. We are told that normal electrocardiograms were excluded, ergo those who had ECGs had abnormal ones. We are also told that there were no prolonged QTs other than the two that have already been dealt with. So that makes it unlikely in that group.

We would also anticipate, as with drugs such as cisapride, that some patients who don't have significant structural heart disease, perhaps have left ventricular hypertrophy, would have had sudden death. We don't see all the reports in the FDA documents, but the ones that are highlighted all have very severe coronary artery disease. So I think that in terms of a signal, the things that we would look for do not jump out, but of course, a signal perhaps could be there.

However, in looking at the information in these 192 cases, again less than 80 deaths in 4 years, I would suggest that a better way of understanding this is what we are seeing is what might be anticipated in a relatively high-risk population or in a high-risk population for sudden death. That is, these are patients with erectile dysfunction, and the ones reviewed have significant disease in the cases. Patients with erectile dysfunction we know have an increased risk of coronary artery disease. Death is expected in coronary artery disease. Death during or after sex is a well-recognized phenomenon in coronary disease. In fact, the two studies I quoted you were performed before Viagra or any other similar drug was available. So there was no cause and effect there. 1 to 3 percent.

We have had no, as I've said, association of

syncope with any report of QT prolongation in 88 syncope/seizures, and I would suggest once again that the data that we've seen in these small number of patients over 4 years is entirely consistent with patients dying of the natural history of their coronary artery disease coincidentally around the time of sexual intercourse. I feel from my review of this that a signal for torsade is a much, much less likely factor than just a statistical association between sudden death and sexual intercourse.

Thank you.

DR. BORER: Thank you very much.

Are there any questions or comments from the panel?

(No response.)

DR. BORER: No. If not, thanks very much, Dr. Falk. That's useful information.

Is there any other public comment, any other comment from the public?

(No response.)

DR. BORER: If not, we'll move ahead with the FDA presentation, which will be introduced by Dr. Griebel.

DR. GRIEBEL: Good afternoon. My name is Dr. Donna Griebel. I'm the Deputy Director of the Division of Reproductive and Urologic Drug Products. The division would like to extend our thanks to you all for agreeing to

meet here today to discuss two urologic drug products.

We are going to be merciful this afternoon and we have created a Reader's Digest, Cliff Notes version of our talks. So we've really honed it down to just a few slides, and it should be relatively quick. But I won't guarantee that it will flow very well.

The first slide is the review team. It lists the people who worked very hard getting the briefing document together and preparing for this meeting. The clinical team was led by Dr. George Benson. The clinical pharmacology team was led by Dr. Ameeta Parekh. The Office of Drug Safety was very important in our review. They helped us identify the post-marketing adverse events that you found in our briefing document. They were led by Dr. Debra Boxwell. And our biostatistics team lead was Mike Welch.

Again, in the interest of time, we are just going to move straight forward with the alfuzosin review by Dr. Venkat Jarugula.

DR. JARUGULA: Good afternoon. I'm Venkat Jarugula, clinical pharmacology reviewer for the alfuzosin NDA.

This morning we have heard about the results of the alfuzosin study in detail. So I'm just going to focus on a few important slides of my talk to highlight the

results of the alfuzosin study, PDY 5105.

What I have here is a table giving a comparison of the mean QTc change from baseline versus placebo for different methods of correction for the alfuzosin 10 milligram dose, 40 milligram dose, and the moxifloxacin 400 milligram dose.

As we can see here, different methods of correction give different results on the mean QTc change for alfuzosin, as well as moxifloxacin. The Bazett method gave the highest QTc effect ranging from 10 milliseconds to 14 milliseconds. The Fridericia method also gave higher QTc changes, higher increase in QTc's ranging from 5 milliseconds to 8 milliseconds, compared to the population and individual methods where you see only a 2- to 4-millisecond increase. In fact, this is about half of the effect that you see with the Fridericia method. The Holter monitor method, on the other hand, showed the lowest effect on the QT interval.

As we can see from this slide, there is a dose-related increase with alfuzosin 10 milligrams and 40 milligrams with all the correction methods and also with the Holter monitor method, although the magnitude of these QT changes are up for discussion later on.

One thing that I would like to point out regarding the Holter monitor method is the time course

effect on the QT interval was not captured with this method because the QT intervals were classified into RR bins and averaged in each RR bin and compared between the baseline and the treatment group. As a result, there is no time course effect that can be captured with the way the study was conducted with this Holter monitor method.

Next I'm going to show the number of outlier subjects again with each correction method. As one can expect, based on what we discussed so far and what we know, the Bazett method yielded the highest number of outliers for all the outlier groups.

Just to focus on the outlier group that was not mentioned this morning and that was also discussed somewhat to be sensitive, the delta QTc between 30 milliseconds and 60 milliseconds group, with the Fridericia method there were 9 outlier subjects with a 40 milligram dose and 1 outlier with the 10 milligram dose, compared to 2 outlier subjects with the population and the individual correction method at the 40 milligram dose, and 0 with placebo with all these methods of correction.

For outliers of delta QTc greater than 60 milliseconds or QTc greater than 450 milliseconds, you have virtually 0 number of outlier subjects with all the methods except for the Bazett method of correction.

Again, you can see there is some dose-related

trend, especially if you look at the Fridericia method.

What this slide shows is a concentration of alfuzosin and QT relationship calculated by the individual correction method. What I have here is a panel of 45 subjects that participated in the study, that completed the study. Each panel represents 1 subject in the study. On the y axis, I have QTc values plotted against the plasma concentrations of alfuzosin on the x axis. The red colored trend line is the individual trend line, and the blue line is the population line which is the same for all subjects.

As you can note here, there are some subjects, this one, this one, here, here, that have increasing QT intervals with increasing plasma concentrations. Please note that when you pool all these data and plot in one single plot, the individual trends may be masked and you may see a plateau. So that is a point we want to make on this slide.

So these are the highlights of the results that I want to bring into perspective before we go into the discussion. I want to point out the main review issues that arose from the review of this alfuzosin QT study. I'm going to read my review issues from the slide that I'm not going to show here.

So the main issues that were identified and to be discussed in the questions are, which QT interval

correction method is most appropriate for assessing the proarrhythmic risk of alfuzosin? I guess this will equally apply to vardenafil also. How should the QT data derived from the Holter monitoring method be interpreted? Is a single-dose study adequate to assess QT prolongation?

Thank you very much and Dr. Leslie Kenna will present on vardenafil.

DR. KENNA: Good afternoon. I am Leslie Kenna, and I was one of the clinical pharmacology reviewers for the vardenafil submission.

Today I will just highlight the results of the drug-drug interaction studies with vardenafil and also concentration-response analyses.

First, the impact of the pharmacokinetic interaction between various clinically relevant CYP3A inhibitors was studied, including concomitant administration with ketoconazole and two protease inhibitors, indinavir and ritonavir.

One reason the protease interaction studies are important to consider is that a series of small studies have reported a higher incidence of sexual dysfunction, including erectile dysfunction in patients with HIV. The incidence of erectile dysfunction ranges from 33 to 50 percent.

Cross-sectional studies have also shown that

patients with HIV, including those on triple therapy, use PDE5 inhibitors.

This bar plot demonstrates ritonavir's effects on exposure to vardenafil as measured, one, here in orange, by maximum concentration, or Cmax, and two, this blue bar here, area under the concentration time curve, or AUC. What this shows is that ritonavir causes a 12.7-fold increase in vardenafil's Cmax and a 48-fold increase in vardenafil's AUC. It is unknown whether AUC or Cmax correlates better with QT interval.

There was a question raised during the morning session regarding the nonlinearity of vardenafil pharmacokinetics. Vardenafil has a nonlinear pharmacokinetic profile for doses greater than 40 milligrams.

This plot shows how the 80 milligram dose of vardenafil investigated relates to the case of a drug-drug interaction with ritonavir. Vardenafil concentration is plotted on the y axis and time is plotted on x axis. The green line, this little one down here, shows the average concentration of vardenafil as a function of time after administering a single 5 milligram dose of vardenafil alone. The blue line shown here shows the concentration of vardenafil as a function of time after a single 5 milligram dose of vardenafil is co-administered with 600 milligrams

of ritonavir taken b.i.d. The red line shown here shows the average plasma concentration of vardenafil as a function of time after a single 80 milligram dose of vardenafil.

As expected, based on the previous graph shown, the Cmax reached when the 5 milligram dose is taken with 600 milligrams of ritonavir is approximately 13 times higher than when the 5 milligram dose is taken alone. The average maximum concentration of vardenafil observed after an 80 milligram dose is administered is nearly 3 times greater than that observed for the interaction with ritonavir. This shows that the choice of the 80 milligram vardenafil dose covers the Cmax expected when dosing 600 milligrams of ritonavir with 5 milligrams of vardenafil.

Note, however, that this red line dips below the blue line at about 5 hours. So this says that the area under the curve observed during this interaction was not covered by this study design.

And note again that it is unknown whether Cmax or AUC is better correlated with the response to vardenafil.

Note also that the sponsor collected data on concentration, QT and RR up until 4 hours after dosing.

This is my final slide. The sponsor presented results of a concentration-response analysis this morning

suggesting that the average response plateaus within the range of concentrations of vardenafil tested. As the sponsor also pointed out, there is large inter-individual variability in concentration and response.

This slide shows individual data plotted separately. Here are 59 plots of QTcF and concentration. So there's one plot for each subject after 10 and 80 milligram doses of vardenafil. The black dots are the data points. The blue line in each panel shows the linear trend through the data when all the data are pooled. The orange line shows the individual trend in that particular panel. We are not suggesting that there is a linear relationship between concentration and response. However, the point of this slide is that although some subjects have a shallow concentration-response relationship, others may not within the range of doses tested.

So just like the former speaker, I'm just going to summarize the review issues that were raised by study 10929.

In evaluating the risk of QT prolongation, first, should the results with respect to one particular correction method be favored over another? Second, were the vardenafil doses investigated adequate? Third, was the duration of concentration and response sampling adequate? And finally, is it appropriate to set the 90 percent or

some other percentage level upper confidence limit for the mean change in QTc from baseline relative to placebo at 10 milliseconds or some other cutoff value?

Now, Donna Griebel will provide concluding remarks.

DR. GRIEBEL: Well, it's not exactly concluding. I'm going to give a quick, abbreviated version of Dr. Marcea Whitaker's post-marketing review that was presented in a lot of detail in the FDA briefing document. I would like to just focus on the torsade events, the torsade categories, and I'm going to go through the two drug classes. I just want to do that to put into perspective what was reported this morning for moxifloxacin in post-marketing for torsade.

For the alpha blockers, we've pooled at the top of this slide IMS data that we had, estimated sales since 1998 for all three of the drugs that are listed at the top of the three columns, and over 110 million prescriptions have been sold since 1998 according to a sample in the IMS data. Of those, you see for terazosin, two cases; doxazosin, three; and tamsulosin, one. The dates of approval for these drugs were 1987, 1990, and 1997.

Viagra we've heard discussed this afternoon as well. At the top we have 58 million prescriptions up to December of 2002 in the United States. There were only two

cases reported of torsade, and as we've heard discussed, and I think that we made clear in our briefing document, these were dubious cases when you read the narrative.

Then if you look at moxifloxacin, here we have Bayer reported 19 million patients exposed, and this is patient exposure as compared to prescriptions sold in the previous slide. Those were a sampling of prescriptions.

There were reported to ODS in our search, or the Office of Drug Safety at the FDA, 15 cases of torsade, and one of those the sponsor is seeking additional information to clarify the report. 9 were U.S., 6 foreign. There were risk factors in these patients. The majority of them were female; age greater than 70, 9. Some confounding factors or potential risk factors for developing torsade included underlying cardiac disease and electrolyte abnormalities and concomitant drugs in 5 that included amiodarone in 2 and the other 3 were diuretics. These 15 cases were temporally related. Most of them ranged 1 to 3 days. There was one that occurred 8 days after starting dosing.

We were struck by that number 15 after we had gone through all of those reports that we had talked about in our post-marketing review. We believe that may indicate that the moxifloxacin active control does indicate that it is an active control in these studies.

The moxifloxacin label does contain a bolded warning about QT prolongation and it includes a patient package insert of information to provide to patients on clinical events that they need to report to their physicians, as well as reporting their concomitant medications and medical histories. I don't know if that was a component to the heightened reporting that you might have seen with moxifloxacin, but it was of interest.

Bayer did mention that they had a pharmacovigilance plan for vardenafil and we would be interested in hearing that.

I think this concludes our comments and our presentation. We do look forward to hearing your discussion of our questions this afternoon, and we'll be happy to take any questions regarding our reviews. Thanks.

DR. BORER: Thanks very much, Dr. Griebel.

We may have some questions for the FDA, and we'll also go into additional questions we may have for Bayer and for Sanofi-Synthelabo.

Beverly?

DR. LORELL: Yes. I have a question that relates not just to post-marketing, but to clinical development. We heard this morning from both sponsors data regarding a lack of any signal of torsade de pointes during clinical development trials, phase I to III. Can you or

perhaps another member of the panel or the audience put that into perspective?

If one were to look at -- let's just take three examples of drugs that are known to have a heightened risk of torsade de pointes. Let's take, for example, two cardiac drugs, sotalol and amiodarone, and a noncardiac drug cisapride. Was there any signal whatsoever in clinical development of a risk of torsade de pointes, or can you give us those numbers to put that piece of safety into perspective?

DR. GRIEBEL: I'm going to call on Doug Throckmorton to see if he can help me out here with that.

DR. THROCKMORTON: The cardiac drugs, you said sotalol and amiodarone?

DR. LORELL: Yes.

DR. THROCKMORTON: I can't give you the amiodarone NDA. Its rate of torsade is pretty low. Even in post-marketing, it's been hard to show clearly that it's a torsadogen. Sotalol had clear torsade. No problems at all.

Another compound a little closer to home here might be bepridil, which was an anti-anginal drug that was developed. That again had cases of torsade in the NDA, but it prolonged the mean QT 50 milliseconds, something like that. It had a different level of signal perhaps.

Cisapride had no signal in its NDA database. Its first hints were a post-marketing report of rapid heart rates in an Australian study that came out shortly after it was published, as I recall.

DR. BORER: Beverly, did you have a follow-up to that?

DR. LORELL: No. I think that's a little bit of a useful perspective. Certainly I think if one saw unsuspected, even a cluster of cases during clinical development, that would be very worrisome. But I just wanted to, I think, make sure that I understood correctly that the lack of a signal is not useful.

DR. THROCKMORTON: The occurrence of a case of torsade in a development program, outside the antiarrhythmic world, really is a signal that we take very seriously. I can think of it occurring on two occasions in the time that I've been familiar with this problem, and in both cases it was a real thing that was taken seriously. It's pretty rare.

DR. BORER: Tom, then Peter, then Paul.

(Laughter.)

DR. FLEMING: One of the questions that I had, listening to Joel Morganroth's presentation, I think has been -- relevant additional information has come from FDA. Bayer's slides 58 and 59 were comparing what was known from

our post-marketing surveillance for occurrences of torsade de pointes with moxifloxacin and with Viagra. On slide 58, there was an indication that there were 4 cases in 7.7 million. That seems to be fairly consistent with what we just heard from FDA of 15 cases in 19 million. That's 1 per 2 million cases from the sponsor's review; 1 per 1 million cases in the FDA review.

Then for Viagra on slide 59, they had said there were no cases reported in 39 million prescriptions of Viagra, and similar figures were given by Pfizer saying 20 million patients receiving a billion doses have had no cases of torsade.

Statistically those are strikingly inconsistent rates that you would have no cases in 20 million to 40 million versus 15 cases in 19 million. Either it tells me that the Pfizer passive surveillance system is leading to a gross underestimate of torsade or it tells me that in fact their experience does represent natural history. The cases are, in fact, incredibly rare and that moxifloxacin is, in fact, clearly an agent that induces an increased risk of torsade. Only one of those two statements can be true. Either moxifloxacin does increase or it doesn't, and the Pfizer surveillance is grossly under-representing cases of torsade when they exist. Any insights?

DR. KOWEY: Tom, is it possible, just as a

question, that generally Viagra is not given to women, which is an issue in torsade? And the other is that Viagra is given for a very short period of time, intermittently, and the time of exposures would be grossly different between the two compounds. I'm just speculating, but there are very big differences in how these drugs are used.

DR. RODEN: We don't know how many of those cases for moxi were in hospital in monitored patients, which is not the way Viagra is ever given.

(Laughter.)

DR. FAICH: Mr. Chairman, I'm Jerry Faich. I actually reviewed the moxifloxacin cases and maybe let me just elaborate on them to give you a better picture.

I looked at 12 of them. Four of them were in patients who were getting intravenous therapy and those patients were severely ill and were monitored. So you have a different patient population that I think you have to consider. So that's a major factor in doing this.

Also, I think it's fair to say that there's a reporting artifact here. You've got torsade in the label of moxifloxacin, and that may well stimulate reporting. I have no way to measure that.

I would point out for the 8 oral cases that I went through, actually 6 of them have severe cardiac disease, a pacemaker in place and prior syncope, for

example. Two of them were immediately post MI and post resuscitation. A couple of them were congestive heart failure and sick sinus syndrome. So these were patients with severe cardiac disease. There are two exceptions to that. One of them we have no information on and the other might be a less confounded case.

So it looks like the patient population may well be markedly different. These are patients who have pneumonia in large part. Some of them have bronchitis.

DR. KOWEY: How many were women, Jerry?

DR. FAICH: You know, I didn't tabulate. I would point out that almost all of them were in their 70s and 80s, and I think -- there we go. All but one were female. I hope that's helpful.

DR. BORER: Thank you, Jerry.

Paul?

DR. ARMSTRONG: Two questions, perhaps the first to the FDA and the sponsors, if they want to respond. The heterogeneity in the kinetic and the QT interval data on those individual plots was interesting, and these are in healthy male volunteers, I guess, as I understand it, who are between 18 and 40 years of age. I understand they're between 50 and 90 kilos. So I guess the question was, do we have any information dosing by weight, or is there other information about baseline laboratory data amongst these

admittedly normal but perhaps heterogeneous individuals that might give us some insight into the heterogeneity of those individual plots?

And the second question. I don't know whether we're going to get more information on the blood pressure or heart rate that we raised this morning, Mr. Chairman. But ketoconazole, which was administered concomitantly with the alpha blocker, as I understand it, is also approved for prostatic cancer, 400 milligrams t.i.d., and this was a 400 milligram single dose. So does the sponsor have information on concomitant use in the large population outside the United States who would presumably have prostatic retention but potentially also have prostatic cancer where the opportunity for both drugs might lead to potentially problematic results?

DR. GRIEBEL: With regard to the first question, we can't answer the weight question.

In terms of the laboratory, if you're talking about were there electrolytes, they were required to have normal electrolytes to enter the trial.

Perhaps the sponsors could address the weight and population issues.

DR. DURRELMAN: Sylvain Durrelman again.

We have not looked at the weight effect on the PK of alfuzosin in our study of 45 subjects that were in a

range of rather homogeneous populations.

We were not surprised, however, by the different pattern that we saw on the FDA slide earlier today because we think that if you look at 45 data plots that start with a few data points per subject, you would have some natural random fluctuation around the mean. We believe that it's what is the biological variations.

But we have not seen any strong effect on weight and we have not done a subset analysis on that.

DR. BORER: Dan?

DR. RODEN: A couple of comments and then a question.

The first has to do with the issue of whether a single dose is, of necessity, safer than multiple doses. I'd just point out there are data in the literature that suggest that the extent of QT prolongation after a single dose of a QT-prolonging drug -- and we haven't decided that these are or not -- is sometimes greater than the effect seen during chronic therapy. There are data for sotalol, for example. So I'm not sure how much reassurance to take over the fact that we're looking at single doses.

At the same time, the issue of heart rate. There are data also in the literature that if you manage to monitor someone who's going to have drug-induced torsade, for the half-hour or so before they have an event, their

heart rates actually increase. So there is this complex interplay among adrenergic activation and direct effects of drug on QT and indirect effects of drugs through blood pressure mechanisms perhaps on the heart rate and QT. So I think again the heart rate stuff is a little bit more complicated than may have been perceived this morning.

My question -- I am not sure who to address this to -- is, is it a surprise that the extent of QT prolongation with 80 milligrams of vardenafil is not 8 times higher than it is with 10 milligrams of vardenafil or the same with the 400 versus 50 milligrams of sildenafil? The drugs, if anything, would be expected to achieve higher peak concentrations. We just saw that. Yet, the QT effect is almost trivially -- I mean, they seem to be the same.

So does that say something about a heart rate effect?

Does that say something about some other mechanism of action that is not being factored in here?

Does it say something about some artifact of the way the studies have been conducted? I just don't know but it's clearly something that's unexpected and needs to be explained.

DR. MORGANROTH: We might get an insight into that very flat dose-response curve because that is unexpected. With moxifloxacin, as was pointed out, you

double the dose, you double the effect, which is true for terfenadine, et cetera. Very linear, very clear.

These PDE5 inhibitors have the opposite effect. You give huge increases in dose and concentration, it looks it's hard to detect a change.

It may be, in fact, related to the effect on hERG because vardenafil was not able to produce a 50 percent inhibition of the current. I think it only made it up to about 30 percent and one had to extrapolate to 50. Perhaps what that might mean is it's such a weak hERG blocker, assuming that's the mechanism, that in fact what we're seeing is a weak effect that really isn't linear and dose-related.

I mean, that's my guess. The answer is it was a surprise to us too. It was a surprise to me to see that very flat dose-response. You usually don't see it, and it either suggests this is -- I don't want to call it an artifact, but clearly a totally different kettle of fish than we're used to for QT-prolonging drugs like moxi and others.

DR. RODEN: I would actually think along the lines that Paul Armstrong has been suggesting, and that is, with the high doses, you probably produce vasodilation and you get sympathetic activation. That, in turn, shortens the QT no matter how you correct for it. That may be

playing a role as well. Something like that.

DR. MORGANROTH: Against that theory would be that if you do use the individual correction which does show you that at the higher heart rates achieved at the 80 milligrams, meaning the 60, 70, 80, 90 beats per minute, you designed it not to have an effect on the QTci. Presumably that's the value of the QTci. So I'm not sure it's purely a heart rate effect.

DR. ROEHRBORN: My name is Claus Roehrborn. I'm a urologist at UT Southwestern, and I'm here as an expert on BPH on behalf of Sanofi. I just wanted to provide a comment and correction on the issue of ketoconazole in prostate cancer.

I'm not sure ketoconazole is approved for the use in prostate cancer, as was stated. But it has been found, when used at 400 milligrams q 8 hours, to reduce serum testosterone level to castrate level within a few hours. It is used only in extremis if a patient presents with advanced metastatic prostate cancer, and if that patient for some other reason cannot at the time undergo a bilateral orchiectomy, which is the standard treatment in those kinds of cases to prevent, for example, spinal cord compression and paralysis. So it is in very extremely rare cases used and, if so, only until the patient is stable enough to an orchiectomy. I just don't think that those

are the same kinds of patients treated with either an alpha blocker, certainly not with vardenafil at the time.

Thank you.

DR. BORER: In the planned studies that were performed by the sponsor, there's been a fair amount of investigation of PK type interactions, which is very valuable. We didn't see any planned effort or direct effort to assess PD type interactions. Now, Beverly Lorell raised this point during a break, and maybe she wants to take it forward.

But I understand from Dr. Griebel's comment that patients who started out with electrolyte abnormalities were excluded from study, and that's fine. However, I assume there were patients in the database who had hypertension, who were on diuretics, and whose electrolytes were monitored, and the electrolytes may have varied.

Obviously, there were no studies planned to create hypokalemia, for example, but on sparse sampling or some other assessment, there may have been patients whose electrolytes were abnormal at one point or another. And one might like to know whether there was a clustering of effects in terms of QT prolongation in those patients while they were on experimental drug versus placebo versus active comparator. Do we have any data at all that would give

some insight into that kind of issue?

DR. SEGERSON: I think in terms of the vardenafil database, we haven't looked specifically at hypokalemia for a clustering of either adverse events that might be signals or other pharmacodynamic effects in our studies.

DR. BORER: I wasn't really thinking of adverse events because I think there were very few. I was thinking about the primary endpoint. If you think that there could be a deleterious interaction between drug and disease or between drugs, that's not a metabolic and elimination interaction, which is the interaction you studied. If you think there is such a thing, then presumably we might see it by looking at the surrogate. I'm just wondering if you have such information.

DR. MORGANROTH: Well, in the vardenafil trial, things are so tightly controlled in these definitive QT trials, the chance of having someone develop hypokalemia would be an unusual if not an impossible thing to happen.

DR. BORER: Right, but some subpopulation could drop over time from 4.5 to 3.6 or something. They'd still be normal. One might be able to look at that to see an effect, if it's there. I don't know.

How about for alfuzosin?

I'm sorry. Please say your name when you come

to the microphone so that the transcriptionist can get that.

DR. SALLIERE: Dominique Salliere from pharmacovigilance in Sanofi-Synthelabo.

I can give you some information related to the co-prescription in post-marketing experience with alfuzosin. These data come from IMS and were collected in five European countries. May I have slide 27, please?

So for alfuzosin, 50 percent of the patients, as expected in this age group, receive a co-prescription, and 50 percent of these co-prescriptions are cardiovascular drugs.

May I have slide 29?

Among these cardiovascular drugs, maybe it is not easy to read, but nearly 10 percent of these co-prescriptions are related to diuretics and some others combined with particularly beta blockers. So you can see that patients, nearly also in 10 percent, received beta blockers. From the larger post-marketing experience, no clinical interaction was suspected despite the large use that we have had in more than 3.7 million patient-years.

DR. BORER: Thank you.

Beverly, this was an issue that you raised. Do you want to carry this any further?

DR. LORELL: Yes, I would like to carry it a

bit further.

I think one of the themes that's come out in the morning's really excellent discussion and presentations has been the uncertainty about the ability to use QT interval, no matter how we slice or measure it by any of the methods that have been discussed, to predict a very rare but catastrophic event of torsade de pointes.

I'd like to actually discuss a little bit further and particularly get comments from our two cardiology speakers this morning discussing risk about the issue of whether we shouldn't be focusing more or thinking about ways to focus on higher risk backgrounds in looking at a relationship between Cmax and QT corrected by whatever method.

We heard two perturbations this morning that made sense. One was looking at the relationship to RR interval itself, and the second was looking at a background with a drug that inhibits metabolism.

I would suggest that there are two populations that we know may be of higher risk from experience in very high risk groups with QTc prolongation, and one background includes mild intranormal fluctuations in potassium and magnesium. So I'd enjoy hearing some discussion at the microphone as to, if no bad effect is seen in normal 20-, 30-, or 40-year-olds doing the kind of studies that were

seen this morning, whether a next step might not be in a controlled, highly ethical, clinical environment to deliberately modestly reduce potassium and magnesium to lower limits of intranormal range, which can usually easily be done with diuretics.

And a second related question is whether or not there should be a consideration in the future as to specifically looking at populations of women and older women since this is a group that clearly is at some higher risk in many long QT syndromes.

So I'd welcome your thoughts about whether we should perturb metabolites and how should we look at women.

DR. BORER: Doug, did you have a comment there?

DR. THROCKMORTON: Yes. Beverly, that is an important part of what we're interested in hearing, but let me frame that a little bit. Let me tell you the way these studies were thought about.

The studies were, in essence, designed to ask a question, does the drug affect repolarization, yes or no? In that context, we perhaps mistakenly thought that a normal volunteer population would inform that question, not whether there would be additional risk factors that would make someone at higher risk or not, but just simply whether or not the drug affected repolarization. A normal volunteer population would inform that question, as well as

a population that's at higher risk. You heard this morning from one of the speakers that we don't have any reasons to believe that that's in error, that is, that there might be a drug that didn't do something to normal volunteers that did to a high risk population.

But I'm interested. Is that what you're suggesting? That is, that for a reason that I'd like to hear some comment about, a normal volunteer population doesn't provide you enough assurance as to the absence of a potentially relevant effect on repolarization.

DR. LORELL: Doug, I'm not sure that I would even pretend to know the answer to that.

I guess I would look at it in a slightly different way, and that is, one might postulate that one would always start with a normal, highly controlled population, but that that may be necessary but not sufficient, given what we know already clinically about the specific issue of risk of torsade with QTc prolongation, and in particular, that a heightened vigilance might be necessary to deliberately test a perturbation which is extraordinarily common clinically and that we know enhances risk, and that is intranormal perturbations in potassium and magnesium.

I guess the separate question that's related to your thinking about this is the issue in women, whether the

gender issue needs to be somewhat independently addressed rather than sort of mixed in as part of a broad population.

DR. THROCKMORTON: The latter is a good question. These are typically men.

Again, the structure we've been using has been that normal male volunteers would adequately answer the question of whether or not there was an effect on repolarization. If the answer was yes -- and you'll tell us later how to decide when there's an effect or not, what that magic number is -- then all those studies would be things that would be very important so you can think of development programs that have uncovered such effects and then had to look in phase III to look at interactions by race and interactions with other drugs and that kind of thing. But the notion was that absent an effect on that male healthy volunteer population, those looks were less rigorous, were less structured.

So I'm asking again, is that something that you're suggesting we need to rethink? Because I'd need to know why.

DR. LORELL: Yes, I am putting forward the notion that it may be useful rethinking about what is done in phase I-II in a very rigorous way in comparison with and complementing but not the same as prospectively looking at much noisier data in phase III.

DR. KOWEY: Beverly, Doug said -- and I think he's correct -- there are two questions that are being asked. The first one is, is there fundamentally an effect on repolarization? Actually, Doug, I think that if you had a drug that you weren't just going to give to men, which is what these two drugs ostensibly do, you wouldn't do a phase I trial in normal volunteers in just men, would you? Wouldn't you do women too?

DR. THROCKMORTON: I think we have not said that you needed to do both. I don't believe we've made specific statements about that one way or the other.

Tell me why I should require women, which is what you're suggesting?

DR. KOWEY: Because I think that if you're looking at repolarization -- I agree, that's the experiment you're doing in phase I -- that women fundamentally have a different repolarization response than men. I think it's fairly clear that they do. And if you only did men in phase I and came up with nothing, you would still probably not have your fundamental experiment concluded. That's why.

DR. THROCKMORTON: Could I ask for some comment from the rest of the QTers around the sponsors and the table, please?

DR. BORER: Dan, do you have some comment?

DR. RODEN: I think the question is whether a drug that has absolutely no signal in a normal healthy volunteer population could, in fact, generate a signal of concern in a more at-risk population. Another population that has been used actually, Bev, is the heart failure population who often have these electrolyte abnormalities, and even if they don't have longer and funnier looking QTs. That was actually done in the terfenadine experience, and at high dose terfenadine in that widely cited study, there was actually a fatality at 300 milligrams twice daily of terfenadine. So you can push that trial design and cover those kinds of events. I don't think anybody wants to uncover a fatality.

But if the question is, does this drug prolong the QT, then that's adequately addressed by these sort of normal volunteer studies. Then the question is if I know that the drug prolongs the QT, are there populations in whom it's going to prolong the QT a lot due to metabolic reasons because they're older women who are exposed. That's a separate set of questions. I guess it might be logical to recommend that if you had a signal, the next step might be to investigate the extent to which that happens under rigorously controlled conditions in a higher risk population. I'm not sure how far to push that to answer a question that may already have been answered. Do

you see what I'm saying?

DR. LORELL: Well, just to be brief, I think we've already seen an example of that being done in looking at co-administration with a drug that inhibits metabolism.

DR. RODEN: Right, and the whole idea of giving higher than normal doses just to sort of expose -- but the question there is just to find out if the drug prolongs the QT. And if it does, then you have a whole separate set of questions like are there special populations. Terfenadine is a great example. I think terfenadine is an extraordinarily safe drug as long as you don't give a metabolic inhibitor. There are lots and lots of people who took it and nothing happened. But if you give it with a metabolic inhibitor, there's a real problem. So you have to ask yourself are the pharmacokinetics well behaved. Is it likely that a lot of patients with heart failure or hypokalemia will get this drug? And those are separate questions.

DR. BORER: Toby?

DR. BARBEY: There is, of course, then the other component of the perceived benefit from the drug. In other words, when arsenic prolongs the QT interval but can cure leukemia, you kind of proceed differently. But I would be more a believer that indeed your phase I studies which should be -- I agree with Peter -- in men and women

are designed to tweak and challenge the system as much as possible to get a flavor for that propensity. And then you derive some clinical strategies based on that saying, we will up front be more prudent with this drug in these situations, rather than necessarily bring in on the research unit. That would be my instinct.

DR. BORER: Mike, did you have a comment about this particular issue?

DR. ARTMAN: Yes. Getting back to Doug, I think that you're right. The question is does this drug affect repolarization. And if you test it in healthy young males and there's no effect on repolarization, then I think you can safely conclude that there's no effect on repolarization in healthy young males.

That doesn't answer the question whether or not it would affect repolarization in healthy young women. I think we do know that repolarization in women is different and they respond to drugs differently. So I believe that if a drug is going to be used in a female population, it ought to be tested in females in these phase I tests.

DR. RODEN: At higher doses.

DR. THROCKMORTON: This is not one of the questions, Jeff, but this is something quite different from what we've heard before. So I'm sort of sorry to keep pressing on this, but I'm seeing nodding heads.

DR. BORER: What I'd like to do -- we have Jeremy. We have John Camm. We've got Joel here. I'd like to hear from all of them.

DR. THROCKMORTON: I'm really interested in some conversation about this.

DR. BORER: Jeremy?

DR. RUSKIN: With regard to the gender issue, most of the phase I trials that I have heard about in the last year have included women, often 50/50 for specifically the reason that's been brought up. And I think it's very important to do.

That said, I don't know of a single situation where there's a drug that has no effect on repolarization in men that will have an effect on repolarization in women. It's really a question of relative sensitivity. There are drugs that have been studied very closely with regard to gender differences. Some drugs, you can see no gender difference at all, and others you do. And when the difference is there, it's relatively small but unequivocal.

What's very clear is that the susceptibility to drug-induced torsade is much higher. About two-thirds of reported cases both with antiarrhythmic and non-antiarrhythmic drugs are in women and a third in men.

But it's very unlikely, almost unimaginable, that a drug that had no effect in men would have an effect

in women. I don't know if Dan or other people agree with that.

DR. KOWEY: Jeremy, just to answer your question, I agree with you in general terms, but I guess I'm having a hard time understanding. I agree that we don't know of a drug like that and we're not really talking about drugs with zero effect. We're talking about drugs with some effect. Since we're talking about basically screening, as Joel said in his talk, almost every new chemical entity, I don't want to really get into the situation where we're imagining we can tell the future and that there's not going to be some compound sometime that does that. What is the harm, really, of doing women in a phase I trial?

DR. RUSKIN: None whatsoever, and my opening remark was that all the phase I trials that I've seen in the last year that have been talked about and are in design generally include 50 percent women. And they should.

DR. BORER: John, can you give us your opinion on Joel?

DR. ARMSTRONG: Could I put a question to John as well through you, Mr. Chairman, since he has written on this dynamic nature and the notion of association/disassociation between the QT and the heart rate and the notion are all QT intervals the same and QT

prolongation the same? Clearly, they're not, and I wonder if he could address that before we come to these questions because I must say I've learned a fair bit today, but I'm still confused about the multiple causes, whether they be patient comorbidities, the metabolic substrate, or the drugs or concomitant medications, all of which can affect the QT interval but may have different implications regarding, I guess it's torsadogen. You used the word, Doug.

DR. CAMM: Well, thank you very much for that very long list of questions.

(Laughter.)

DR. CAMM: I think we should start by the issue of the dynamic nature of the QT interval. Most of what was referred to this morning was related to the time that it takes for a QT interval to adjust to a new heart rate. So, for example, a step change in heart rate that might be induced artificially, for example, with a pacemaker, will be followed by 30 or 50 beats during which there's progressive shortening of the QT interval if the step change was an increase in heart rate. So there is a definite hysteresis involved.

Of course, changes in heart rate are usually gradual, and the QT interval changes therefore do tend to keep up relatively well with the changes of the RR

interval, but nevertheless, there is a significant hysteresis. The way that that's dealt with in clinical trial circumstances is usually by trying to ensure that there's a relative stability of the RR interval before recordings are made from which RR/QT are measured and QTcs are computed. So that's the general issue about the dynamism of the QT interval.

But there are many more intriguing elements about it than that. For example, if a patient with bradycardia and a long QT interval suddenly has an increase of heart rate, the situation that I think Dan was alluding to a moment ago, that might well be a particularly torsadogenic situation because the prolongation of the QT interval is not rapidly attenuated by the change in heart rate that occurs. So the QTc, for example, would then fairly dramatically prolong, and this, no doubt, is one of those torsadogenic situations.

I don't know if I've dealt adequately with what you asked me, but if I could turn to the general questions that Beverly has raised. I think that they are very intriguing possibilities that we could take patient subsets that are of particular risk. I think you were asking more about volunteers, and I understand that within the volunteers, clearly we can choose one gender or another or both fairly easily and we could certainly measure potassium

and perhaps modulate potassium by co-administration of diuretics.

We have very little information about how an intranormal variation of potassium would affect the QT-prolonging effect of any drug that blocks the IKr current or prolongs the QT interval for any other reason. We do know that more extreme changes in potassium are, of course, very relevant. Dan Roden, for example, published a paper with quinidine, heart failure, and hypokalemia in which he managed to demonstrate that very well. I'm not sure how in normal volunteers relatively small changes within the normal range of potassium would amplify the QT effects, but it's certainly something that's worth considering.

With reference to whether we could extend that to take vulnerable patients, I think this then enters a much more difficult arena, taking heart failure patients, for example, or patients with severe ischemic heart disease or severe hypertrophy. Reasons for this are practical reasons, feasibility reasons, and ethical reasons.

Amongst the practical reasons are the fact that patients with some of these characteristics are often on considerable numbers of co-medications and it's difficult to control for them. They may have different electrolyte levels, again difficult to control for without very large studies. Importantly, they often have very distorted

electrocardiograms with T waves that are not particularly stable anyway because of the disease process, and it becomes a tour de force to try and measure consistently the QT intervals. So there are definitely difficulties with this.

Amongst the ethical concerns I think are the issues of whether one can expose a patient particularly to supratherapeutic doses of any medication with the notion of trying to use that patient and his condition as an amplifier to show a potential QT problem. Usually the IRB comes back to the investigator, when such trials are proposed, to say, please use a much lower dose of the drug, something less than therapeutic. And you get involved in a lot of difficulties in practically trying to promote such studies. Although they are, I agree, of considerable practical importance, I think they are in practical terms very difficult to conduct.

DR. LORELL: If I might make, Mr. Chairman, one comment. I think one of the impressive things that we have heard this morning -- and I very much appreciate your comments -- is that in looking at these rare, isolated case reports, what are sort of being discussed as confounders are actually the substrate that we're worried about. In thinking about the earlier presentation with, I thought, the very provocative slide that we should be looking not

just at central tendency, but for -- the term that was used was categorical analysis looking for outliers, it may be that we're actually throwing away some of the richness of the data that's terribly important in designing a well-done and ethical phase III trial by not looking earlier, even with the difficulties you describe, at some of the groups for the QT prolongation issue that we know may be at higher risk. So I'm not sure I can even suggest how to do it, and clearly there are some formidable challenges.

DR. BORER: Joel?

DR. MORGANROTH: The question regarding the population composition for a definitive QT trial that was raised by Doug, I agree entirely with Jeremy. Since we first learned about the enhanced sensitivity of women compared to men for a QTc-prolonging drug, it seemed common sense to put men and women, usually 50/50. If you have a 40 group, you'd have 20 and 20, so it's almost enough with 20 not to be totally spurious that you might have a reasonable good point estimate of the effect. And the problem with putting women in is that women volunteers are just not very plentiful compared to men, and as these phase I definitive trials get more popular and there are large trials, it's not anything more than a pragmatic issue that women are not going to be so easy to put in. So it's a real good question.

I personally think the focus of a lot of the answers to the discussion in the last few minutes should remember that in this definitive QT trial, the key group in my opinion is the supratherapeutic dose of the new drug being investigated. And if, in fact, that dose is really very high, as it should be, and you see no magnitude of an effect or a very small magnitude of an effect of a few milliseconds, I have never ever seen that women, as Jeremy's experience is also, gave us any more information about the degrees of magnitude, number one. Therefore, they may not be really that necessary to put into these trials if, in fact, one does employ a proper supratherapeutic dose.

And if you do put in a supratherapeutic dose, that should cover these issues that are vexing and interesting of what about patients with heart disease or hypokalemia or other higher risks where clearly those are going to magnify the effect of a QTc drug. But we don't believe that they'll magnify them more than a supratherapeutic dose of the drug that's inducing the QTc. And I'm talking about using 5-fold, 10-fold the dose. If you can go to that kind of level and you see whatever that magnitude is, I can't imagine that you're going to see much out of that range by some intranormal changes in potassium or people who happen to have left ventricular hypertrophy

versus a normal heart. So I think one should gain great comfort in the precision of that.

DR. BORER: Thank you.

I'd like to make a comment here that is not a conclusion, though it may sound like one. We're musing about possible investigations that might be helpful in identifying high-risk situations or drugs that may cause problems. But as I read and hear the data, we really don't know how to interpret much of what we're observing. We're looking at a surrogate and we don't know how to interpret the surrogate. We don't know what it means. It's important to remember that.

That suggests to me that a good deal more, I will call it, fundamental research, although I don't mean that in the sense of basic science, but a good deal more information is needed so that we can better interpret these data. If we translate our suppositions about what the interpretation might be, without a real firm basis for the interpretation, we will request a large number of studies to be done that cost a great deal of money and will put some people at risk without actually justifying that with data that will be beneficial because we don't know how to interpret them.

So I would keep that in mind as we go through these questions here. There are a lot of things we'd like

to know. There's a lot research that needs to be done, but I think that research needs to be done and we need to know those things before we mandate certain kinds of studies in drug development efforts. So that's an observation. It's not a conclusion.

Dan?

DR. RODEN: I think I got to talk before Tom because you were looking at me before him. I'll take the opportunity while I have it.

I'd just like to amplify that, Jeff. It seems to me I would be the advocate of basic science and there are some interesting things in basic science that might shed some light on this, QT morphology kind of issues. But I think we're a long way away from that.

But there is an experiment that is going on as we speak and that is the ongoing examination of the moxifloxacin outcomes, the ongoing examination of ziprasadone outcomes. So we ought to be able to, at some point, get a sense of whether a 6-millisecond increase in a well-characterized normal volunteer population can be translated into some estimate of risk of torsade de pointes, and then the question will become whether the risk is so vanishingly small at some level as to be ignorable.

It seems to me we put ourselves into an awkward position when we say here's a drug where we're quite

confident the incidence of a really serious adverse event is going to be one in a million. It's tough to weigh that in the grand risk-benefit scheme, but it does make you uncomfortable because you have the confidence that you're able to say that. Obviously, that's tempered by what population you're studying and all those other things. The data that we need are the real clinical outcomes data, and I don't think anything short of that is going to help very much.

DR. BORER: Tom.

DR. FLEMING: I think my question for the FDA and comments are a further amplification of this and maybe even further discussion of the gender issue.

My own sense as well is that what I really care about here is are these interventions associated with meaningful increased safety risks on clinically tangible outcomes. They may be. It may be sudden death. It may be cardiac arrest or other events that unfortunately happen with sufficient frequency in the untreated population that being able to discern what's truly causally related increases in those risks in a passive surveillance setting is going to be almost impossible unless we do large randomized trials or unless we look at events that are, in fact, so profound when they occur that we can reliably assume they'll be reported, which is possibly the role of

torsade.

Which is why I'm struggling with still trying to understand the 20 million patients that we have data presented to us from a number of sources today with moxifloxacin and the 20 million patients that have received Viagra where in one case we have 15 torsade cases, in the other we have 0. Given that in the Viagra setting, if I understood, it was a billion doses, so that means that's quite a bit of exposure for each of those 20 million. So that doesn't seem to explain it.

I don't know what the actual rate should be of torsade in the natural population. Is it unusual that the Viagra reporting experience is too low for what I should expect? I've heard gender as one possible explanation for this difference, although I've heard a statement that maybe two-thirds of torsade cases would be expected in women. I'm still left with a very striking difference here, and I'm trying to understand it because it's one of the few clues that I've got here about whether the measures that we're looking at are relevant to clinical endpoints. So I need to understand this.

Has the FDA torn this apart? Have you looked at these 18 cases in 19 million exposures to moxifloxacin versus the Viagra experience to be able to see whether it's explainable by gender? Or is there something real here

that would give us a clue to be able to say, okay, for the experience that we've seen with moxifloxacin, there probably is a relationship that's causal at a rate of, let's say, one in a million?

DR. GRIEBEL: The answer to your question is we today had similar questions that you raise. We have not torn the data apart. I think our briefing document outlined the difficulties in interpreting voluntary reporting which is what we have in the AERS database. Certainly we can go through what was reported in the case report forms and in some instances ask for additional information. Bayer mentioned that they were asking for more information on one of the cases. Certainly the majority of them were female, and that's the kind of information that you get.

But at the end of the day, it is voluntary reporting and I don't know that we would be able to answer the question that you have because what we have in this AERS database, which is post-marketing reports that come in from safety, is what somebody decides to report. Some of them can be a pharmacist. It may be a reporter that heard something, a drug rep who's detailing in a physician's office. You are at the mercy with that system of what is voluntarily reported.

Now, there was a pharmacovigilance study that's

going on with moxifloxacin that I'm not aware of.

DR. RODEN: I didn't mean to imply that there was a formal study going on.

But in my opinion -- and I can be corrected by the agency -- the agency is in the middle of conducting an experiment -- they may not want to call it that -- where they say, here's a drug that prolongs the QT interval by 6 milliseconds -- that's the number that's in the package insert -- let's see whether we get any signal. And I think that's a legitimate experiment. And ziprasadone may fall into a similar kind of category. So there's not an experiment, but I think you guys are pretty sensitized to looking at the reports as they come in to see if that becomes a problem or not. That's the only way to work forward from this.

DR. BORER: Jerry?

DR. FAICH: I'm Jerry Faich again.

Just to expand a little bit on the moxifloxacin post-marketing large studies, there were two of these done, one called the ASA study and one in Europe. The combined number of patients who were followed was 55,000 patients. There were 4 sudden deaths. It turned out they were all in patients with underlying cardiac disease. All the deaths and all the hospitalizations and all the syncopes were carefully followed. So if we're talking about estimates of

risk, getting a numerator and a denominator and following populations and characterizing them, that's probably the best we're likely to do between, on the one hand, well-done controlled preapproval studies and, on the other hand, AERS data which are difficult to interpret.

One can also look at epidemiologic databases, but for this particular endpoint, it's not likely to be diagnosed in any way that you're readily going to be able to follow up on it. It will present as either a sudden death or an MI and it won't actually enter into a diagnostic code. So that's simply a way of saying probably the best estimates are going to come out of large, simple safety studies, and of course, FDA has recently talked quite a lot about those.

That was done in the case of moxifloxacin. The exercise was one to look for assurance. Will it help the unusual complicated patient with lots of underlying reasons to have a torsade anyhow, and then you observe that patient who has it and also has an exposure to moxifloxacin, and you try to tease apart which is it, and has moxifloxacin, or whatever QT-prolonging drug it is, contributed to it? I think that's just a conundrum that we're not likely to be able to solve in using the usual kind of causality assessments either in an individual case sense or in a statistical sense of saying do we have more than we expect.

DR. FLEMING: Could I just follow up? Certainly the levels of rigor that we feel we need to undertake for assessing safety will depend on the nature of the efficacy and benefit-to-risk, and we haven't gotten into those discussions yet. But if we perceive benefit to be of a substantial nature, then uncertain levels of risk that would be profound but incredibly rare could readily be acceptable even without our knowing exactly what level they are. On the other hand, when benefit is less profound, then we have to worry seriously about whether, even if it's very rare, there are profound adverse events that are occurring.

It seems to me what I'm hearing, just in response to the FDA response, is that if we're looking at somewhat more frequent and very important endpoints such as sudden death and cardiac arrest, et cetera, the concern about using passive surveillance for those is that they could readily be under-reported because of the frequency of occurrence in natural history. But a randomized trial of the size of 20,000 to 50,000 could readily provide a sensitive measure assuming that the safety risk in the context of benefit is of such a level that you would consider that justifiable and very often you wouldn't.

But if we wanted to rely on passive surveillance and we said an endpoint like torsade, however,

is so rare and so profound that we could, in fact, rely on passive surveillance, I'm hearing from FDA, maybe not. Maybe not even torsade would necessarily be reported with the level of capture that could make us confident that passive surveillance would be adequate.

DR. BORER: Before you go on, Alan, because you had a comment to make, I think I would just reemphasize something that Jerry suggested earlier in response to the concern about the 15 out of 20 million and 0 out of 20 million issue that you raised earlier, Tom.

The people who take sildenafil generally do that at night. An event that might occur would either be fatal or it wouldn't be perceived. The drug washes out rapidly and therefore it's unlikely that the event, if it were an arrhythmia, would be repeated in the morning when it would be more likely that someone would seek medical attention, and a fatal event would be more likely to be attributed to natural history than to anything else. I'm troubled by the fact that there's a discrepancy, but I think that there may be an explanation for it that is plausible beyond the fact that maybe sildenafil does nothing. So I'd just offer that for what it's worth.

DR. FLEMING: And I'm with you on that. I'm just saying my logical conclusion from what you're saying is that even an event such as torsade in passive

surveillance could go readily unrecognized.

DR. BORER: Exactly.

Alan?

DR. HIRSCH: Just to emphasize that point again, I think following Bev's comment and Dan's comment, what we have here in my perception is a real de-linking between what we understand about the biology of the drugs on QT interval, their impact in a population at risk, and the trigger for torsade. I've been bothered all day by not knowing how to interpret a healthy male or female population's events in a short-term trial with what would happen in real life.

Again, before we get to the major discussion, we're talking about drug classes that are widely used, the billions of prescriptions utilized, so that the effects are important.

I've been trying to think, Tom, about this surrogate issue. To me an effect on QTc that is brief in a young male volunteer group is sort of similar to looking at a 2- to 5-millimeter blood pressure increase in a young healthy volunteer and then extrapolating to patients with heart disease who might over years of use, over 2 or 4 years, have a sudden heart attack.

I just can't help but believe that the small phase I trials are critical. We had an advance in

technique of understanding how heart rate and concomitant conazole use might affect QT interval, but the inevitable next step, as you were sort of implying, to try to get an estimate of what that would be like in a somewhat disease concomitant drug, LVH or heart failure population because I don't trust the post-marketing surveillance.

Though I don't want to burden sponsors and FDA with large, 50,000-patient, 5-year trials, I think it's inevitable that the next step in our understanding of the biology is to take drugs with ambiguous signals and follow them in relevant populations so we can get some reasonable estimate of risk before these drugs are more widely used.

Thank you, Mr. Chairman.

DR. BORER: 50,000 patients in surveillance is different from 25,000 randomized to one drug and 25,000 to another.

DR. HIRSCH: I'm only 25 and naive, so I'm just estimating.

(Laughter.)

DR. BORER: Udho.

DR. THADANI: Thadani. I was on the FDA committee when sotalol was approved and we saw the noise there even in patients who were getting exposed during the trials. I think, Jeff, you were on bepridil too, and we were doing angina studies. The QT just got long. They got

very cardiac. So I think the whole relevance -- I'm not sure that any of us understand that QTc of 5, 10, 12 has any clinical relevance.

When your incidence rate is one in a million, how on earth can you detect it? A patient passes out. He has a syncope. You can't be sure it's not due to QT prolongation or torsade because a few hours later, his ECG could be totally normal. All of us have seen the ECG, even on sotalol, the patients don't keep on getting torsade. Sometimes they have it and sometimes they don't because of autonomic influences, potassium channels, or whatever.

So I think the only way to address the issue -- I realize that you have to study the population at risk, and the only way you can address it is by a larger database in the population at risk, not necessarily measuring very expensive technology or 20 Holters. You look at the event rates. I think the data they showed you on vardenafil in 2,000 and some patients, the event rate is .1 percent, the same on placebo, 800 patients. And the sildenafil database -- at least that gives you some reassurance. It doesn't answer the question whether you have torsade or not. I think it's absolutely impossible, when you've got a one in a million chance of getting it, to be absolutely sure whether it happened or not.

DR. HIRSCH: But to follow up on that, my point

would not be to be reassured by the sildenafil database alone, but look at precedent for all the other drugs that are coming down the pipeline where we may have differential mechanisms on both QT and torsadogenic foci.

DR. THADANI: I think you're absolutely right. That's why I said vardenafil has been used in patients who have ED. A lot of these patients are about the age of 50 or maybe a younger population as well, and a lot of them are on concomitant therapy. If you look at the database on concomitant therapy, they're on ACE inhibitors, beta blockers, et cetera. In them the incidence of serious adverse outcome -- I'm not talking about dizziness -- is no different.

We have even looked at patient with stable angina, put them on the treadmill, and produce ischemia. Small numbers, 30-40 patients are on 10 milligrams, and we actually saw improvement in ischemic ECG changes, and exercise tolerance doesn't get worse. That's a very small observation. And the same with 20 milligrams, but at least it reassures you during ischemia, which is very equivalent to sexual performance in ED patients, you're not producing a problem. But that doesn't say that if you did thousands or a hundred thousand patients, you won't see an incident. All you could do is the control studies.

I think we have been burnt again. Look at the

estrogen study. Even the observation studies produced totally conflicting results. We did angiograms and we said, well, it is cardioprotective, and you do a definitive study, it goes the wrong way. Today on the morning news, estrogen has been shown it doesn't even improve Alzheimer's.

So I think we have to be very careful when we're dredging data which is just dragged out by reporting. I may not report the incident. He might report it. So you know that physicians don't report all adverse events. So unless you've got mandated by the FDA and by each hospital every adverse event should be reported, we are going to under-estimate and not know the true results.

DR. BORER: Doug?

DR. THROCKMORTON: I just wanted to make a general observation. Interesting course, the last few minutes here.

I might agree that I don't know as much as I'd like to about the relationship between mean QT and risk. I've got no troubles with that. I think anybody that said they did probably I'd disagree with. But let's not behave as though we know nothing about that relationship or that, in fact, we have no post-marketing data that we can look to, or that we're uninformed at all as regards to the relationship between prolongation of QT with all its

vagaries and risk.

Drugs that prolong by large degrees have universally caused torsade. There's not an example I'm familiar with that I can't explain by other pharmacology, amiodarone or something like that, where a clean QT-prolonger didn't kill people. That's just an observation. You go over 30 or thereabouts, that's the world you'll be living in.

I don't know where you stop living in that world. Dan, you pointed that out or Alan or someone, that you wish you knew where the bottom end of that is. In a sense, that is the fundamental question that you're being asked today.

The agency, with Health Canada, with the regulators as a whole, has looked at the available data sets, for better or for worse, and identified a low threshold of around 5, looking at moxifloxacin with its good data and its lack of data that you might like, data from terfenadine, data for cisapride, and said, these drugs inform us as to the effects of small mean effects, prolongations in QT. Now, you can disagree with that or agree with that, but that is the mechanism. Those data are the way that lower bound was arrived at. It has to be. I agree with you. That has to almost be the way that you arrive at that because you can't otherwise make inferences

from mean changes.

I take your caution, but it's not as though we know nothing here.

DR. BORER: That's a wonderful introduction.

DR. BARBEY: Before we leave, though, could I just, Mr. Chair, ask?

DR. THROCKMORTON: I'd like to hear from Toby because he had a particular experience with post-marketing sort of detection with torsades that I think might be useful.

DR. BARBEY: Thank you, Doug.

The only thing I would have said is that, yes, pooh-pooh-ing the quality of post-marketing surveillance that we have -- it's true in a way, but if you think back to terfenadine, the index case was much better understood and put in perspective, thanks to finding other cases and is actually what has altered. So that's very likely why drug interaction and women are included in these trials in such phase I studies now. So as imperfect as our system is, it does influence some. It would be ideal.

But indeed, to understand what the threshold is -- and we haven't discussed that -- where you'll be worried, and maybe having women who get a little longer -- help you a little bit, worry you a little bit sooner. But unfortunately, these events are often rare enough in these

ambivalent drugs where mortality is not the valid endpoint. You can't just say we'll follow 100,000 people. So you actually need a fairly proactive and complex analysis of the cases.

I had a chance to review cisapride cases. That's what Doug is alluding to. Of the 500-plus cases reported as possible, there were probably 100-plus that were clearly torsade and others who were much more ambiguous. In that situation, the risk-benefit considerations played a big role because the drug was not beneficial enough to make that risk acceptable. A label of fatigue was the other thing that these findings suggested a strategy that you could use the drug more safely, but after 23 Dr. Doctor letters, nothing was happening.

So there are limitations, but there are some things that you can learn from that. It needs to be kept at a high standard, people who look at these events and understand them, not just say somebody died and that's it.

DR. LORELL: May I ask a question of information? In thinking about those two experiences, was there data for those two drugs such as what we've been discussing this morning in normal volunteers? Was there any data looking at Cmax and QT corrected by any method? In other words, is there any data at all in those two examples that a strategy, such as we've heard a lot about

this morning, might have given some kind of a signal either as general behavior or as presence of outliers?

DR. BARBEY: Doug probably knows. My impression is no. However, the blueprint that was used to understand the problem with terfenadine was then preemptively applied to other antihistamines of the same class and we like to think that that has worked pretty well.

DR. THROCKMORTON: Yes. Moxi would have that sort of combination I think that you're asking about. Terfenadine had it. I could obtain it maybe later on. Cisapride did not have any that I'm aware of.

DR. FLEMING: Just to follow on the same, it's such a key point. You've pointed out, Doug, that we do have some insight based on prior experiences of agents that, in fact, have induced serious safety concerns. Of course, part of the problem is we've heard this morning that there is a wide array of different ways that we might want to measure these adverse effects.

My question is you put forward a preliminary concept paper that we've been provided, in fact, we were provided by the sponsor, and it gave the kinds of categorizations that you were just referring to, Doug. If values are less than 5, then I think it was coded as no association with torsade; 5 to 10, clearly associated; 10

to 20, of concern; more than 20, substantial likelihood of being proarrhythmia. Yet, it's not clear to me. Is that based on Bazett? Is that based on Fridericia? If we're told to use different measures and different measures, in fact, give very different scales, how am I supposed to use it?

I like your logic, and that is let's go back to the wide array of agents that we know are proarrhythmic and that we know aren't, and then let's apply -- of course, I think the answer is we don't have the ability to do it -- all these various measures and find out what, in fact, is a highly sensitive and specific indicator. Is it above 500? Is it above 450? Is it a certain change on Bazett or on Fridericia or population? What do we know about that? And specifically your guidelines are based on what? Bazett?

DR. THROCKMORTON: Two parts. First off, we need to be clear about what the preliminary concept paper is, which is that it's not a guidance and it doesn't have any sort of regulatory standing. So you need to understand that it's a thing that we're working on. It's a thing that we're asking people to think about. A number of people in this room have helped craft that. Obviously, there have been some changes to it and some things that are in an ongoing discussion.

The document currently doesn't have the

categorization you're talking about, Tom. I think those are categories that come from a place other than the document. The document refers to a power to detect a 5-millisecond mean change. It says that you need to be able to exclude that you would miss that.

DR. FLEMING: I don't think so, Doug. I think it's much more specific than that. And you're correct. This shouldn't be interpreted, I guess, as a guidance. It's a preliminary concept paper.

But it says fairly clearly in wording that to date drugs that prolong the mean by an interval of 5 to 10 seconds have not been associated. Drugs that are 10 to 20, it's of concern, and drugs that are more than 20, there's a substantial increased likelihood. So there seems to be a very relevant attempt here to say in the context of our experience with previous agents, if we then look back to see what the changes were, what are the associations?

DR. THROCKMORTON: Yes. I just reviewed in rough outline the data set that we have. I think you could add ziprasadone to that maybe, as far as places where we have reasonably substantial post-marketing for drugs that prolong the QT in the range, something less than 20.

DR. FLEMING: And are these values Bazett or are they Fridericia or?

DR. THROCKMORTON: Historically -- cisapride,

for instance. All of the data we have are uncorrected because the original data -- we don't have the RR intervals on. Terfenadine I can't speak to. It would be Bazett's is my guess. Ziprasadone, a mixture of things I would guess, Fridericia a little bit.

I'm not sure that getting terribly hung up on the corrections is going to matter, again, in the context of the kinds of trials that we're talking about. If we're talking about a trial where you have a reference agent that you've included in a drug that you believe you understand the pharmacodynamics of well enough, the exact number that you get there may differ from trial to trial. We saw that this morning from the moxifloxacin. You might say that the correction matters less in that you're able to have an anchor in a sense to provide you a way to interpret those previous data.

Both of these sponsors did an admirable job, I think, of conducting a series of analyses, in addition to whatever analysis they chose as their primary. That gave reviewers, maybe you an ability to think about those effects in the context of the other drugs that you might have more clinical familiarity with, more understanding. So if Bazett's was something that you believe in your heart of hearts is really terrific, you could look to the Bazett's experience that's been reported from some of these

other agents. That's part of the reason why that series of corrections was suggested by the sponsors, and I think they did a good job of conducting those corrections.

DR. FLEMING: Well, the last brief comment. I think your point is well taken, that there is some insight that comes from a wealth of experience in pervious agents. But I'm persuaded by what I've heard this morning, that it matters on what scale QTc and QT have been measured, and one has to be aware of that when you look at these associations.

DR. BORER: Last comment from the audience because we're going to go on to the moment you've been waiting for, Dr. Throckmorton and Dr. Griebel, answering the questions.

DR. SHELL: Dr. Shell, Laboratory Industry Services.

There are a set of cisapride Holter data analyzed by bin methodology with placebo control that show a dose-response relationship between central tendency, mean QTc, and the dose-response curve.

DR. BORER: You're asking here, FDA, for our best judgment because clearly we don't have sufficient data, as you've heard, to draw firm conclusions, but we'll do our best.

This voting is a little bit complicated here.

This response is a little complicated. I want to tell everybody on the committee that if you look at the questions, where you see questions that have yeses and noes in them, we need individual votes for the record. That's number one.

Number two, if you want to give a reason for your vote, that would be good, but if the reason has been given already and you're 13th up, you don't have to repeat it all. Just say yes or no for the reasons already indicated.

Then we have to respect the conflicts issues with regard to who can vote. John and Dan, unfortunately, cannot vote on anything. Beverly can vote on alfuzosin, but not on Levitra. With all those caveats, we'll begin. So, Bev, when you do vote, please specify which drug you're voting about.

Number one, the alfuzosin and vardenafil studies evaluated the effects of a single dose on QT/QTc. Were the studies for alfuzosin, a drug that will be dosed daily, adequate to evaluate the drug's effect on QT? Yes or no, and a reason if you like. I will expect to hear 14 votes. I'm not sure that we actually will have that. Steve is gone. It's 14, okay.

Mike, why don't we begin with you?

DR. ARTMAN: My answer is yes. As the first

one, I guess the slate is clean so I can explain my answer. I think it's based upon the pretty comprehensive pharmacokinetic data that were presented both for conventional dosing and with super-maximal doses. So I think that the data were clear and solid, so I can vote yes.

DR. BORER: Blase?

DR. CARABELLO: Yes, I also vote yes. I thought that the data were convincing that steady state had been reached, and although the argument was raised that perhaps there was a difference between the steady state effects on drug concentration versus those on the QT, there was no data presented to suggest that that was the case. So I say yes.

DR. BORER: Toby?

DR. BARBEY: I say yes also based on the conglomerate of the data. I was, as a clinical pharmacologist, still disappointed that the study was only single-dose, but the data that are available override this regret that I have. So I would have preferred it to be in terms of metabolites, but I don't think it would have changed by vote, but I just regret it.

DR. BORER: Alan?

DR. HIRSCH: Sort of mimicking Toby's answer, yes, for this drug with the panoply of data offered. I

think in general for these classes of agents, multi-drug dosing would be superior.

DR. BORER: Tom?

DR. PICKERING: Yes, I agree with the last speaker. And I'm not sure how well the stability of the plasma levels reflects what's going on in the tissues with the long-term dosing.

DR. BORER: Paul?

DR. ARMSTRONG: Well-done studies, but for me, Mr. Chairman, once is not enough. So I vote no.

DR. BERNITSKY: I'm going to abstain on voting since I don't believe I was asked to be here as a cardiologist or from the perspective of cardiology.

DR. BORER: Beverly? Remember, we're only voting about alfuzosin.

DR. LORELL: Yes. For alfuzosin, my answer would be yes.

DR. BORER: Susanna?

DR. CUNNINGHAM: My answer would also be yes.

DR. BORER: JoAnn?

DR. LINDENFELD: Yes, but I also would have preferred to see a multiple-dosing study.

DR. BORER: I'll vote yes. I want to reemphasize Tom Pickering's point about the desirability, had they been available, of tissue levels, at least in an

experimental setting, because of the lack of information about temporal relationship of blood level and effect. And I understand the FDA concern about the AUC issue, and I think that's important. But nonetheless, the overarching impression is that this would be sufficient.

Tom?

DR. FLEMING: In a certain context, yes, I believe the studies are adequate to give us an assessment of what the average change in QT is.

In a very important sense, though, no, because the studies really are not adequate to get at outliers. It's really not adequate to understand what the effects are on QT in terms of changing by large amounts by 60 milliseconds or the frequency at which QTc values might be in the right-hand tail. I've become persuaded that that's a very important aspect of what we need to understand, and these studies were not, by design, powered to address those issues.

DR. BORER: Phil?

DR. HANNO: I would vote yes, with the caveat that this is a drug that will be used in women for several reasons, for pelvic floor dysfunction, elderly women who don't completely empty their bladder, and it doesn't look to me like the studies in women were done.

DR. BORER: Peter?

DR. KOWEY: First of all, I think that the QT interval is just a really rotten way of measuring repolarization.

(Laughter.)

DR. KOWEY: It is. It's a surrogate that nobody really likes very much. It doesn't really reflect what we really want to know.

There are really two ways to answer this. Tom's idea of having real outcomes data, and Beverly said the same thing. That's really, obviously, very, very important, very hard to do.

The other way is to have a better way of measuring repolarization. So, I don't know who it was that said earlier that we need better science. I think it was Jeff. I can't emphasize enough to people in the audience that although that this is clearly by us all voting yes, this becomes a way of going through the process of finding out about repolarization for new chemical entities, I don't want anybody to walk out of here thinking that we like this because I really don't like it very much. The biggest part of the problem here is that we just don't know how to measure the thing that we really want to know which is repolarization abnormality, repolarization reserve, individual susceptibility, all those things that scientists are still working on. So I would encourage people in the

audience not to take this as the door is getting shut. It's just opening I think.

So the answer, Jeff, is a long-winded yes.

DR. BORER: Thank you.

What's the number that we have? We did it.

Okay, now we'll go to the second part of this question where we should only have 13. Were the studies for vardenafil, a drug that will be dosed intermittently, adequate to evaluate the drug's effect on QT? Peter, why don't we start with you this time.

DR. KOWEY: I'm going to vote yes again because I think that that's appropriate.

I was a little disappointed that when the sponsor presented the information with single dose, that we didn't see the area under the curve data that the agency brought to us. I think that's a very important analysis because one of the big questions that we've wrestled with all day is whether Cmax really reflects the time or the way of looking at the worst case scenario in terms of what the drug is doing at membrane level, and area under the curve may be just as important. Obviously, there's a big difference between Cmax and area under the curve for those two analyses. I was a little disappointed that we didn't get that from the sponsor, but got it from the agency. Well, maybe I should be happy that that happened.

But in any case, despite that, I think that the study design was adequate and it did answer the question that it sought to answer. So I would answer yes.

DR. BORER: Phil?

DR. HANNO: I'll answer yes. I think it's so difficult to make a decision on any of this listening to all of the arguments just because the marker is so poorly characterized and we don't really know what we're aiming to get here or what it means. So I had a lot of trouble with that, but I would say, as far as we can do it, yes.

DR. BORER: Tom?

DR. FLEMING: Well, I think the response is the same as I gave for alfuzosin. The only thing that I would add is that in the vardenafil trial, I'm also struggling to know whether the answers that we're getting -- it's, I think, one of Beverly's earlier points -- in this population in which the study was conducted are relevant to the target population that we're going to be treating. I'm struggling as to how much that compromises the interpretability of this result.

DR. BORER: I will vote yes also, and I'd like to echo Peter's point, the several points that he made. But nonetheless, I think my overarching opinion is that we do know how this drug affects QT, for whatever that's worth.

JoAnn?

DR. LINDENFELD: I'll vote yes as well for the same reasons.

DR. BORER: Susanna?

DR. CUNNINGHAM: I'll vote yes, but I think being forced to answer yes/no for these questions is terribly simplistic and actually not appropriate.

DR. BORER: Gay?

DR. BERNITSKY: Again, I'm going to abstain on any cardiology issues.

DR. BORER: Paul?

DR. ARMSTRONG: In trying to be consistent, Mr. Chairman, I'm reminded that Oscar Wilde said that consistency was the last refuge of the unimaginative.

(Laughter.)

DR. ARMSTRONG: But I will say that if the question were in normal healthy volunteers who were male, I would say yes, but because it isn't, I'm continuing to vote no.

DR. BORER: Tom?

DR. PICKERING: Yes.

DR. BORER: Alan?

DR. HIRSCH: Yes. I'm going to praise both sponsors for using adequate but different techniques to assess effects on QTc. Relevant populations should always

be studied.

DR. BORER: Toby?

DR. BARBEY: Like before, I will say yes, but as a clinical pharmacologist, I'm disappointed that there was not a higher dose tested in a drug interaction study. Only the 5 milligram was combined with ritonavir, and even if the label initially will sort of address this issue, I think that issue needs to be explored further, how it should be done. But with the data presented, I would say yes, but I would like that.

DR. BORER: Blase?

DR. CARABELLO: Yes.

DR. BORER: Mike?

DR. ARTMAN: Yes.

DR. BORER: We've made it through the first question. We'll move faster as we go along.

Number 2, the patients enrolled in these studies were healthy male volunteers -- and I think we've begun to discuss this -- mean age 27, et cetera, with normal electrolytes and baseline cardiac function, which I assume means that they had normal cardiac function at baseline. Was the effect of alfuzosin on QT for the population intended for actual treatment adequately studied?

We've heard some comments about this already,

but I think we need to hear at least a summary of them again. Let's begin with Mike.

DR. ARTMAN: Yes, this is very difficult because, as Doug mentioned, the question was, do these drugs affect repolarization, and the FDA said the way to determine that is to take a small group of young, healthy male volunteers and see if the drugs affect repolarization. But that's clearly not the population that's going to receive these drugs. So I'm not going to reiterate all the things that have been said by the smarter people here than I, so I just have to vote no.

DR. BORER: Blase?

DR. CARABELLO: And, of course, that puts me at a disadvantage because everybody is smarter than I am.

(Laughter.)

DR. CARABELLO: But I would vote no with the caveat of so what.

(Laughter.)

DR. CARABELLO: Surely -- what everyone said -- we would like to know what happens to the poor guy that both has an enlarged prostate and erectile dysfunction because he's on a diuretic that's reduced his potassium to 2. What happens, when he takes both of these drugs, to his QT? We're not going to know that unless we have some very large trial that encompasses everything.

On the other hand, I believe that the studies that were done have raised the bar. I suspect we know more about the QT interval in these folks than any other drug that we've looked at. And the data suggests that the fact that even though it was tested in healthy people, that the small changes in QT that occurred there are likely to be replicated in the study population.

So, yes, we didn't study the study population in question, but I'm not sure that it's a relevant question.

DR. BORER: Toby?

DR. BARBEY: No, but I don't believe it's a grave concern.

DR. BORER: Alan?

DR. HIRSCH: No. I still believe that other dysrhythmias, including torsade de pointes, probably are more common, not just with structural heart disease, which is not relevant in this population, but with other factors we yet biologically don't understand.

DR. BORER: Tom?

DR. PICKERING: No, because this drug is one that's going to be used almost exclusively in people older than the ones studied.

DR. BORER: Paul?

DR. ARMSTRONG: No.

DR. BORER: Gay?

DR. BERNITSKY: Even to me it appears that we didn't study it in the population that's going to receive it.

DR. BORER: Beverly?

DR. LORELL: No, I don't think it was adequately studied in the target population.

DR. BORER: Susanna?

DR. CUNNINGHAM: No.

DR. BORER: JoAnn?

DR. LINDENFELD: No, I don't think so. And also, even though these drugs were intended for men, they'll be used in women, and this will be used in women, and it would be nice to have some data there.

I'm not quite so convinced as everyone else that it doesn't matter. I just would like to see some data that it doesn't matter, that this population reflects what we'll see in a population on antihypertensive drugs and diuretics. And if we just had a body of data that showed me that, I'd be much more confident about it.

DR. BORER: I'm not sure how to answer this question. I guess literally I'll say no, but let me explain why because I agree with what's been said several times here.

Was the effect of alfuzosin on QT for the

population intended for actual treatment adequately studied? The answer is I don't know because we didn't really look at QT in that population, so I can't say rigorously that what we saw in the normal volunteers mirrors what we would have seen in the patients and that there isn't some unusual drug-disease interaction.

Having said that, I think that just as Blase said and just as Toby said, I'm not sure that that really matters. I'm convinced by Dan's points about the value of looking at the high dose in the optimal situation where you're looking at relatively normal membrane function to infer whether it's likely that there will be overwhelming drug-disease interactions or PD interactions between drugs as opposed to PK interactions.

So maybe I would have requested that the question be worded a little bit differently, but I think you get the idea. It's either yes or no, but it doesn't much matter because we have, as Blase said, more information here than probably we've ever had before, and that puts us in a better position to try to make a best guess about what the likely outcome of using the drug will be than we would have been before.

So you can count that as a yes or a no.

(Laughter.)

DR. BORER: Tom?

DR. FLEMING: Well, in the absence of having direct evidence to show that these results in young male volunteers can be extrapolated to the target population, I have to say no.

DR. BORER: Phil?

DR. HANNO: No.

DR. BORER: Peter?

DR. KOWEY: No. The answer is an unequivocal no. You can't tell.

But I do care and I wish I knew, so I can't be quite as glib as to say, so what, Blase. I understand what you said, but my feeling is that you can't do that study. It's too difficult. It's almost logistically impossible to do the study in the intended population.

Having no information in that population and knowing what I know about what these patients usually get in terms of drugs and electrolyte abnormalities, the committee needs to know very clearly that these drugs will cause torsade in somebody some day. I don't think there's any question in my mind about that. I'm not grappling with "if yes or no." I'm grappling with how many, and I can't answer the question.

So the answer is no, I can't tell the QT effect, but even worse than that, I don't know what the torsade risk really is, but I know it's not zero judging

from what we know about QT-prolonging drugs when you put them into patients that are sick. So it's a concern to me and it makes me uncomfortable, but that's how I would answer it.

DR. BORER: Well, while you're answering, why don't you go on to the effect of vardenafil? Was the effect of vardenafil on QT for the population intended for actual treatment adequately studied?

DR. KOWEY: No. Again, the answer is no and my concern is the same.

DR. BORER: Phil?

DR. HANNO: I agree. No, and for the same reasons.

DR. BORER: Tom?

DR. FLEMING: No, for the same reasons.

DR. BORER: My answer would be the same as before as well, although my answer was a little more complicated.

Since Peter moved beyond QT to the meat of the issue, which is what QT is supposed to be a surrogate for, I have to say that I'm not unimpressed by the post-marketing data that were presented. That gives me some degree of comfort and makes me think that I'm not really totally off base by suggesting that it may not matter so much that the effects on QT weren't looked at specifically

in the population that would be expected to be at risk.

JoAnn?

DR. LINDENFELD: No, for the same reasons.

DR. BORER: Susanna?

DR. CUNNINGHAM: No.

DR. BERNITSKY: No. I would also like to add, though, that in hearing the data both on sildenafil and vardenafil, as a clinician I feel much more comfortable that these are safe drugs in the context that we use them. I think the context that we use them is very different than moxifloxacin with a patient in the ICU receiving an IV antibiotic. They appeared to be pretty safe drugs.

DR. BORER: Paul?

DR. ARMSTRONG: No, and more exposure in women with this one than the previous one.

DR. BORER: Tom?

DR. PICKERING: I would say yes here. My previous complaint was about the age. I think it would have been incredibly complicated to try and do it in people with all sorts of medical conditions and all sorts of other drugs for an initial phase I study.

DR. BORER: Alan?

DR. HIRSCH: No.

DR. BARBEY: I would say a softer no because everybody who watches the evening news gets encouraged to

use one of these drugs. So there will be people that age without disease who will take the drug.

DR. BORER: Blase?

DR. CARABELLO: No.

And I'm sorry if my "so what" sounded cavalier. It's not that I don't care. It's just I know I can't have the data as none exists.

DR. BORER: Mike?

DR. ARTMAN: No.

DR. BORER: Doug, those answers were a little convoluted relative to the way the question was worded. Did you get the idea? Is this good enough since we all gave reasons?

DR. THROCKMORTON: Yes, I think I heard what you had to say.

DR. BORER: Let's go on to number 3. Is it appropriate to use pooled baseline and placebo exposure data for calculating linear and nonlinear regression correction formulae? And we'll need to explain that.

I'm going to start at the middle of the table here. Tom, will you give the initial response to that, please?

DR. FLEMING: I was hoping to follow the chair on this.

(Laughter.)

DR. FLEMING: I'm assuming this question is specific to the computation of the individual adjustment. We have the Bazett's adjustment, Fridericia, the population, and the individual. Is this asked in the context of that individual calculation?

I clearly understand that our goal here, of course, is to understand how the agent's effects on QT are giving us the best clues about what meaningful safety risks would be and that we have to adjust based on the heart rate changes. What I struggle with is I don't know the truth. And I think we've heard a lot of discussion here today that we don't know what the truth is for the way you're supposed to be adjusting for the dual effect on heart rate changes and QT in order to get at the best measure of QTc. And because I don't know the truth, I can't answer this question as to what is in fact the best way.

As we've heard earlier, if one is looking for constancy of these slopes and you're looking to use a general formula, a power that's the same for all patients, that power .33 rather than .5, the Fridericia rather than the Bazett's, does seem to give better performance, if that in fact is what the truth should be.

If the idea is to do even better than that by having a patient-specific power, which is what I see this is all about, at a certain level, that's appealing. Maybe

the power is different for every given patient. But the data that I'm going to use that's going to capture more than just the change in heart rate could readily be noise as much as it could be signal. So philosophically I'm not saying this individual approach is worse than Fridericia, but I haven't heard enough evidence here today to convince me that it's better.

And given that I'm not persuaded that it's better, it's hard to get into the fine-tuned details about whether, when I'm doing it, I should use only the individual's baseline data or use the placebo. I think I understand the issue. The individual's baseline data, as Dan was talking about earlier, may not be sufficiently voluminous to be able to set what that power parameter should be, so you want to use the placebo but now you're extrapolating to a broader population that may not be specific to that individual.

So I think I understand the issues here, and yet it doesn't leave me in a position to answer the question because of a fundamental inability of knowing what the truth is. What is the true way that you should adjust given the treatment is dually affecting both heart rate and QT to adjust that nature of the change in heart rate to tell me what the meaningful residual change on QT is. And until I know that, I couldn't answer the question.

DR. BORER: Well, okay. I'm to the left of you. I agree with everything Tom said, but.

(Laughter.)

DR. BORER: I think the way I'm interpreting this question is that if you're going to use an adjustment, is it reasonable to pool the baseline data in the individual patients and the data that were obtained on placebo perhaps by a crossover design in the individual patients, the way you did it or perhaps some other way? I'm not sure what other way you could do it. And it seems to me that if you believe that an adjustment is a reasonable thing -- and intuitively I do -- then I would try to make the basis of the adjustment as representative as I could, and I would pool the baseline and the placebo. So I think that that is a reasonable thing to do if you're going to make the adjustment.

I, of course, agree with Tom. I don't know what the right thing to do is. Which technique for defining QTc is best? And we'll get to some of that, I think, as we go along, so I'm not going to go beyond that comment. But I would favor pooling the baseline and placebo data. Am I responding to what you're asking here?

DR. GRIEBEL: Yes.

DR. BORER: Okay.

Let's go around the table. You don't have to

give an additional opinion if it doesn't differ from what you've heard. JoAnn?

DR. LINDENFELD: I agree with what you just said. It just seems to me that pooling the data is a very reasonable thing to do, knowing that we still don't know the best way. I agree.

DR. BORER: Susanna?

DR. CUNNINGHAM: I don't know, so I'll abstain.

DR. BORER: Beverly, this is not drug-specific. You may vote.

DR. LORELL: Yes, I will abstain too. I don't think I have sufficient expertise statistically to answer this question.

DR. BORER: Sorry, you don't have to vote.

Let me just ask. Does anybody else have an opinion that differs from what you've heard?

(No response.)

DR. BORER: We're on number 4.

DR. ARTMAN: Jeff? Jeff, over here. Maybe not an opinion, but I want to make sure I understand what you're asking. Are you asking in an individual who may have had multiple ECGs at baseline and multiple ECGs under placebo treatment, is it acceptable to pool that individual's data into -- okay. So I'm not sure others were answering that question, it didn't sound like from the

discussion.

DR. BORER: That was the question I was answering.

Tom.

DR. PICKERING: The question was actually is it appropriate, not is it best, and I would say it is appropriate because I think at this stage we need to look at all possible methods and encourage everybody to do different analyses. So I would say yes.

DR. BARBEY: I'm sorry. With the caveat that if the subject is perfectly still in bed, there will be very few heart rates to work with, which sort of defeats the purpose of this. If you start to move around, then you don't know the plasticity of all that. So it's not easy, but pooling to get a broader range for each individual would seem appropriate.

DR. BORER: Paul?

DR. ARMSTRONG: Just picking up on what Mike said, then if we're talking about the baseline from those who would be exposed to drug, plus the multiple observations from placebo, as long as there's not a time-dependent covariant interaction in the placebo that's demonstrated such that the data in the placebo over multiple points is homogeneous, then I'm fine. But that would be the caveat.

DR. ARTMAN: You'd like to be able to show that if you do a Holter bin method, that the baseline line lines up with the placebo line. And if it does, then you have no placebo effect and it's perfectly appropriate to pool those data, but if they're separate, then it's not appropriate.

DR. BORER: Number 4. Because of uncertainty about an optimal correction methodology for determining QTc, it is likely that sponsors will submit the results of multiple correction methodologies. A, should trials specify and adhere to a primary endpoint, i.e., primary correction methodology.

This is the issue that Joel raised in his discussion and I guess we need to get to it. Although it is sort of a statistical question, it's more than a statistical question so I will not begin with Tom this time. Let's go to Peter. Again, everybody does not need to respond to this, but if you have something that you want to contribute, please feel free. Peter?

DR. KOWEY: Well, this sort of gets back to something that Tom said a couple of minutes ago, which is that if you don't know what the real truth is, and you don't know a priori what method is the best, then I always enjoy looking at data, like these tables that we're going to be looking at in a minute, where you get to see the data broken out by different formulae.

It is obviously a very data-driven decision. I don't think that anybody can really anticipate what's going to happen, for example, with the heart rate in any given trial before you do the trial.

So I really don't like the idea of a primary prespecified way of doing it. I really like the idea of a menu of correction formulae to examine after the study is finished. So I guess my answer is no to A.

DR. BORER: Tom, since you are our statistician and this strikes at the heart of statistical purity, let me ask you if you have an opinion here that differs from Peter's.

DR. FLEMING: I don't know about the "differs," but I have an opinion.

DR. BORER: Please give us your opinion.

DR. FLEMING: I think it's very important in clinical trials to set up studies in ways that allow for confirmatory analyses and exploratory analyses and to distinguish between the two, and it's in this context that levels of statistical significance, p values, et cetera are really interpretable. So if in fact we've designed our trial properly, and if in fact we're in a setting in which we can rationally determine in advance what is the most clinically relevant endpoint, the primary endpoint should be chosen to simultaneously satisfy the criteria of what's

clinically most relevant, what's going to be sensitive to the treatment effect, if it's real, and what's measurable and interpretable. Under those criteria, there may not be a unique answer, but we should strive to achieve, as best we can, that endpoint that satisfies those criteria.

And if we're going to rely on statistics, then those statistics are most formally interpretable in the context of the prespecified primary analysis of that prespecified endpoint. So if we're going to rely on p values and strength of evidence and all these kinds of issues, then it is important to go through the care in advance to specify a primary endpoint.

Even in that context, though, of course, we definitely always want to do exploratory analyses to get as broad a view as possible about benefit to risk, about primary and secondary endpoints, about safety issues, about external results, et cetera. All of that is important. The interpretation of significance levels and all, though, is much more problematic in those secondary endpoints.

Having said that, in a setting in which it's not clear what in fact should be the essence of the signal we're trying to measure here, i.e., where you don't have a clinical endpoint, where you have a surrogate, and worse yet, where there's a lot of uncertainty about what that right surrogate should be, then I understand why in these

trials the sponsor and the FDA, in working together, were not able to achieve what I would call the ideal I would be asking for, which is a very clear specification up front of what that best endpoint would be. In that context, and even more so, it's going to force us into the exploratory mode, but then it still leaves us in a setting where we have to interpret all of these results with much more caution. Data-driven hypotheses can give conclusions that look very impressive, but in fact they're not nearly as impressive if they are, in fact, suggested by the data rather than prespecified and confirmed by the analysis.

So what I would want to say is, yes, in general, we absolutely should be specifying and adhering to a primary endpoint and requiring and adhering to a formal statistical plan where we in fact then, to the extent that we care about significance levels and all, are going to be in a position to adjust our sense of strength of evidence. But here we have a circumstance, as we've spent the whole day laying out, making it very clear that it's extraordinarily difficult to know whether the Fridericia method, which was specified in the second setting, was in fact the best measure.

So I'm very understanding for why, in this setting in particular, we're giving less focus on the primary compared to the secondaries, but in fact, that's

not a carte blanche or a freebie here. My own sense is all of these analyses are leaving me at considerable uncertainty. I agree, Doug, they're giving us clues, but they're not the level of clues that I would typically have wanted to have seen, and I'm not saying that critically because the sponsor and FDA haven't given this thought. These are inherently extremely difficult situations to understand what is in fact the best measure that reliably represents or reasonably reliably represents an unacceptable safety risk.

DR. THROCKMORTON: I guess the other distinction you might make, Tom, is that when we're talking to sponsors about clinical outcome trials, if they propose an endpoint that we know to be not an endpoint that's valuable to us -- I don't know -- serum porcelain levels or something -- we say, no, that's not a primary endpoint we can understand in a clinical consequence as beneficial. Here we're not in a place where we're able to do that. I think we're maybe saying the same thing. Is that about it?

DR. FLEMING: This may be what you're saying. I want to emphasize the point. As much as I believe strongly that to use statistical inference in an interpretable way, it should be in a confirmatory sense. If one elevates to a primary endpoint a measure that, as time goes on, becomes increasingly clearly inadequate in

capturing the essence, then I think logic has to come forward and dominate our thinking. We can't adhere to a prespecified primary endpoint if, at the end of the trial, we have an enhanced understanding that would tell us this really was a poor choice.

Now, as the FDA guidance document on monitoring committees, released in November of 2001, clearly said, one of the great things about keeping results confidential is that that allows the sponsor and the FDA throughout the course of the conduct of the trial to refine their thinking about what the endpoint should be, and so long as that refinement is separate from the insights emerging in that trial, you are in a position where you still can view a refined analysis plan or refined analysis endpoint as being confirmatory.

But the essence of what I hear you saying that I would agree with is if there is a strong objection to the previously specified primary endpoint as capturing the essence, then it's certainly appropriate for us to give it less weight than we otherwise would.

DR. BORER: I think Tom has said it all, and I don't think that Peter and Tom are in disagreement here at all. I cannot restate all that as eloquently as Tom did, but let me just make a short comment.

I think that in a situation like this where the

value of the surrogate in a quantitative sense is not known -- it isn't a qualitative sense, as you pointed out, Doug, but in a quantitative sense it's not really known, and the best way to measure the surrogate hasn't been determined yet, when you come to us, when the FDA comes to a panel like this asking these questions, you're asking for our best judgment which is, in essence, a synthesis of our intuitions, our opinions, some data. And that's what we're going to give you. By its very nature, the development program that provided these data was, as Tom said, exploratory, and it has to be because the answer is not known. The best method is not known.

So given that, although I think it's always appropriate to provide a formal analysis plan a priori and to adhere to it, I think in a situation like this, it's mandatory that multiple methodologies should be evaluated. And at the end of the day, a group like this and more importantly the FDA is going to make its best judgment from what it has seen, and it is to be hoped that when enough data are gathered of this sort, with all the methodologies being looked at and all the outcomes being evaluated, it will be possible, at some point, to define what the best predictor is and to apply that in the future.

So I've just hit part A and part B, I think. I think we're all in agreement so far.

Does anyone else, Phil, JoAnn, anyone, have any other comments you want to make that would add to this? Beverly?

DR. LORELL: I have just a short comment. I agree with everything that's been said. I think this still in a transition phase and that it would be foolhardy to have a single, primary, rigid measure.

I would put forward as a suggestion, given the I think extraordinary, careful collection of data that we've seen from both sponsors this morning, that this might serve as a comparator template over the next year, two years, three years, as we learn more, to say we would like to see this menu showing data with Bazett's, Fridericia, and individual approach, and perhaps if available, the Holter approach.

And I would suggest there are two more things that might be included so that a data set collects. One is using moxifloxacin as a positive control. You have a large database to work with.

And I would suggest a third component. We didn't talk very much about it in Jeremy Ruskin's presentation this morning, but I think his slide 72 was sort of a wake-upper for me, and that was the slide that actually showed the QTc prolongation with terfenadine and ketoconazole. That actually provides some kind of a

signal. We don't know how reproducible it is, but we saw that that intervention caused a QTc prolongation of about 80 milliseconds.

So it may be, while everyone is learning what this means and how to do it, that it would be useful to suggest to future sponsors to include not only this menu, to include a standard positive control, and to include metabolic inhibition, if appropriate for that drug's metabolism, with ketoconazole.

DR. BORER: Blase?

DR. CARABELLO: yes, I would agree that certainly until we have a gold standard, we need to use all the standards.

I just want to point out that both the sponsors and we are getting off pretty lightly here today because all of the data are fairly concordant. We'd be in a hell of a mess if particularly Bazett's, which hangs out there, if there had been wide changes in heart rate, said one thing while the other data said something else. We'd be in a real quandary about knowing what to do.

DR. BORER: That's true.

Any other comments?

DR. ARTMAN: Jeff?

DR. BORER: Mike?

DR. ARTMAN: Yes, I just would suggest that you

encourage the sponsors to continue to use the Holter bin method. I think that does represent an innovative, a newer approach that I think is likely to turn out to be quite valuable.

The other point is I think if they come to you and they say we're going to use Bazett's correction as our primary endpoint, I think you should discourage that. I think that's the one that doesn't fit very well.

DR. THROCKMORTON: So that would be a bad primary endpoint?

DR. ARTMAN: That would be a bad primary.

DR. BORER: C here is, explain how the totality of the data obtained from a comprehensive panel of these methodologies should be evaluated to assure valid conclusions. I think we have discussed that already. So we won't formally respond to that question.

We'll go on to number 5. The table below summarizes the mean change of QT from baseline, both uncorrected and corrected, of alfuzosin 10 and 40 milligrams and moxifloxacin relative to placebo, as observed in study PDY 5105.

Here's a voter again. Are the results of any one correction methodology more valid than the others? I think we dealt with that.

So let's go to B. Do these data demonstrate a

clinically relevant QT prolongation associated with alfuzosin? Okay, this is an important one and we should vote.

Mike, why don't we start there. That's B, do these data demonstrate a clinically relevant QT prolongation associated with alfuzosin. Yes or no?

DR. ARTMAN: My answer is no.

DR. BORER: Do you want to explain that or is that pretty obvious?

DR. ARTMAN: No, I don't want to explain it.

(Laughter.)

DR. BORER: Okay. Blase.

DR. CARABELLO: My answer is no one could possibly know, but I think the answer is no. I'm certainly not persuaded that there has been a clinically significant prolongation of the QT interval.

DR. BORER: Toby?

DR. BARBEY: No, and I don't have any great further insight on that.

DR. BORER: Alan?

DR. HIRSCH: No, but with no insights, I have an opinion.

(Laughter.)

DR. HIRSCH: Going back to Doug's comment --

DR. THROCKMORTON: Which we value.

DR. HIRSCH: We have just a small number of drugs where we can really calibrate a QT change with outcomes. So I think the answer is no, but until the database is enlarged, I think that range of small, medium, and incredibly long QT intervals needs to be defined. So I don't know how to define clinically relevant.

DR. THROCKMORTON: Alan, what I heard from Jeff actually helped me understand your answer to question 2 a bit. What I heard was unhappiness with the absence of quantitative information. There's a qualitative relationship here that some of you were unhappy with. It's that qualitative nature of it. Is that fair?

DR. HIRSCH: You can't define clinical relevance on a QTc alone by any of the methods. It will be outcome on human clinical events. We don't have that correlation very well defined. We have just a very few data points in our drug approval data set.

DR. BORER: Tom?

DR. PICKERING: No, and there is the post-marketing surveillance data.

DR. BORER: Paul?

DR. ARMSTRONG: No.

DR. BERNITSKY: Abstain.

DR. BORER: Beverly.

DR. LORELL: No.

DR. BORER: Susanna?

DR. CUNNINGHAM: No. Probably not. How can you say no for sure?

DR. BORER: Okay, that's a probably not.

JoAnn?

DR. LINDENFELD: I would say no, and I think of some of the data we've seen today, including the post-marketing data, helps me say that this moves me more toward no than I was earlier today.

DR. BORER: I say no also. I'd like to add one point here, though. I think that the data in the table are useful. This has been said before, but I think the fact that there are two comparators to the clinically applicable dose, one being a relatively high dose, which doesn't show all that much, it seems to me, quantitatively, for whatever that may be worth, but whatever it shows seems to be less impressive than the results from the active control.

Given the fact that the active control sounds as if it is not associated with some overwhelming frequency of horrible events makes me feel more secure against the backdrop of what we know from the totality of associations that have been made between QTc and outcomes in other development programs, makes me feel reasonably assured that a no is a reasonable answer, although of course, I don't have rigorous data to support that statement.

DR. THROCKMORTON: Jeff, could I ask if that's a part of other people's thinking as well; that is, that the numbers were, in a sense, less than the active control? Was that part of the reassurance that people drew? Just in a general sense. I'm not asking for a vote necessarily. Was that part of the thinking that led to some of the votes previously, just a nodding-head thing.

DR. BORER: Don't talk all at once, or in fact, you can talk all at once in this case.

DR. ARTMAN: I'm answering and nodding my head. I think it was reassuring and it was very helpful to have that active control.

DR. CARABELLO: Yes, the fact that the active control had at least some signal, albeit small, was very helpful.

DR. HIRSCH: Good job having active control.

DR. BORER: Tom?

DR. PICKERING: Yes, I agree.

DR. BORER: The other Tom, for an answer, a yes or a no.

DR. FLEMING: A comment first.

(Laughter.)

DR. FLEMING: The easy part of it is, is there QT prolongation? Yes, there is. The important part of this is, is it clinically relevant? I do want us to take a

moment to think through this because this is, I think the critical issue that we have to address.

The way I would normally think about addressing this is in benefit to risk, and we haven't had a lot of discussion about that today. Here we're talking about BPH. What is the benefit? What is the magnitude of benefit? Understanding first what that magnitude of benefit would be, hopefully, would then guide us as to what would be an acceptable level of risk in the context of that benefit.

So when I see an agent that induces a QT prolongation, my answer as to whether or not this is a clinically relevant QT prolongation has to take into account the magnitude of benefit that I know this agent provides and whether this risk -- in other words, I'm saying a one in a million chance is clinically relevant in one setting but not in other settings in a manner that depends on what benefit is. So in answering this question, I would ask that there be careful thought as to what is the known benefit of this agent in this setting, and in that context, what would be an acceptable level of risk according to which endpoints and of what magnitude and frequency would be acceptable.

Then the next question is now how do I assess whether or not I have that increase in risk. Obviously, I'm using a surrogate. What is the best surrogate? How do

I know it's the best surrogate?

And if we're using historical evidence, based on a lot of experiences of other agents that use QT, back to a point I was saying earlier -- and that's relevant here to look at that, but if it's all based on Bazett's, then I have to translate it, if that isn't my current view of what the best measure is, to be able to assess what is in fact the safety risk.

So my own assessment of this says, even though we've had a very informative discussion today, there's a lot of answers to questions that I just mentioned that I don't have that technically speaking I believe I should have to answer this question.

Having said that, my inclination is to say this is a sufficiently modest increase that in a way that I'm inadequately informed by not knowing the answers to a lot of these other questions, I'm inclined to think that this is a not a clinically relevant prolongation, but with an awful lot of uncertainty about those issues that I don't know answers to.

DR. BORER: Phil, in giving your answer, perhaps you can add two or three sentences about the benefits of providing alpha blockade in patients who have prostatic hypertrophy, because they are important.

DR. HANNO: I think the issue here is these are

very useful drugs. For both of these drugs we're looking at today, there are already similar drugs on the market. So in a way, these are me-too drugs that are coming out.

I think Tom's questions are exactly right, but there's no way to answer whether these drugs have a lower risk from this or an equivalent risk to what's already out there or a higher risk. Without knowing the comparative risk, if we don't move ahead with these drugs, it's not like we're preventing people from taking these drugs that are already on the market and having a risk which is uncharacterized.

So based on the data here, I would say, no, there is no increased significant risk from everything that I've heard and read. But I really don't think we know whether we're helping people or increasing the risk or lessening the risk because we don't know what the risk is of the similar drugs that are already out there.

DR. BORER: Forgetting for a moment about the relative benefits and risks of the different drugs in this class that might be used in patients with BPH, what are the benefits you might expect from drugs like this? Prevention of surgery that might otherwise be done with all its attendant risks.

DR. HANNO: I think there's tremendous benefit in terms of alleviating symptoms of BPH, actually

preventing the need for surgery, postponing the need for surgery. The improvement in the quality of life with these drugs has been very dramatic and has really changed how we approach outlet obstruction in the last 15 years. So I think this drug class is a very important class of drugs, and there's tremendous benefit.

DR. BORER: Thank you.

Now, what was your answer to the question? Yes or no.

DR. HANNO: No.

DR. BORER: No, okay.

Peter?

DR. KOWEY: No. The answer is no, and I'm also persuaded a good deal by the post-marketing information we have about this particular drug.

DR. BORER: Since nobody answered yes, we don't have to explain how the risk might be managed.

Six. The table below summarizes the mean change of QT from baseline, both uncorrected and corrected, of vardenafil 10 and 80 and moxifloxacin relative to placebo, as observed in study 10929. Are the results observed from any one correction methodology more valid than the others? Again, I think we've sort of dealt with the fact that we don't know.

Mike made a comment earlier and I see there is

no other place for us to talk about this, about the list mode acquisition method, the Holter bin method, that was set forward. Mike made a statement. I'd like to add a little bit to it, and if anybody disagrees, then say so.

You asked if any one correction methodology is more valid than the others, and of course we don't know.

What's called the Holter bin method, however, as Ed Pritchett said earlier, appears very attractive. It seems like a very logical way to approach this problem and to try to determine what the correction really should be or what the QT really is. Then, of course, we have to find out what that means, but as a way of determining what the fundamental characteristic of the QT is, subject to the limitations that Tom said earlier, this is a very creative and innovative and interesting approach that sounds intuitively like it should be good.

However, we have no information about the results of that analysis relates to any outcome because this is the first time it's ever been used.

So I would emphasize what Mike said earlier. I think that in future studies where you suggest to sponsors that multiple methodologies should be employed, because we really don't know which one is best or how to relate any of them to outcome, that the sponsors should be encouraged to apply this new method, together with all the others,

because it does seem intuitively to be good.

Blase?

DR. CARABELLO: Yes, just to amplify on Toby's comment. If the Holter bin method could be applied with a patient up and active -- that is to say, if motion artifact doesn't preclude its usefulness in measuring QT when the patient is moving -- that would seem to me to be the goldest of all standards.

DR. BORER: Having said those things, I think it's important at this point to reemphasize what JoAnn said earlier, which is that if this method is going to be applied, particularly in the way that Blase is suggesting that Toby had suggested, with people moving around, that it is important to be certain that we have some assessment of the impact of all that movement on the evaluability of the complexes and what it may mean in terms of distortion of results if a lot of complexes can't be evaluated. So that still has to be worked out.

Does anybody else have any comments about that? Susanna?

DR. CUNNINGHAM: I have a question. All this discussion is all around QT intervals, and I wonder if anyone out there is looking at anything better or different. We're all fixated on it because we can measure it, but just because we can measure it doesn't make it the

right thing.

DR. BORER: Yes, I don't think that people are fixated on it because they can measure it, but because empirically marked abnormalities in QT have been associated with bad things. I think that there is research ongoing that does deal with perhaps developing other ways to look both in in vitro models and elsewhere. We don't have to go into that in detail here I guess, but I think that that's the construct. It's not that it's easy to measure, but that somebody measured it and it correlates with something, qualitatively at least.

DR. CUNNINGHAM: I think that it's not just that it's easy to measure, but I'm still not convinced that it's necessarily the right measure.

DR. BORER: Not the best maybe. That's for sure.

Tom?

DR. PICKERING: Yes, just a comment about the Holter bin. I also think it's a promising method. I think for the initial studies, though, I would favor the approach that was used with the subjects supine because once you have people moving about, you're going to have huge standardization problems, particularly when you're trying to compare the active drug and placebo because the conditions are almost certainly not going to be the same.

DR. THROCKMORTON: Tom, this study used a single lead. Would that be a recommendation that you'd use?

DR. PICKERING: I'm not the one to answer that.

DR. BORER: Paul?

DR. ARMSTRONG: Certainly 3-lead would be welcome, and the choice of those leads might be ascertained based on surveillance of the 12-lead electrocardiogram which would be a standard approach in some other monitoring studies that we've done.

DR. BORER: JoAnn?

DR. LINDENFELD: I was going to say I think that these studies were done in the 12-hour daytime period, the Holter studies, and the QT interval varies. There's a big circadian variation, more so I think in women than men. Just as you explore that technology, I wonder if we don't need to think about when those recordings need to be done. And if we just look at baseline QT as a measure without a correction, that would be very different in the nighttime than during the day. So I can't make a specific comment on that, but I think it's just something that needs to be thought about.

DR. BORER: Let's go on to B. Do these data demonstrate a clinically relevant QT prolongation associated with vardenafil?

And for this one, we need a vote. Peter, let's start with you.

DR. KOWEY: Well, we could have the same discussion, but I think the answer is probably no. The answer is no.

DR. BORER: Phil?

DR. HANNO: I would say it's very small, but yes.

DR. BORER: That it's a clinically relevant QT prolongation. If the answer is yes, how might this risk be managed?

DR. HANNO: I don't think I could answer that.

DR. BORER: Tom?

DR. THROCKMORTON: Sorry. Could you go just a little bit further about what it is about this that makes you consider it -- I'm just interested is all.

DR. HANNO: It's very similar to the moxifloxacin numbers, and apparently there is a very minor but clinically relevant increase in that. It's higher than the other drug. It's in the 5 to 10 range. That's all.

DR. THROCKMORTON: So it is that it's closer to the moxifloxacin outcome -- I'm sorry.

DR. HANNO: I'm sorry.

DR. THROCKMORTON: I should have waved my hand. So it is that it's closer to moxi? I don't want to put

words into your mouth.

DR. HANNO: Looking at this as a urologist with a tremendous interest in QT intervals, just based on what I have read from everything and what I've heard, this is in the range where you start to think that there might be a problem. And I don't think the data is there to say for sure that there isn't. That's all.

DR. BORER: Tom?

DR. FLEMING: This is a tough issue to resolve here. On the one hand, the data to me look like the change in QT, QTc by various measures, is similar to moxifloxacin. The sense I get, at least from what we currently have put before us, is that moxifloxacin has effects on QTc that may well, in fact, provide some level of an increased risk of major cardiac events. Let's say, in fact, moxifloxacin is associated with one in a million in risk of torsade. That, of course, may be related to a much more frequent risk of sudden death, cardiac arrest, et cetera, other events. We don't know. But on the one hand, I would look at these data and say that certainly these results are consistent with some level of increased risk.

On the other hand, I have to look at this as a benefit-to-risk issue and say, what is the benefit here for a patient with ED and would participants, in fact, accept this level of risk for the benefit that they would derive

from this? We've seen data that indicated that sexual intercourse is in fact a risk factor for increased risk of major fatal cardiac events, and certainly these agents are correlated with an increase in sexual intercourse. Yet, presumably people would say, nevertheless, the benefits would outweigh that risk that they are undertaking or accepting even if this isn't adding to that risk through its proarrhythmic effects. So when I look at it in that regard, maybe if there is some level of risk, people would, in fact, accept that in a benefit-to-risk.

So I'm left with real uncertainty here, and as a result my vote on this -- pardon the pun -- is I'll abstain.

(Laughter.)

DR. BORER: We have one abstention and maybe more.

I'm going to vote no. I don't think there is a clinically relevant risk, and I'll tell you why I think so.

First of all, the dose of vardenafil that's most likely to be used, forgetting about the higher dose that would encompass the problems that might occur if a metabolic inhibitor were used simultaneously contrary to, I'm sure, what the label would say, I think that the results with vardenafil 10 milligrams, at least, suggest less of an effect than with moxifloxacin. But I don't see

moxifloxacin as having been demonstrated as associated with important arrhythmic and event risk.

I'm impressed with the data that Jerry Faich gave us. The torsade events were predominantly in women, two-thirds. Now, that may be a problem if this drug is ever going to be applied in women, but for the moment, that's not what we're talking about. Two-thirds of the events were in women. These were people who were hospitalized. They were sick. They were taking other drugs. There were all kinds of things going on here. I have a hard time relating the drug moxifloxacin to those ECG findings. It may be related, but I think that at least in a large number of those cases -- and it was 15 out of 20 million -- that that relationship is not correct.

So I have less concern about moxifloxacin. I think it's a reasonable positive control, and therefore, if we accept that and we accept the reasoning that QT prolongation, at least qualitatively, is associated with problems and this has less QT prolongation than moxifloxacin -- and I don't think there's much of a problem with moxifloxacin -- I don't think that there is a clinically relevant QT prolongation associated with vardenafil.

And the final part of that path of reasoning is what Tom said; that is, that you must look at benefit-to-

risk relation. That people might have events as a result of sexual intercourse is true, but that's a choice that they can make. The perception is that there is an important benefit -- and I think that there are many, many studies that would support this -- to enabling sexual intercourse in patients with cardiovascular disease particularly, because those are the patients I see, who otherwise might be precluded from having this activity. So I think that's a potentially important benefit and that the risk is, in absolute terms, probably quite small. I don't know if it exists, but quite small.

Therefore, I think that this is not a clinically relevant QT prolongation. I answer no.

JoAnn?

DR. LINDENFELD: I agree with what Jeff said. I would answer no.

DR. BORER: Susanna?

DR. CUNNINGHAM: I think maybe I'd vote a strong maybe. It's hard to tell because we can't really tell. So it's a little less certain than the previous one. Because it's closest to moxifloxacin makes it a little more of a concern, so it's hard to say an absolute yes or no.

DR. BORER: I'd like to add one thing. I know I'm going of turn here, but there are some perks to being the chairman.

I think that Joel made a very important point about the variability of these results relative to moxifloxacin and the extent to which you can interpret the difference that we saw in one study and the difference we saw in the other study. So that they're in the same ball park at least is something that I would find comforting. I wouldn't want to over-interpret data like this that I've never seen before and from studies which I don't think have actually been done before. So that's just another point.

Anyway, I'm sorry. Go ahead. Bev?

DR. LORELL: I don't get to vote.

DR. BORER: I'm sorry. Thank you, Jayne. Sorry, Bev.

Gay?

DR. BERNITSKY: I will abstain on the issue of the QT interval changes, but having said that, I looked at this data very carefully before I came to the meeting and the data that compared Viagra to the new drug show almost identical QT interval changes. We have pretty good evidence here that it's been used in very large populations and pretty safely. Again, I won't vote, but I would say if I knew more about QT interval data, I would probably support this drug.

DR. BORER: Paul?

DR. ARMSTRONG: No.

DR. BORER: Tom?

DR. PICKERING: No.

DR. BORER: Alan?

DR. HIRSCH: I'm going to abstain with an explanation. We have a QT change at this clinically relevant dose which is equal to the control. The control is made to be a control for a reason because it is a signal of some potential concern even though we don't know the actual event rates associated with it.

And for guidance, since I don't have a large clinical experience or an epidemiologic database, I went back to the FDA concept paper where I'm again guided by the less than 5, 5 to 10, or 10 to 20 millisecond rule. We're getting close to the some concern range, but I don't know how to calibrate that concern.

So not being able to calibrate the concern and then not being able to translate that to event rates, I really can't answer the question, which leads to abstain.

But I'm going to take the chair's words about trusting the patient, and I'm going to challenge them. I think when the public looks at our judgment of risk-benefit and there is an unknown, uncalibratable, I believe, risk for a drug used for erectile dysfunction, I'm not sure that clear, rational, conscious decisions are really made vis-a-vis concomitant medications, exposure length, et

cetera. So I abstain because I can't calibrate the risk.

DR. BORER: Toby?

DR. BARBEY: No.

DR. CARABELLO: No, and I would just add that there really is a remarkable difference between the moxi data in the two studies between table 1 and table 2. I don't know what that means, and I'm sure Tom would think of all the reasons why you couldn't do this. But if you looked at the moxi data from table 1 and compared it to the QT prolongation for vardenafil, they're not close. Anyway, no.

DR. BORER: Mike?

DR. ARTMAN: No.

DR. BORER: Doug, I'd like to ask you a question here about number 7. Both A and B ask whether you should look at QT effects in other drugs of these classes. My intuition is that everybody is going to be in agreement about this. May I ask that rather than go around the table and ask for yeses and noes and stuff?

DR. THROCKMORTON: Sure. Let me give you just a little context maybe around this as well.

One of the things that the concept paper that we heard at the meeting in January was that if you were a member of a class that you had some concerns about for whatever reason, and there was another member that had an

effect on QT you needed to compare yourself to, you needed in some sense understand the relative effects there. That's part of where this question is going. When do we need to understand those kinds of things? Obviously, in this case, do we need to ask specific questions about the other drugs in these two classes?

DR. KOWEY: Doug, are you talking about drugs that are already marketed in this class or drugs that will be marketed in this class? Are you talking about drugs that are already on the market?

DR. THROCKMORTON: Making no particular pre-judgment, I think we'd probably be interested in comments about both situations.

DR. KOWEY: I can start since it sounds like we're not going to do it clockwise or counterclockwise.

The answer for marketed drugs is no, I don't think you should. For all the reasons that you heard today, I think that drugs that are already out on the market, if we're going to ask pharmaceutical companies to do anything in terms of this issue, it seems to me that it should be better pharmacovigilance looking for real events in real patients rather than asking them to go back and look at a surrogate that we have a lot of difficulty tying to events.

So I guess if you had the ability to ask

companies to spend their resources, I would like to see them spend their resources on two things. One is very good pharmacovigilance, and the other is very good basic science so that we can understand this issue better and not have to do this anymore or maybe not so many more times. So that's my opinion.

DR. BORER: What about for --

DR. KOWEY: For new drugs? I think it's clear that for new drugs that are brought forward, new chemical entities that are brought forward, I think it's fairly clear that this needs to be done.

I have a difficult time generalizing to say that if it's a drug in the same class, that you don't because when you say a drug is in the same class, obviously there can be other pharmacological effects that you can't --

DR. THROCKMORTON: Very broad. I agree.

DR. KOWEY: Yes. So I'm a little concerned with saying carte blanche we don't need to do this anymore within this particular class of drugs. I don't think that's appropriate. I think it should be taken on a drug-by-drug basis that you guys have to look at the compound and decide whether you think that information.

Clearly for new chemical entities, I think this is the standard. And it's also very important -- and I

think it's been said likely several times today -- but the bar has been raised clearly by the DIA discussion and now today by these data that are presented in that we should expect now to see this kind of precision in measurements of QT interval for new chemical entities. I think it clearly will become the standard way you're going to look at things.

DR. BORER: Paul?

DR. ARMSTRONG: Mr. Chairman, I'm struck, before we conclude, that the agency has not asked us about the possibility that the two drugs under discussion today would be used together, both of which have an effect that potentially affects the QT. I don't know whether this discussion should be entertained or not, but I wouldn't want to leave the table without raising the fact that the juxtaposition of these two was surely not by coincidence, and we're talking about two medicines which might well be used in men who are aging for two different reasons. Is that a question that we should be entertaining, discussing, or is that a brandy/cigar discussion?

(Laughter.)

DR. THROCKMORTON: Well, I'm not sure that the two specific drugs -- we'd need to discuss whether these particular two drugs would need to have a formal study. We know very little about the consequences of concomitant use

of two drugs that affect repolarization by however you measure it. I can think of maybe two studies, one of which I think is an abstract. Dan, correct me if I'm wrong. So we know next to nothing about even the consequences of that concomitant use on this biomarker, far less whether that adds additional risk or anything like that. You can make lots of models about any which way you want to.

So when we should ask for that information is a good question. We've not gotten it even enough to know whether it's a concern under, I believe, any circumstance. Dan, correct me.

DR. KOWEY: Doug, I just wanted to ask you a question, and that is, hearing what you heard today, what do you think that you'll have in the label for these drugs? Will these drugs be labeled that they should not be given with other QT-prolonging drugs, or that you need to be careful about potassium and magnesium? Or what's it going to be?

DR. THROCKMORTON: I wouldn't want to comment on the labeling of these. It would not be my decision, and so I'm not sure that that would be appropriate.

You could think of moxifloxacin. You might look at the moxi label and say that's a place where we've described the effect on repolarization and suggested potential pathways to risk management. I don't remember

that label well enough to say that I'm using specific language there. That might be a path forward. Again, it's not my label.

DR. KOWEY: I wasn't trying to get you to tell us what the wording was going to look like, but there clearly is a decision to make. We were voting on a question that none of us are very comfortable with that said "clinically relevant" or "clinically significant" QT prolongation. And we all voted no. But I think that's different from saying that there isn't an effect on repolarization. There is an effect on repolarization. It just looks like it's pretty weak.

I guess then the question is if you believe that, which I believe, what do you need to tell doctors about the drug? Is it adequate to just describe what the studies showed or does there have to be more than that?

DR. THROCKMORTON: Why don't you make a suggestion? We'd be very interested in hearing your --

DR. KOWEY: I'll start off by making the suggestion that I think it would be worthwhile to have in the labeling some comment about the fact that we don't know -- and you said this a few minutes ago. We simply don't know what would happen -- and this relates to Paul's question -- if you were to put another QT-prolonging drug on top of one another, whether it's these two or others. I

think, therefore, in the labeling it is reasonable to tell doctors that, to tell them exactly the fact that we don't know what the liability of that combination or any of those combinations would be.

DR. RODEN: Can I just extend that just a little bit? I realize that maybe my time for saying anything is gone, but we're in open discussion now.

There is one very provocative dog study that suggests that if you use the appropriate two IKr blockers, you can actually get one to reverse the action potential prolonging effects of the other. So I think that's a very open question and needs some more basic science.

I'll extend what Peter said, though. So I would include something about using two drugs, both of which prolong the QT. And I'd extend it to the idea that there are patients out there who have other conditions that may predispose them. So not just a drug plus another drug, but a drug plus bad heart failure, plus severe LVH. Those are the risk factors, plus a lot of diuretics, plus a history of hypokalemia.

I don't think you want to go so far as to say every patient who gets these drugs needs to have a baseline electrocardiogram. I think that's sort of making you feel better but it's probably not going to accomplish anything. But I think that if you can get clinicians to identify

people who are at very high risk and just avoid them or think twice about them, that's probably as good as you're going to get right now. Off the top of my head.

DR. BORER: Doug, I want to bring closure to question 7 here. I think you've heard everything. But you're asking a question and I want to make a proposition and we'll -- oh, I'm sorry, very sorry. Wrong questioner. Well, in any event, a question has been asked.

The issue is, do the QT prolongation results from these data that we've seen warrant study of QT effects of other drugs in these classes? I think we've heard a proposition that that isn't the right question, that in fact preclinical data are not dispositive, and therefore some clinical data have to be available. And that means study of QT effects of other drugs. You haven't said how, just should you do it.

In the briefing document and the position paper or whatever paper it was, there's an algorithm provided that involves study in phase I in normal volunteers and then some action or no need for action depending upon the results.

If in fact we really can't draw firm conclusions or inferences from preclinical data, then I think the class of drugs is not relevant. The fact that a new molecular entity with multiple pharmacological effects,

some of which we may know and some we don't know, is being studied may be sufficient to warrant obtaining some clinical data. Now, I'm not going to say what kind of clinical data, how extensive the studies have to be.

But I would propose, from what we've heard here, it's important to get some data about QT prolongation in patients when a new molecular entity is being developed. And that goes beyond the issue of these two classes or the classes, if we can define those, of which these drugs are a part. So I would suggest that as a proposition.

If there's anybody who disagrees with that, now is the time to say so.

DR. KOWEY: Jeff, I think you said it very, very well. We haven't really spent a lot of time today talking about preclinical signals, but in the pre-guidance document, if you will, there clearly is a diagram that talks about what Jeff just said, which is trying to understand early on in the life of a new chemical entity what the liability is. And I think preclinical studies actually help you a good deal in making these kinds of decisions about what you need to do early on in clinical development. So all those things I think are very important and should guide you in making these decisions about what kind of an onus you're going to put on a drug company that's bringing forward a new chemical entity.

DR. BORER: Dr. Griebel, we have you to thank for convening us today. Have you received the results that you need?

DR. GRIEBEL: Yes, we appreciate everything we've heard today. It's been very helpful. Thank you.

DR. BORER: Then I will close the session and make two post-closure announcements immediately.

Number one is that tomorrow morning there's a closed session that will be held in the Chesapeake Room at 8 o'clock not to consider specific NDAs.

The second announcement is that if anyone on the committee is interested in having dinner tonight, we're going to try to get together at 6 o'clock in the lobby at Crisfield's to celebrate the departure of our departing members.

(Whereupon, at 5:05 p.m., the committee was recessed, to reconvene in closed session at 8:00 a.m., Friday, May 30, 2003.)