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CARDIOVASCULAR AND RENAL DRUGS
ADVISORY COMMITTEE

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88TH MEETING

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THURSDAY,

APRIL 29, 1999

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The meeting took place in the Jack Masur Auditorium, Clinical Center, Building 10, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland at 9:00 a.m., Milton Packer, M.D., Chairperson, presiding.

PRESENT:

MILTON PACKER, M.D., Chairperson
JOAN C. STANDAERT, Executive Secretary
ROBERT CALIFF, M.D., Member

PRESENT: (CONT'D.)

THOMAS GRABOYS, M.D., Consumer Representative
CINDY GRINES, M.D., Member
MARVIN KONSTAM, M.D., Member
JoANN LINDENFELD, M.D., Member
LeMUEL MOYÉ, M.D., Ph.D., Member
ILEANA PIÑA, M.D., Member
UDHO THADANI, M.D., FRCP, Member
J. THOMAS BIGGER, M.D., Guest Expert
MICHAEL CAIN, M.D., Guest Expert
ROBERT FENICHEL, M.D., FDA Representative
PRAN MARROTT, M.D., Sponsor Representative
PETER KOWEY, M.D., Sponsor Representative

ALSO PRESENT:

Lloyd Fisher, Ph.D.
Ed Pritchett, M.D.,
John Williams, M.D.
Daniel MacNeil, M.D.
Alexandra Kapatou, Ph.D.
Judy Jin, Ph.D.

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

(9:03 a.m.)

CHAIRMAN PACKER: This is the 88th meeting of the Cardiovascular and Renal Drugs Advisory Committee. At today's meeting, we have the usual members of the committee. We have, also, two experts who have been invited specifically to join us for today's deliberations. And just so that we can do this in the appropriate fashion, I'll ask the -- those who are seated at the -- on the podium today to simply go down and introduce themselves.

Lem, why you start. And just name and affiliation.

DR. MOYÉ: Sure. Lem Moyé, University of Texas, School of Public Health.

DR. BIGGER: Tom Bigger, Columbia University.

DR. GRABOYS: Tom Graboys, Brigham and Women's Hospital, Harvard.

DR. KONSTAM: Marv Konstam, Tufts University, New England Medical Center.

DR. CALIFF: Rob Califf from Duke

University.

MS. STANDAERT: Joan Standaert, Executive Secretary.

CHAIRMAN PACKER: Milton Packer, Columbia University.

DR. LINDENFELD: JoAnn Lindenfeld, University of Colorado.

DR. CAIN: Michael Cain, Washington University in St. Louis.

DR. PIÑA: Ileana Piña, Temple University, Philadelphia.

DR. THADANI: Udho Thadani, Oklahoma University Health Sciences Center.

DR. FENICHEL: Bob Fenichel, Division of Cardiorenal Drug Products, FDA.

CHAIRMAN PACKER: We'll ask Joan Standaert to read the administrative matters for today.

Joan.

MS. STANDAERT: Yes, 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

conflict at this meeting.

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

In accordance with 18 USC Section 208(b)(3), waivers have been granted to Dr. Milton Packer, Dr. Cindy Grines, and Dr. Marvin Konstam. A copy of these waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A30 of the Parklawn Building.

In addition, we would like to disclose for the record that Dr. Robert Califf and Dr. Lemuel Moyé's employers have interests which do not constitute a financial interest in the particular matter within the meeting at 18 USC 208, but which would create the appearance of a conflict. The Agency

has determined notwithstanding these interests, that the interest in the government in Dr. Califf's and Dr. Moyé's participation outweighs the concern that the integrity of the Agency's program and operations may be questioned. Therefore, Doctors Califf and Moyé may participate fully in the committee's discussions and vote concerning Betapace.

With respect to FDA's invited guests, there are reported interests that we believe should be made public to allow the participants to object and reevaluate their comments. Dr. Michael Cain would like to disclose that he has been invited to attend an arrhythmia board meeting sponsored by Proctor & Gamble. 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 involvements with any firms or

products they may wish to comment upon.

And that concludes the statement for April 29th, 1999.

CHAIRMAN PACKER: Thank you, Joan.

We'll call for any public comment.

There being none, we'll move on to evaluation of today's NDA. It's NDA 19-865, sotalol or Betapace. The sponsor is Berlex Laboratories. Proposed indication for the treatment of, or prevention of, recurrence of atrial fibrillation/atrial flutter. And I think that Dr. Marrott that will being the presentation, please.

DR. MOYÉ: I'm just asking what the preference is for asking questions today?

CHAIRMAN PACKER: Well, I think the sponsor would always like to have the questions held or segregated in distinct groups and I think that in general we have followed that policy. If there are certain issues of immediacy in clarification that you feel shouldn't or cannot be held to a specific break in the presentation, simply ask for a clarification.

DR. MOYÉ: But questions should occur at

the conclusion of each presenter's session?

CHAIRMAN PACKER: Well, we're going to probably divide the presentation this morning into the distinct categories which are listed on the agenda and we'll take questions after each of them.

DR. MOYÉ: Thank you.

DR. MARROTT: Mr. Chairman, members of the advisory committee, and Dr. Fenichel, good morning. I would like to thank you, first of all, on behalf of Berlex Laboratories, the sponsor, for inviting the sponsor to make a presentation. Details of our presentation can be seen on the slides.

After a brief introduction, Dr. Peter Kowey, Professor of Medicine at Jefferson Medical College, will provide an overview covering clinical pharmacology, efficacy, safety, and dosing recommendations.

The conclusion will be presented by myself.

Betapace or sotalol, or d,l-sotalol as our products will be referred today, has been approved in 57 countries worldwide and is being used in both the

beta blockers as well as the arrhythmia indications. And NDA's files by Bristol-Myers Squibb, the previous owner, was approved by the FDA in October '92 for the indication life threatening ventricular arrhythmia. Soon thereafter, the product was licensed in the U.S. only to Berlex and Berlex launched Betapace in January 1993.

You will see from this slide that between 1993 and 1998, a considerable proportion of total prescriptions, 60 to 77 percent, have been written for patients suffering from supra ventricular arrhythmia, chiefly atrial fibrillation and flutters. Thus, of the total 3.6 million prescriptions, or thereabout, 2.5 million have been written for this disease.

This degree of use in atrial flutter and fibrillation does not come as a total surprise to the sponsor. Published articles in peer review journals provide evidence of efficacy, safety, and benefit risk to the physician of d,l-sotalol in atrial fibrillation. Leading physicians have participated in investigation trials undertaken by Bristol-Myers Squibb in this population.

And last, treatment algorithms for atrial flutter and fibrillation presented and discussed by academic cardiac electro-physiologists at heart meetings emphasize the use of sotalol in patients with and without structural heart disease but in the absence of heart failure.

Ever since we heard of this use in atrial fibrillation, we have begun to consider what steps the company should take because we would have liked to be in a position to provide detailed information regarding the safety of our product to the physicians in this disease population. The next logical step for us, therefore, was to complete the clinical program of studies initiated by Bristol-Myers Squibb and which, by the way,w as well underway. This, we did, and we filed a supplemental NDA in June of 1998 for the atrial fibrillation flutter indication.

Our proposed indication reads as follows. d,l-sotalol is indicated for extending the time to symptomatic recurrence of chronic or paroxysmal atrial fibrillation or flutter in patients without or with structural heart disease in the absence of heart

failure. We have present here today our consultants who will participate in today's discussion. I have already mentioned that Dr. Kowey will present the overview on our behalf. In addition, participating in the discussions are Doctors Pritchett, Fisher, and Barbey. The titles and the affiliations of these experts is mentioned on the slide.

We also have here today Dr. Dan MacNeil, Executive Director of Clinical Research at Bristol-Myers Squibb. Dr. MacNeil was responsible for some of the clinical trials undertaken by Bristol-Myers Squibb for d-sotalol; d,l-sotalol.

That concludes the introduction, Mr. Chairman. I thank you for your attention. And with your permission, I would like to ask Dr. Kowey to come forward to present his overview.

Thank you.

CHAIRMAN PACKER: As Dr. Kowey is coming forward, let me just, to facilitate communication, I think it would be entirely appropriate for the committee to refer to this drug as sotalol as opposed to continuing to say d,l-sotalol unless someone wants

to. And that when specific reference is made to d-sotalol, that a clear distinction be made. But I think it would be perfectly okay just to refer to sotalol all through today's presentation except when the distinction is important.

DR. MARROTT: Thank you very much.

DR. KOWEY: Mr. Chairman, Dr. Fenichel, Dr. Lipicky, welcome back, members of the advisory committee and ladies and gentlemen. It is with a good deal of pleasure that I represent the sponsor this morning to present information regarding the use of sotalol in patients with atrial fibrillation and atrial flutter. I will present this in four distinct sections and as Dr. Packer already said, we will pause between sections in order to take questions. But if you have any points of clarification when the slides are up, please feel free to let me know.

We're going to talk about clinical pharmacology first, followed by efficacy, safety, and dosing recommendations. We'll start with clinical pharmacology.

A good deal of this information that I'm

going to show you this morning is already contained in the package insert for sotalol since the pharmacokinetics are the same for the compound that's currently being used for patients with ventricular arrhythmias.

This is a drug which has linear dose proportional and predictable pharmacokinetics. It is nearly 100 percent bioavailable. It's t-max is 2.5 four hours. In cases of normal renal function, the half life of the drug is 12 hours. In case with abnormal renal function, the half life is prolonged.

Notably, the drug is not metabolized by any enzyme system in the liver. Most importantly, not by the P-450 enzyme system. It is excreted -- More than 75 percent of the drug is excreted in urine. It's renal elimination is mainly by glomerular filtration and protein binding is negligible.

We would like to make a few comments about special populations because this is important in dosing the drug. Most importantly are patients who have renal dysfunction. Remember, the plasma clearance is reduced and the half life is prolonged in

patients who have renal dysfunction described by creatinine clearance. Therefore, in all of the clinical trials, dose adjustment was needed and was carried out in patients who had reduced creatinine clearance, or patients were excluded from the clinical protocol on that basis.

The observed effects in patients who are old, and males versus females, are almost entirely accounted by differences in renal function. Hepatic dysfunction has no effect on the kinetics of the drug.

Finally, a statement regarding the pharmacokinetic drug interactions: There is a 20 percent reduction in area under the curve in patients who have been fed. There is a specific drug interaction with Maalox and not to our knowledge with other antacids which causes about a 20 to 25 percent reduction in C max in area under the curve.

There are no demonstrable interactions between hydrochlorothiazide, warfarin, or digoxin. I would point out that for hydrochlorothiazide and warfarin, there is no effect either on sotalol or warfarin or hydrochlorothiazide blood concentrations.

Digoxin levels are not increased in patients who receive d,l-sotalol but there have not been sufficient studies to document what happens to d,l-sotalol in the presence of digoxin.

Dr. Packer, that concludes my section on clinical pharmacology.

CHAIRMAN PACKER: Okay. I don't see any questions. Why don't you proceed.

DR. KOWEY: Thank you.

I'll now cover efficacy. This is a somewhat longer part of the presentation. We're going to be presenting information regarding a number of the clinical trials in the d,l-sotalol efficacy database. I want to point out that we will be discussing the eight control trials in the database and in addition, we will be presenting a bit of information regarding the use of sotalol as it occurred in dofetilide, database Study 345, which you're familiar with and was presented at the last advisory committee meeting in January.

On the top, I have listed the categories, the broad categories, of atrial fibrillation type,

prevention, for chronic atrial fibrillation prevention, which really, according to the indication that we've listed, doesn't really mean prevention but extension of time in recurrence. For paroxysmal atrial fibrillation, one study that considered not only prevention of chronic atrial fibrillation but also conversion of the arrhythmia. And then finally two studies which examine the interaction between the drug and digoxin.

The studies which are in pink are those studies for which I will provide fairly detailed information. We do have information regarding Study G which is a subpopulation study in AF and for the two digoxin studies, and we have that available if you have questions about those trials. They will be included in the safety database, but for efficacy I won't be covering them this morning.

Let me start with Study 004 which was a study in patients with chronic atrial fibrillation and atrial flutter. And "chronic" in this study, and in most of the clinical trials I'll describe to you this morning, is defined as greater than two weeks in

duration and less than one year. These patients were cardioverted and were in normal sinus rhythm at the time that they were randomized. And they needed to be in normal sinus rhythm for greater than two hours before they were randomized.

This was a study that was done in out-patients and patients were randomized to placebo d,l-sotalol. The d,l-sotalol dose was 80 to 160 milligrams twice per day. And this drug was given in a blinded titration fashion. Or d-sotalol in doses between 100 and 200 milligrams twice per day. Again, this dose was blindly titrated.

I would point out in this study, patients who had a creatinine clearance of less than 50 ccs per minute were excluded from the study. Patients not tolerating d,l-sotalol at a BID regimen received the drug 80 milligrams once per day.

This dose titration process went on for two weeks and was followed by 22 weeks of maintenance at the fixed titrated dose. There was an opportunity to, again, titrate to tolerance. I want to point out that discontinued patients were followed in this study

for the full six months of the trial.

This study had three distinct primary endpoints: time to recurrence of symptomatic ECG documented atrial fibrillation, the time to recurrence of ECG documented atrial fibrillation including patients who did and did not have symptoms (so asymptomatic patients were found on routine telemetry monitoring), and the number of patients remaining in sinus rhythm after six months of therapy as proportioned. There was a secondary endpoint, change in defibrilar rate in patients prior to therapy and on therapy, which I won't discuss in detail but we can show you, if you'd like.

Let me discuss each of these primary endpoints when we get to the efficacy evaluation.

First of all, I want to point out, in the statistical analysis of efficacy, for this and for most of the subsequent studies that I'm going to show you, that the pre-specified analysis was done by log rank with Kaplan Meier survival. Included in your briefing document and in the analysis is a second statistical test, a generalized Wilcoxon test called

the Gehan statistic. The Gehan statistic is useful for demonstrating efficacy in the early portion of the Kaplan Meier. Whereas, the log rank is more valuable in the latter portions of the Kaplan Meier.

This is a chi squared for the number of the patients remaining in normal sinus rhythm, which was one of the endpoints of the study. I want to point out in this and several of the subsequent studies that we carried out a Cox proportional hazards model to describe the relative risk of sotalol use compared to placebo. And we also used this analysis to determine the effect of prognostic risk factors, which I'll show you. And then finally, for quantitative data, we used an analysis of variance, an ANOVA which was a one-way analysis of variance.

These are the demographics for Study 004: age, gender, race, and creatinine clearance, pointing out that there were patients in the trial with creatinine clearance of less than 60 ccs per minute who were not excluded from the study because its cut off, as you'll recall, was 50 ccs per minute. So these patients were in sort of the borderline range.

The groups were well matched according to the clinical characteristics. Similarly, they were well matched with regard to the cardiac history. Majority of the patients in this study were a New York Heart Association Class I and II. About half the patients had structural heart disease. You see the percentage here: patients who had coronary artery disease; and a smaller subset of those patients who had a previous myocardial infarction; and a 20, 30 percent, 40 percent incidence of having had hypertension.

Remember, this was a study in which the endpoint of the study was symptomatic recurrence of atrial fibrillation or atrial flutter. This is a slide showing you what the symptoms were in these patients, and what their arrhythmia history had been. This, on the top line, is the number of months since the first episode of atrial fibrillation that the patient reported. This is the duration of the atrial fibrillation episode that got the patient into the study. And as you can see, it was about four months.

These are sort of the typical symptoms

that you would expect in patients who have atrial fibrillation: weakness, palpitation, shortness of breath, and dizziness, chest pain being the most common.

Now, remember, in the sotalol arm of the study, patients were titrated between 80 and 160 milligrams twice per day. And so it's important for you to know that the majority of patients, two-thirds of the patients, in the maintenance phase of the study, during that 22 week period, were actually on 160 milligrams twice per day. Smaller percentage on the lower doses.

This is the Kaplan Meier curve for the first primary pre-specified endpoint in the clinical trial which was time to first ECG-documented recurrence of symptomatic atrial arrhythmia since randomization. And you can see how the groups are colored here: sotalol in blue, d-sotalol in yellow, placebo in red. And these are the statistics for the analysis. This is the log rank statistic, and this is the Gehan statistic. And in all the Kaplan Meier curves that I'll be showing you, you'll be seeing this

kind of a lay out for the statistical analysis.

Following several of the Kaplan Meier curves I'm going to show you, I'll also show you tabular data which comes from the same data set. This is medium time to recurrence in days with placebo group, for the d,l-sotalol group, and for the -- I'm sorry, Milton. I'll try not to do that too many times. For the sotalol group and for the d-sotalol group.

The reason why this is greater than 180 days is because fewer than 50 percent of the patients had a recurrence of arrhythmia in those groups at the endpoint of the study.

Percentage of relapse-free patients. This is the p value you've already seen. And this is the relative risk by the Cox method that I describe in the statistical slide. And these are the confidence intervals for those observations. Point 56 for sotalol at these confidence intervals.

Let me just back up to that. Can I back up to that slide? I'm sorry.

I just want to point out that two deaths

did occur in this study. Neither one was on sotalol. One was on d-sotalol, and one was in placebo. And it's important for you to know that they were censored in the analysis at the time of the death for the Kaplan Meier curve that I showed you.

This is effect of prognostic factors on the hazard risk of sotalol versus placebo at six months after randomization. What this slides lends is the fact that the covariates did not provide an alternative explanation of the clinical benefit. This is the unadjusted clinical benefit. This is the clinical benefit adjusted for the baseline factors. And you can see that they line up, indicating that there was balance in the randomization.

I also want to show you a subgroup analysis of these data using what we consider to be important clinical variables; and that is age, gender, structural heart disease, New York Heart Association class, years since the development of the arrhythmia. And you can see that there is good consistency of the data with the point estimates lining up on the side favoring sotalol.

I do want to point out that this consistency held for patients older and younger than 65, for men as well as women, and for patients who did and did not have structural heart disease in this clinical trial.

I also want to point out that this is the remainder of that same subgroup analysis. This is part two. I want to point out that it also held up for patients who had a creatinine clearance less than 60 ccs per minute and greater than 60 ccs per minute.

This is the Kaplan Meier curve of similar data from Study 004. This is time to first ECG-documented recurrence of symptomatic atrial fibrillation or atrial flutter. We now have added in death or discontinuation since randomization. Since there were very few deaths in the study, and since there were actually very few discontinuations in the study, the log rank p value looks very similar to what you had already seen and so does the statistical Gehan analysis.

You remember that the second primary endpoint in this clinical trial was time to ECG-

documented recurrence of any atrial fibrillation or atrial flutter since randomization. This is the Kaplan Meier analysis for that data set, again showing separation between sotalol, d-sotalol, and placebo; and these are the p values for that observation.

Finally, the third primary endpoint in Study 004 was the percentage of patients in normal sinus rhythm at six months as a proportion. There were 32 percent of the placebo patients in normal sinus rhythm at six months compared to 50 percent of patients in the sotalol group with this p value.

You have received the communication from the Food and Drug Administration and the staff regarding a possible concern about Study 29. Study 29 was a center in Stockholm which enrolled patients in the latter phases of the trial. And as you can see from these numbers, for d,l-sotalol and for d-sotalol, that there was a robust treatment effect for Study 29 or for Center 29.

We have a difficult time understanding why data are being extracted for a single center. And this is more or less to play chance on a clinical

trial. We want to point out that there was a center in this study, Center 24, that had a particularly bad effect. And in fact, if the data for Center 24 and Center 29 are both taken away from the analysis, the best and the worst, the p values remain statistically significant.

We've prepared more of a discussion regarding this issue which we'd be very happy to have with you. Dr. Lloyd Fisher, who is here with us today, has looked at these data very carefully and is prepared to offer some of his interpretation of the data as well.

The second study in the efficacy database which I'd like to address briefly is Study 345 which, again, is a study that you've seen in January, which was the dofetilide Study 345. In Study 345, which consisted of 671 patients, 137 patients received d,l-sotalol, and the same number of patients received placebo. As you'll recall, these are patients who had chronic atrial fibrillation or atrial flutter at entry. The duration was one week to two years which looks familiar to the enrollment criteria for our

trials. And these were all patients who had been successfully converted to normal sinus rhythm either pharmacologically or electrically.

This study was a 12-month randomized parallel group, double-blind, placebo and active control study. And again, the active comparator in the study was racemic sotalol. The primary endpoint of the study was time from conversion to normal sinus rhythm. So once the patients were in normal sinus rhythm, it's the time it took for them to recur with atrial fibrillation, atrial flutter. The statistical analysis for the Study 345 is the same as the statistical analysis that we had used for our data.

I apologize. This slide is not colored in the same manner as the slides that we've used this morning, but that's because we obtained this information from the Freedom of Information and we weren't able to really do much with it. It was scanned. But I just want to point out that we have put a red arrow on this for you so you can see the 80 milligrams twice per day of sotalol dose arm, and this is the placebo arm. Remember that this is the lower

end of our dose range for our clinical trials but it was the dose that was included in the dofetilide experience. And this is the p value for the observation of the difference between sotalol and placebo. This is the percentage of patients in normal sinus rhythm at 12 months.

I should point out that we will return to Study 345 in the safety analysis because we do have some safety information to show you also from that trial.

I want to now move from the chronic atrial fibrillation cohort to move into the patients in the paroxysmal atrial fibrillation cohort.

CHAIRMAN PACKER: Peter, if I could just have you pause. If there is anyone from the sponsor's point of view for dofetilide 345, I think it would be appropriate for us to hear their comments later on. I just want to give everyone a heads up on that.

Second is just a clarification. Freedom of Information normally applies to access of information for drugs that have been approved. I don't know of any specific action on the approval of

dofetilide. How does Freedom of Information apply here?

DR. KOWEY: I don't know. Milton, it was presented at a public hearing in January. So I would have assumed that that means that it is in the public domain, but I --

CHAIRMAN PACKER: No, I --

DR. KOWEY: I'm not an attorney, so I can't really tell you.

CHAIRMAN PACKER: I think the reason I'm bringing it up is that I think it is in the public domain. But I don't think it could possibly have been obtained by Freedom of Information.

DR. KOWEY: Okay. I stand corrected. But I don't think there's anything wrong with having shown the information on the other hand. Do you agree?

CHAIRMAN PACKER: I'm sorry?

DR. KOWEY: There's nothing wrong with having shown the information?

CHAIRMAN PACKER: No, no. There's nothing wrong. I just want to clarify.

DR. KOWEY: And there's nothing wrong with

the FDA taking this into account in the approval process route for racemic sotalol.

So I apologize if I misspoke. Actually, all I was trying to do was tell you why it was such a crappy slide. I probably should have just kept my mouth shut.

Let me move on to Study 05 which is the paroxysmal atrial fibrillation cohort. Again, this says prevention. I want to make sure that everybody's very clear. We read the indication. Milton read the indication. Pran read the indication. It's prolongation to time to recurrence. Not overall prevention of the arrhythmia.

Study 05 was a study that included patients who had atrial fibrillation within the last three months. But at the time that they were actually enrolled in the clinical trial, they were in normal sinus rhythm. The majority of these patients, the vast majority of these patients, had spontaneous reversion to normal sinus rhythm. It did not require cardioversion in order to have them in sinus rhythm at the time of randomization.

I'd like to point out that this is a unique study in the database because it is the only study in which inpatient dosing was mandatory, was mandated. And it was mandated for patients who had structural heart disease. Investigators had the option of using the drug outpatient for patients who did not have structural heart disease but they didn't have to use it outpatient. So inpatient was mandatory; outpatient wasn't. Patients were randomized to placebo and to one of three doses of sotalol, 80 milligrams twice per day, 120 milligrams twice per day, and 160 milligrams twice per day.

Now in this study, in contrast to 04, patients who had creatinine clearances of 40 to 60 ccs per minute received the drug once a day rather than being excluded from the protocol. If they were under 40 ccs per minute, they were out. Open label treatment, as I would point out here, was optional for the remainder of the 12 months if the patients had a recurrence. So the patients could have treatment for 12 months open label after recurrence; and the duration of the study, as you can see here, was 12

months.

I want to point out and it's important to realize and remember that these patients were titrated to their dose and that was the dose that they had to receive. If they couldn't tolerate the dose, they were dropped from the study.

The primary pre-specified endpoint in the analysis was the time of the first recurring symptomatic episode of atrial fibrillation or atrial flutter during the efficacy evaluation period. What does that mean? That means that after the patients had been dosed for three days if they were receiving the drug twice a day, or six days if they were receiving the dose once a day, to get to a presumed steady state plasma concentration.

There were a number of secondary endpoints in this trial. We will present you some of this information. For example, time to the first recurring symptomatic episode of arrhythmia after the first dose of study medication, which has been referred to by some people as the intention-to-treat analysis. Also, the proportion of patients free of recurring

symptomatic atrial fibrillation and flutter at six and 12 months, another secondary endpoint. And time to occurrence in patients who were receiving the drug twice a day or once a day.

Again, I won't go through this. It's exactly the same statistical methods that were used in 004. These are the pre-specified analyses. The Gehan was not pre-specified. It was used post hoc in order to examine the data because of the high incidence of early recurrence. And this is the Cox proportional hazards for relative risk, prognostic risk factors, and dose response relationship.

These are the demographics of the study. I want to point out that about a quarter to a third of the patients had creatinine clearances of less than 50 ccs per minute and may have therefore received a once-a-day dose of the medication. These are the patients' race, female, gender, et cetera, which are well matched.

This is structural heart disease by dose groups. Pointing out patients, again, a relatively similar percentage of patients with coronary artery

disease. This is the subgroup with myocardial infarction. And as I pointed out already, the majority of patients in this clinical trial had been designated by the investigator to have had defined paroxysmal atrial fibrillation. The remainder had what the investigator called chronic atrial fibrillation.

This is the time for the first ECG-documented recurrence of symptomatic arrhythmia from presumed steady state. So this is the primary pre-specified analysis. Again, looking at log rank and Gehan statistic, the Gehan showing a more robust p value than the log rank, 120 milligrams used in this analysis, showing a more robust p value than the 160 milligram group.

These are the tabular data. We begin by the number of patients in the trial who discontinued because of adverse events. Again, I would point out that because the patients were placed in a dose arm and could not leave that dose arm or be titrated, there was a higher, and an expectedly higher, discontinuation rate in patients who received 160

milligrams, either twice a day if they had normal creatinine clearances or once a day. Median time to recurrence: Again, you can confer from the Kaplan Meier that it would have been longer for the d,l-sotalol group. This is the percentage of patients at the end of the 12 month period who are relapse free, one of the secondary endpoints. Because the 160/120 milligram lines crossed towards the end of the study, it turned out that more patients for 160 milligrams group by that analysis were in sinus rhythm.

These are the p values by log rank and Gehan. And these are the same point estimates for relative risk of the confidence intervals for each of the dose groups.

This is time to first ECG-documented recurrence of symptomatic atrial fibrillation or atrial flutter since the patient had been randomized. So this starts from the first time the patient took a dose which is obviously earlier than the time of presumed steady state.

There were actually more patients in this analysis because the number of patients were dropped

during that initial phase of the study. And because of that, the p values are perhaps a bit more robust for both the Gehan and the log rank. And you can see here that there is a step up to 160 milligrams with a -- there is a significant p value attached to the 160 milligram dose for the log rank and also for the Gehan.

This is an analysis which is a very draconian look at the data. It involves taking patients who not only had recurrences in the study, but were also were discontinued since randomization. It is an analysis that I showed you for 004 which happened to show a better outcome because there were few dropouts. In this analysis, it cancels out the statistical benefit by log rank although not by Gehan. Since, again, in the higher dose groups, as expected, there were a larger number of dropouts. This is a question that's been addressed to the committee, and we think it's a very important statistical question. And actually, Dr. Fisher also has some comments perhaps we could have later during the discussion regarding this question of handling of

discontinuations in patients in clinical trials of this nature.

This is the same evaluation to determine the covariant. Covariants do not provide an alternative explanation for the clinical benefit. We're looking at several of the clinical characteristics that I showed you from the last study: age, gender, structural heart disease, coronary artery disease, et cetera, in- versus outpatient initiation. And you can see that because of balance there really isn't much of a difference from the unadjusted point estimate.

This is the subgroup analysis as I showed you in the last study. Looking at important clinical variables -- age, gender, structural heart disease, paroxysmal versus chronic atrial fibrillation -- most of the patients here in this analysis obviously were paroxysmal. I'd point out that this particular analysis is done in patients who had received 120 milligrams of sotalol versus placebo, and this is at 12 month since randomization.

This continues the subject analysis I did

in the last study showing that whether or not the creatinine clearance was high or greater than 60 or less than 60, the benefit treatment effect was consistent.

I want to move on to Study 9A which was also a study in patients with paroxysmal atrial fibrillation as a subpopulation of a larger clinical trial.

CHAIRMAN PACKER: Peter, hold on one second, please.

DR. KOWEY: Yes.

DR. CALIFF: Peter, just a point of clarification. On the odds ratios that you're showing, those are the non-intention to treat odds ratios?

DR. KOWEY: That is the non-intention to treat. That was -- let me go back. Can I go back a slide.

DR. CALIFF: That's been true for all the odds ratios you've shown?

DR. CALIFF: Yes. Well, this one is -- you can see here. If you call intention to treat from

randomization -- is that what you mean, Robert?

DR. CALIFF: It's usually what we call intention to treat.

DR. KOWEY: Yes. No, this is not for that analysis. This is for the time-to-presume steady state which was the primary analysis in the trial.

The primary analysis in the trial -- Oh, this is from randomization. I'm sorry, Robert. This is from randomization. So this is the intention to treat.

DR. CALIFF: But it includes patients who came off the drug, even if they weren't --

DR. KOWEY: This does not have the discontinuation. Correct. Yes. These were where the discontinuations were censored.

DR. CALIFF: Right. And we'll come back to it later, but I wouldn't call that intention to treat. I just want to clarify which analyses were being shown as odds ratios.

DR. KOWEY: Yes, this analysis is -- let me just clarify so everybody understands. It is from the time of randomization, and it does not include

patients who were discontinued for adverse effects.

CHAIRMAN PACKER: Peter, just a clarification. You referred to the p value for the log rank as 160 milligrams, .029 as being statistically significant. The alpha assigned to that is .025.

DR. KOWEY: That's correct. You're right. You're right.

CHAIRMAN PACKER: It is statistically significant.

DR. KOWEY: That's correct. You are correct.

The next study in the paroxysmal atrial fibrillation strata is patients with -- in Study 9A which was a sub-study of a larger study of patients with paroxysmal supra ventricular tachycardia. This had a relatively complicated baseline period. Let me just explain to you how this was done.

Patients were observed for the first week. If they had one episode of arrhythmia within the first week, those patients then went through two more one-week observation periods. These were patients that

obviously had fairly frequent arrhythmia, and therefore the period of observation was shorter.

On the other hand, at the other end of the extreme, patients who had an episode every four weeks, or once a month, in the first four-week period, then went on to have two more four-week periods of observation for a total of 12 weeks.

Once they had this baseline quantification of arrhythmia frequency, they were randomized and stratified by their baseline observation period to d,l-sotalol, regular sotalol; or d-sotalol; or placebo. Just to show you that about 60 percent of the patients were in the yellow group, about 25 percent of the patients were in the green group in terms of the frequency of arrhythmia, and about 15 percent were in the red group, randomized to these drugs during a dose escalation phase, and then for the last two periods of the study they were observed.

The endpoints of the study were time to first recurrence of supra ventricular arrhythmia and the percentage of patients without recurrence. The statistical analysis for this was a Kaplan Meier

survival curve and a Cox proportional hazards model, as you've seen before. This is the Kaplan Meier curve for the intention-to-treat analysis for the patients with supra ventricular arrhythmia, including patients with PSVT as well as atrial fibrillation, showing you each of the doses of sotalol and d-sotalol lining up compared to placebo. These are the p values for those overall observations which was the primary pre-specified analysis.

On this slide, we've shown the subpopulation of patients with paroxysmal atrial fibrillation by history looking at sotalol, d-sotalol, and placebo. What is striking about the results is the relatively short time to relapse in patients in the placebo group and the difference between that observation and the time to relapse in patients on sotalol. Yielding a p value which was highly statistically significant with these confident intervals for the relative risk observations, which are here, the point estimates.

There was a single study in patients with chronic atrial fibrillation that examined two issues.

One is conversion of atrial fibrillation or flutter in normal sinus rhythm. And the second was exploration of a higher dose of the drug. That was Study 014 of 161 patients.

This is a study, as I said, in patients with chronic atrial fibrillation, again, defined the same way that the other studies were defined. And these patients were randomized between sotalol and placebo. There was a dose titration phase in the first part of the study. Patients were started on 160 milligrams twice a day and then titrated with 320 milligrams, twice per day at three-day intervals. If intolerance occurred at the 160 milligram twice per day dose, they could be titrated downward to 80 milligrams twice per day. Patients with creatinine clearances in this study of less than 50 ccs per minute were excluded from the protocol. Patients following this period of titration, if they had not converted to sinus rhythm on the drug, underwent direct cardioversion.

After completion of the double-blind treatment phase, an open label treatment for one year

was an option for the patients.

There were three endpoints that were described in the protocol for this particular study. A portion of patients achieving sinus rhythm with double-blind treatment by Fisher exact tests, the time between restoration in sinus rhythm and relapse into atrial fibrillation and atrial flutter analyzed by log rank, and the proportion of patients remaining in sinus rhythm at the end of six months of double-blind treatment.

These are the demographics: New York Heart Association class, percentage of patients with structural heart disease, percentage of patients with coronary disease or previous myocardial infarction. This should look very familiar. This is for the placebo group and the d,l-sotalol group.

Now remember that the first endpoint of the trial and the unique endpoint of the trial was conversion of atrial fibrillation or flutter to normal sinus rhythm with drugs. So this is the pharmacologic conversion rate during the dose titration phase of the study showing a 30 percent conversion rate for d,l-

sotalol compared to one percent of patients on placebo. The 30 percent value is very much in the range of what we've seen with oral Class III for conversion of atrial arrhythmia to sinus. This is the p value like Fisher's exact.

This is the Kaplan Meier analysis, time to relapse of atrial fibrillation or flutter since restoration of normal sinus rhythm. And these are the p values which are attached by log rank and by Gehan. Deaths were censored in this particular Kaplan Meier analysis.

These are the tabular data from those observations. We're looking at number of patients who were discontinued due to adverse events. There was a fairly large number of patients who were discontinued in this trial, remembering that we were using doses in this trial which are higher than the doses which we are recommending today for treatment of patients with this arrhythmia. This is median time to recurrence in days, percentage of patients relapse free, and the statistical tests, log rank and Gehan, and the point estimate with confidence intervals for the relative

risk.

This is adding deaths or discontinuations to relapse of atrial fibrillation or flutter in patients in Study 014. These were the statistical results by log rank and Gehan, remembering, again, that there was a high discontinuation rate in patients who received the drug at these doses.

Finally, the last study that I'd like to outline for you is Study H which was in patients with chronic atrial fibrillation and which sotalol was compared to quinidine.

Again, the same group of patients with atrial fibrillation and atrial flutter now more than two months and less than one year. These patients were cardioverted and needed to remain in normal sinus rhythm following cardioversion for more than two hours before randomization. This was an open label study. And treatment was randomized between sotalol at a dose of 80 to 160 milligrams twice per day including sulphate, 400 to 600 milligrams twice per day. These are the number of patients that were treated with each of these regiments.

This is a cardiovascular history. It's worth pointing out that in this trial, as not in the other trials that I've shown you, that there were patients who had congestive heart failure by history. There were more patients who had cardiomegaly. And in fact, there were about 16 to 18 percent of patients who had Class III New York Heart Association class. The distribution of patients with coronary disease and previous myocardial infarction should look familiar.

This is the Kaplan Meier analysis in which we have analyzed the time to recurrence of atrial fibrillation or atrial flutter, or discontinuation for an adverse effect. And although this was not powered to be an equivalent study, it's clear that these lines are very near each other with this p value.

This is number of patients who are relapse free. We begin with the number of patients who are in sinus rhythm at six months on study drugs and the p value. These are the number of patients who relapsed. These are the number of patients who were discontinued for adverse events. Seventeen percent in the quinidine arm, 10 percent in the sotalol arm. There

was one death on quinidine due to a stroke and there was one death on sotalol due to myocardial infarction.

You would expect that a drug that had beta blocker effect as part of its electrophysiologic profile to slow heart rate at the time of a rhythm relapse. And so another endpoint in this trial which was examined was the mean resting ventricular rate when patients relapsed back into atrial fibrillation or atrial flutter. These are the data for d,l-sotalol. Borderline statistical difference between the value for relapse and baseline. These are the data for quinidine baseline relapse. There was a highly statistically significant difference between relapse heart rate on sotalol versus quinidine with this p value by two sample t-test.

Another unique part about this protocol is that patients were interrogated for symptoms at baseline, and they were then re-interrogated for symptoms at one month after treatment. I would point out that the Ns for these observations are lower than the Ns for the patients that were actually randomized into these arms because a patient dropped out of the

protocol either because of adverse effects or inefficacy within this one-month time period. Twelve for sotalol, 24 for quinidine.

I would point out that symptoms of palpitation and weakness decreased in both sides of the study, both for quinidine as well as for sotalol. It would be expected in patients who were achieving some kind of a therapeutic effect with these antiarrhythmic drugs.

DR. CALIFF: Peter, just to make sure I understand. What you're saying is that, for people who didn't have side effects, they had -- they looked better?

DR. KOWEY: They felt better if they were in sinus rhythm.

DR. CALIFF: If they didn't drop out because of side effects?

DR. KOWEY: Correct. That's correct.

CHAIRMAN PACKER: Let me see if I understand. They were in sinus rhythm at the start at the trial?

DR. KOWEY: Yes.

CHAIRMAN PACKER: They were at sinus rhythm at one month and they felt better?

DR. KOWEY: No, no. The symptoms were -- the way they were interrogated at baseline was, What were your symptoms when you were in atrial fibrillation, not, What were your symptoms when you entered the study.

CHAIRMAN PACKER: So it's not history.

DR. KOWEY: It was not concurrently with randomization.

CHAIRMAN PACKER: It's not the baseline.

DR. KOWEY: It is not the baseline symptoms. It's the symptoms the patient had before they were treated and when they were in atrial fibrillation.

DR. KOWEY: Again, a further comparison. These data you've already seen on a preceding slide. I just want to point out that this is the proportion of patients in the clinical trial who were reported to have had adverse events. These are the discontinuations. These are the values for patients who actually had adverse events. Fifty percent in the

quinidine arm, 28 percent in the sotalol arm.

I want to just summarize, Milton, if I may, with just a couple of slides and then we can answer questions about efficacy.

What's done in this slide, and the two succeeding slides, is look at the clinical trials that I presented to you in each category and describe on the slide the percentage of patients relapse free, the p values for the log rank and the relative risk versus control. This is for the chronic atrial fibrillation and atrial flutter strata. And we're looking at treatment versus control. I'd point out for Study H, the control was not placebo; the control was quinidine.

This is for Study 004. These were also the primary analysis, .56 with this p value. We do not have a point estimate for the dofetilide experience. All we have is the p value for the log rank which you can see here. This is 014, which was the high dose study showing you the relative risk versus control of the point estimate. And this is the quinidine/sotalol comparator study in which there was

really not much to choose between the two therapies.

This is an analysis for the paroxysmal atrial fibrillation, atrial flutter cohort. I've actually -- the reason why there's two slides for PAF is because in the first slide, I'm showing you the data. Rob, this is from randomization. So this is the from randomization analysis, the relative risk versus placebo point estimates and log rank for sotalol at 80; d,l-sotalol at 120, and d,l-sotalol at 160. Remember, this could be once a day or twice a day in this study. And these are the log rank p values.

This is the analysis for 9A at the low dose, 80 milligrams twice per day; and at the higher dose, 160 milligrams twice per day. Again, these are the relative risk point values and confidence intervals.

Let me show you --

DR. CALIFF: These are again -- this is censoring patients when they stop taking the drug?

DR. KOWEY: Yes, that's correct. That's correct.

And let me just show you, Rob, the other analysis which was from presumed steady state plasma concentration for Study 5. So this was what was the pre-specified analysis in the protocol. The relative risk estimates are a bit different here. The p values are a bit less small. And the reason, again, is because there are patients who were lost during the early phases of the trial. These data here are exactly the same as what I've just shown you.

So I would just like to conclude the efficacy portion of this presentation by pointing out that d,l-sotalol extends the time to symptomatic recurrence of these arrhythmias in patients with both chronic and paroxysmal atrial fibrillation and atrial flutter. It would appear that patients with and without structural heart disease obtained a similar benefit.

The study had doses ranging between 80 and 160 milligrams twice per day in some of the trials, with once a day dosing in patients with ultra creatinine clearance. And these appear to be effective.

Conversion rates to sinus rhythm is 30 percent in Study 014. However, doses above what we are recommending for clinical use were required in order to achieve that clinical benefit. Dose dependent increase in recurrence-free rate was seen in Study 05 which was the randomized comparison of dose.

That concludes my efficacy presentation, and I'd be happy to take questions.

CHAIRMAN PACKER: What I'd like to do is to pause here for questions from the committee. In all cases, we're going to begin our questions with JoAnn Lindenfeld who is the primary reviewer for this NDA.

I also think it would be very useful to take the questions in a systematic fashion per study. And so what I would ask the committee not to do is jump around from study to study. We're going to go through all the studies individually. Some of the studies have common issues. Some of the studies have distinct issues. And let me begin, as the briefing document does, with Study 05. So we're going to start the questions with Study 05.

JoAnn.

DR. LINDENFELD: I just want to start--this will involve the entire discussion. Could you give us a rough idea of the average age and the average percent of women with atrial fibrillation in the United States?

DR. KOWEY: In the United States?

DR. LINDENFELD: Just what's the average age of these patients and what percentage are women?

DR. KOWEY: I'm going to take a wild stab at this, JoAnn. I don't know. I don't have precise data, but I do know that it's an elderly population. So this is a group of patients that should be greater than 65 for the most part. And although men may have more disease when they're younger because of their coronary disease, women certainly catch up with them and they have a higher incidence in the elderly.

DR. LINDENFELD: Yes. I think one thing that will go through all of these studies is that this is a relatively young population for this disease and a relatively high percentage of men, I think, for atrial fibrillation. And this becomes important

because creatinine clearance becomes so important with age, I think.

DR. KOWEY: I agree.

DR. LINDENFELD: But that's just to start off.

Now in terms of excluded drugs in Study 05, I want to just address this issue of calcium blockers. Am I correct in saying that dotiazam and verapamil were excluded drugs?

DR. KOWEY: That is correct.

DR. LINDENFELD: And I think that is in all of these studies; is that correct? That will become an important point later on as we talk about adverse effects and bradycardia. At least in 00 -- we'll stick to 05, but I believe that's true in 004 as well.

Let's come back to that because I think it's important dotiazam would be a commonly used drug in this population of patients.

DR. KOWEY: Can we have back up, please, slide 190? This is, JoAnn, specifically Study 05, concomitant therapy.

DR. LINDENFELD: These calcium channel blockers, that excluded dotiazam and verapamil; is that correct?

DR. KOWEY: That was in the protocol, yes.

DR. LINDENFELD: Because I think the point would be that those would be relatively common drugs that these patients might be taking. So just an important point for the future.

And is it also true that the therapy was blinded but the dose was not? In other words, the physicians and patients didn't know which therapy, but the potential dose of therapy was known?

DR. MARROTT: In 35, that is correct.

DR. LINDENFELD: So just as a point of -- people might know that the dose was higher but that would apply to both, of course.

Now I want to get to this issue that I think everybody wants to get to about the dropouts and we'll come back to the dropouts. In including the dropouts, if a worse case scenario is included, that is all the dropouts are considered failures, then the study is non-significant, at least, I think, according

to the FDA analysis. And the analysis that we read suggested that perhaps the truth lies somewhere in between.

But I'm a little bit concerned, and I want to get some opinions from everyone because I'm a little bit more concerned than what I saw in the FDA document that the people who drop out may actually be the people -- people who drop out on sotalol for adverse events may actually be the people at highest risk of recurrence for atrial fibrillation. Particularly, I know, that at least in a few of the studies when it was documented, those were clearly more often elderly people. So maybe we could have some comments on that and maybe from the committee, too. I'm concerned that actually the worse case scenario may apply here.

CHAIRMAN PACKER: Let me just outline what the issue is so that it is clear to everyone what we're talking about because, as JoAnn says, this is an issue which is on the minds of I think every member of the committee, as well as noted as an important issue in the FDA review.

And that is, in Study 05 as well as in nearly all the trials presented on behalf of sotalol, patients who discontinue the drug were not observed to the end of the planned therapy for the occurrence or recurrence of atrial arrhythmias. Consequently, we do not know whether patients assigned to a specific dose of sotalol or placebo had a recurrence of atrial fibrillation. In other words, the data were censored at the time of discontinuation, and we are all concerned that that censoring is informative. That is, it's not random, that censoring was not random.

The FDA reviewer had asked the sponsor to try to gauge the degree of difficulty created by this by including the time of discontinuation in the analysis. And this was done for both treatment arms. This is referred to as the so-called "worst case" analysis.

Let me just make a comment here. This is not a worst case analysis. A worst case analysis would be to censor all of the placebo and to assign events at the time of discontinuation to all the patients receiving active therapy. That would be

worst case.

So an analysis in which all patients are considered to have an event at the time of discontinuation is not a worst case analysis.

DR. KOWEY: Right. Because it will pick up the even worse.

CHAIRMAN PACKER: It could even be worse than that.

DR. KOWEY: Right.

CHAIRMAN PACKER: And therefore, the analysis presented here is not the most conservative analysis. And one could be more conservative than the analysis being presented. But I think it's important to talk about this because it has implications not only for sotalol but it also has implications for almost every long-term trial this committee sees, for any drug, for any indication.

And it is also an issue that is brought up in the committee questions. And so I would like to take JoAnn's lead here and have the committee spend a little bit of time on this because it is so important. And let me do so by --

Rob, do you want to comment on this?

DR. CALIFF: I can just make a few comments because in general, I think, that whenever we discontinue follow up in patients who have been randomized, then we have a violation of the intention-to-treat principle. And we're left with some uncertainty about the implications that has for the analysis.

I certainly agree -- Lloyd, just sit down for a minute here.

Someone mentioned that Dr. Fisher was going to be on the edge of his seat within milliseconds and indeed he is.

I certainly agree that when a few patients get lost, then that would be a reason to censor. But I think the problem that I'm seeing is that trials are being designed where, by design, patients are no longer followed when they stop taking the drug, which I think is a very dangerous approach in doing clinical trials but it seems to be the norm rather than the exception.

Now one could also argue, and I think it

has been reasonably argued, that in practice you try a drug and if the patient has a side effect, stop the drug and try something else. So it's likely that the right answer is somewhere in between but it's certainly not -- the right answer is certainly not at the point of censoring because I think as you and JoAnn pointed out, the patients most likely to drop out -- and this is another thing that worries me -- are not only the ones most likely to fail therapy but in the case of the drug that may cause toxicity -- most particularly related to things like renal function, drug accumulation, electrophysiologic property -- that toxicity is likely to be very much concentrated in a very small group of patients who are at high risk.

And so it leaves you uncertain about judging both the efficacy and safety, I think, of what will happen when this thing is unleashed on the public.

CHAIRMAN PACKER: Now, Lem, do you want to comment?

DR. MOYÉ: Yes. I think that sometimes

investigators don't really know what they're getting into when they start a clinical trial. Much of the emphasis is placed on randomization. There's a tremendous full-court press to randomize patients. And sometimes what gets lost is that when a patient is randomized, that investigator essentially buys that patient for the duration. Essentially, the study pays a price for having that patient enter into the study because the study analysis assumes that patient is going to be followed until the very end of the experiment.

Now sometimes people are fooled by the fact that we randomize so many patients in this study. Sometimes we randomize thousands or tens of thousands of patients. And there tends to be a sense that there's some play in these numbers, that because you randomize so many patients, you can afford to lose a few and still not wind up vitiating the findings.

This is a trap. This is a great trap. Because the findings in the end come down to the delta, the difference in the number of patients who have the endpoint in the placebo group versus the

number of patients who have the endpoint in the active group. And even though you may randomize hundreds of thousands of patients, the delta winds up being five or ten, or 15, or 20 patients. So the entire efficacy of the study pivots on what happens to those ten or 15 people.

If the investigators, of course, knew who these people were in the beginning, they would give them tremendous care. But the investigators don't. So the best that they can do is treat each patient like that patient is the patient that's going to make the difference. That translates to following everybody for as long as you can, or certainly for the duration of the experiment, perhaps longer if possible.

If that does not happen, you have what, to me, is a discordancy. That is to say, that the protocol essentially specified there would be one mode of execution and in fact the actual execution was different. Now, in some sense, the investigators have let us down because we haven't been able to -- we cannot look at the data as we would have expected to

see it from the protocol.

And so the question then becomes, Can you make some kind of adjustment? Well, here you really can't make a persuasive adjustment. I think that probably Lloyd and I could spend all day throwing scenarios back and forth at one another about what would be reasonable and what is not. Essentially, the computation for the effect side and the p value is beyond adjustment. In my word, it's corrupted. There's no way you can compute the p value which actually assesses what is the truth in this experiment in that what -- by that I mean, what it actually mirrors what it tells us about the population.

The best we could hope for, of course, which we don't have here, is the absolute worst case analysis, and I second what Milton's comments were here, and that is we assume the active patients who are lost were the ones who had the bad clinical outcomes and the placebo patients do not.

If you don't have this extreme worst case analysis which lines up with the initial analysis, I think that we must go by the most conservative

analysis. And the most conservative analysis here is that the p values in fact are not significant. This is a conclusion that I am reluctant to reach. However, since the investigators are not able to follow patients as they had initially planned, then I think in terms of -- since the implications of what we decide here are not just for this trial, but the implications are for what the side effects are going to be in the community, the most conservative approach here I believe is the best one.

CHAIRMAN PACKER: Yes. Maybe, let me just see if I can get a clarification.

Lem, you're suggesting that the investigators sort of violated a commitment to the trial. But if I understand correctly, the trial protocol actually said they wouldn't be followed. So it wasn't the investigators violating their commitment. It was the design of the study that encouraged the lack of follow up in the patients who dropped out because of an adverse event.

Is that correct?

DR. KOWEY: That's correct.

CHAIRMAN PACKER: But a different philosophy was followed for Study 04. Why were they different?

DR. KOWEY: 04 was a study that predated 05 and was not done by the sponsor. And I don't have an explanation for why there was a change in the philosophy of follow up. I wasn't privy to that.

DR. KONSTAM: Could we get -- I'd just like this clarified. The analyses that we saw for 004 was a true intent-to-treat analysis without censoring of dropouts?

DR. FISHER: Could I make one comment about terminology? I won't go into my other comments. But I think it would be useful, the term "intent to treat" means everybody's included in the group to which are randomized. And I would maintain that -- for example, you will later see an ICD trial. I don't actually mind an ICD trial which considered a person to have an endpoint at the time there's a discharge for VF to consider that the equivalent of an endpoint had they not had a defibrillator. I would call that "intent to treat," although you can follow them

further for subsequent discharges.

So I would like to distinguish between "intent to treat" where everybody is included in the groups to which they're randomized and maybe we can call it "complete follow up", being even if they discontinue, they go to the end of the study period, just for logical consistency because I can think of situations where I'm relatively happy with discontinuations and others where I am not.

DR. KONSTAM: So in 004, all patients, whether they were discontinued or not, are included in the efficacy analysis that we saw; is that correct?

And in 05, the primary efficacy analysis excluded patients who were excluded because of adverse events, discontinued drug because of adverse events.

DR. MARROTT: In Study 004 -- can you hear me now? In Study 004, all patients were followed until the end of the trial. In Study 05, patients were not followed if they discontinued due to side effects or if they had a relapse. The sponsor's point of view was that being a fixed-dose trial, we expected a larger number of side effects; and it was difficult

to ask the investigator that the patient be followed because it is not easy to follow patients who have discontinued in the atrial fibrillation population because they would have gone on to other treatments and other types of management.

CHAIRMAN PACKER: It is actually easy to follow them. It is very easy to follow them for the planned duration of therapy. It is not hard to do the right thing. What is hard is to accept the consequences of what happens after the discontinuation of treatment.

Because what we're really talking about here is not an intention-to-treat issue. It's an issue of informative censoring, whether the censoring here is informative or non-informative. And I guess that would be the correct terminology. What we're concerned about here is not only is the censoring informative, but it is frequent and it was planned.

Udho.

DR. THADANI: There are several issues which come to mind here. Investigators in some of the trials have medical knowledge. For example, Karl

Rillow's study got around this issue by dropping patients who had adverse effects during open label phase. And those patients were dropped out. So that's one way to do the trial. Unfortunately, this trial was not designed by this, so I think you're stuck with it. You randomize a patient. You will count them all. Had you taken the, say, one month period and done a study in those patients with side effects were the reason they were not randomized, you would not be arguing with this. Also, there are problems there, too.

CHAIRMAN PACKER: Udho, I think --

DR. THADANI: I'm just mentioning --

CHAIRMAN PACKER: You might be fixing a problem with another problem.

DR. THADANI: I'm not fixing. I'm raising some of the issues. So I think what I'm trying to say is that once you randomize, intent to treat analysis should include all the patients. And you might have been actually benefited had these patients who had side effects gone on to other therapy, which is helpful in a fib, might have had less arrhythmia.

You could not have stopped the provisions, and so you said you that you did not follow because it's hard to follow patients. I don't think I buy that. I think probably you would have come out beneficial had they gone on to ALD drugs which also prevent a fib. But that is still intent to treat and that's a real medicine.

So I don't think the FDA reviewing all the files and what is presented, it's not a worse case scenario hasn't identified it out. I think that's intent to treat. So you're going to have to live with it. One is a bit shaky and I sympathize with your patients. The trial was written that way and the investigator didn't follow that.

But, I'm concerned that intent to treat did not show a difference and if you drop the patient -- and it seems like the higher doses, the higher drop out rate. And since the 80 milligram did not work, you are recommending 120 or a higher dose with, unfortunately, a higher drop out rate. And it's possible that had these patients been seen at months 3 to 6, they would have had a higher recurrence and

they would have neutralized the effects.

So I think there are some concerns and all of us have concerns when we looked at the FDA documents as well as the database.

CHAIRMAN PACKER: Lloyd.

DR. FISHER: I wonder if I could make a few comments. First, it's wonderful to see Dr. Lipicky back and he has gone home to watch our festivities on the internet. And hopefully he's there and hears this.

I was actually glad to see this point brought up and I think it deserves very careful consideration. And I would take a very parochial view. I view the cardiorenal committee as the best division and committee within the Bureau of Drugs. And I've now had enough experience with other committees that that may be a true statement. I certainly haven't seen every committee.

First, I'd like to note that the question the FDA stated is not, strictly speaking, correct. The question talks about the assumptions being violated because there's different drop out rates at

different doses. That in itself is not enough to invalidate the censoring.

What has to happen is you have a differential treatment effect, as Milton implied, associated with this censoring. So the real issue is how differential that treatment effect would have been. How robust are the findings. And what Dr. Moyé was talking about is absolutely correct. You're left with mathematically what's called an unidentifiable problem. You can hypothesize different sorts of scenarios, none of which you can tell from the data once you have the censoring. It's sort of like a Zen poem, sound of one hand clapping. What would have happened if these people could have tolerated the drug and taken it.

And I'd like to note also that many areas where we usually don't think about this problem it truly exists. And that is where we measure things continuously and have our last observation carried forward analyses. When the people go out, those observations definitely could have changed also. So this is a problem that cuts across almost every drug

development area.

I think when take Dr. Moyé's hard line, as he tends to take on each and every issue, we will kill drug development in all kinds of areas. It just will not be conceivable because of the tolerability of drugs to get a positive study.

So I think it would be very poor policy to make discontinuations, or even worse, the worse case, a primary analysis that had to be satisfied necessarily for approval, despite all those caveats I've just spread. Normally what we do in observing the amount of discontinuation is, if it's quite low, we tend to ignore it. And in the past, even when it's somewhat moderate like this, we tended to ignore it perhaps inappropriately.

Parenthetically, I push the sponsor, and Dr. Pritchett who is here said I shouldn't introduce his name in my comments, why weren't these people followed up. And he assured -- I don't want to start a big fight among the Duke medical faculty, but he assured me that this was not possible and I'm mentioning him, hopefully, hoping that he will give

this comment first-hand because I think it's very relevant in this particular discussion.

Anyway, what you have to do, then, is use your judgment of the biological plausibility of what's gone on. I would first note, if we could get slide 195. For this particular study, the discussion is going as if this analysis destroyed everything. But in fact, you can see the 120 p value of .034, the sponsor said they would look at the two higher doses and use a Bonferroni correction, which is a little too conservative, of .025. So this is not significant but it's not as if you've destroyed the whole study. And certainly, you would have to agree there's a very strong trend, if not significant. And I think that's important when you integrate all this data in your mind, that you not think of this as a study where when you considered the discontinuation failures, everything fell apart. That's not true. What did happen is the statistical significance dropped.

So what you have to do is use your biological judgment of plausibility and you people are the medical and biological people and I'm the

statistician. But I would suggest that there's a lot of comfort in 04 which, because they had upward titration or because the Europeans are more stoical, I mean, there are a variety of reasons. But they had very few dropouts. And they have the same type of pattern.

So there was a case where this problem didn't enter in and the data are somewhat consistent. And there's a number of other ethics to these studies that you heard about from Peter. So what you would have to do in your own mind is make a judgment about just how robust the findings are, how much the discontinuation might have effected things, and it's hard for a statistician. If we take a very hard line, we would take the absolute worse case. I think in practice, actually I consider this actually a fairly draconian correction and I would agree with, I think, Dr. Califf's comment, the truth is somewhere in between this and the center's situation. And precisely where that truth lies is a very difficult matter of judgment.

DR. THADANI: Rob, before -- sorry, I

believe it's 05, this is 05, right? Right. If I'm looking at the FDA document, I believe on page 10, there's a small booklet. The p value there is point-- is different than what you're showing here.

DR. FISHER: I don't have the document.

DR. THADANI: Point 042. Whether the statistician reviewed the work as which is intent to treat, he found no significance at all. And p values there are -- given are much different. Log rank is .62.

DR. FISHER: I think the difference is the --

DR. THADANI: Why there are differences in that?

DR. FISHER: Okay. I think the difference is the following. The investigators preferred analysis, which is not my preferred analysis nor I think the agency's, was from steady state. Because the theory being until you reach steady state, what could happen. If you -- So they probably have this value.

If you do it from steady state, because

some people drop out before steady state, you lose the protection of the randomized process, just as we do for the discontinuation.

DR. THADANI: No, this isn't randomization. All patients were included and the p values for log rank is point -- this is on page 10 of the document, p value is .62 for 80, .098 for 120.

DR. FISHER: Yes, that's --

DR. THADANI: And .912 for this. And if you look at it against it's .042. It's not what you're showing here with significant. But there is no significant --

CHAIRMAN PACKER: Udho, those numbers are the same numbers that are on the slide. Can you just check?

DR. FISHER: Oh, no, I had a prior -- I apologize. I can explain the difference.

The difference was in the slide that I hastily picked up, did not refer to symptomatic. But it referred to any ECG documented. And .098, which I still say is the symptomatic return on a randomization.

I apologize. I didn't do that knowingly with knowledge.

CHAIRMAN PACKER: I think we have to -- there's two separate issues here. The issue number one is what does the committee think the right kind of design and analysis should be as a general issue. The second is, how does that feeling influence the interpretation of the data on sotalol. And I think, Roy, I think you've actually said that.

DR. FISHER: I would just suggest, before you begin your general assessment, we hear from Dr. Pritchett about the possible practicality. I mean, maybe his views are incorrect but --

DR. CALIFF: But, Lloyd, I would at least like you to make a statement as to what you think the proper study design is, if at all possible.

DR. FISHER: If at all possible, the proper design, the advice I give to people, is you follow them until they -- everybody, even if they discontinue their study drug, they're in the study. You follow them to the end of the study and you try to select all the interim observations. If it's a

survival trial, that's usually very possible. It may be a little difficult depending upon the reason that people discontinue things, and so on, and --

DR. CALIFF: Not to sound like a lawyer, but it can be difficult but it should be the goal to follow every patient to the end of the --

DR. FISHER: Well, I don't know. I mean, I'd like to hear from Dr. Pritchett who has given me --

DR. CALIFF: He can say all the reasons why it's hard to do it, but as a principle, it should be done.

DR. FISHER: If you can -- to the extent you can do it, you should do it. I agree with that.

CHAIRMAN PACKER: I don't know if we want to get into extreme detail as to why it's hard and I'm sure, Ed, you would tell us why it's hard. But, I'm not certain it would change the underlying principles that are important here which apparently, from what I can tell, there's unanimity of opinion. And that is that there should always be a concerted, systematic effort to follow all patients until the planned end of

the duration of therapy for all factors related to the primary or secondary analyses.

And although it could be difficult, and in fact doing so might end up diluting the treatment effect, that is the most interpretable way of looking at the data from any trial. It's a principle which has been exceedingly well established for mortality analyses. And all I think we're saying, and Lloyd, you're agreeing, and I don't hear anyone disagreeing, is that if it's good enough for a fatal outcome, it's good enough for non-fatal outcome.

DR. FISHER: Well, I have no problems with a perfect world. All I'm saying is, I think you have to consider it by particularly the reality of what you're doing. I'm not -- You can judge better than I can.

CHAIRMAN PACKER: Lloyd, we're not looking for perfection. What we're looking for --

DR. FISHER: I understand perfectly. As the guideline.

CHAIRMAN PACKER: What we're looking for is to send out a -- the strongest possible message

that to design trials so that data are systematically omitted is wrong.

DR. FISHER: No, I -- In fact, I have said the same thing, not to the sponsors, not to the sponsor. I was not around when these studies were planned and so on, so I don't -- And one of the replies I get, well, why do that? They're off the drug. They're discontinued. We're going to be censored, then, and people accept that. And I think it is a good thing to change that perception and in the future do things. And it would have been nice if this trial had been done the same way.

DR. THADANI: Lloyd, also, I think that if you allow censoring and excluding patients, we are saying why bother looking at intent to treat and might as well throw it down the drain. Because what you're encouraging then the patient drops out, don't have to follow them. So, I think we can't set the principle that patients who have side effects withdraw them from the study are not counted, even when you're shown they are not statistically significant at the end it's included. So, I think we must insist that once a

patient in a trial, whether it's a mortality trial or not a mortality trial, they should be followed. And what happens, other treatment does it, I think that's different. But otherwise, we would be violating all the rules and at the end as a clinician, I would not be sure. I know, my practice would not change if I have the trial results or no trial results. I'd be doing the same because I would not be any better off looking at this result or any other result if you're censoring patients.

DR. FISHER: Well, just to complicate the issue, it is not always fair what is the best analysis. Let's say you're doing an equivalence trial and everybody who discontinues, then gets put on the drug you're trying to show equivalence to. And then you do the intent to treat analysis and take the entire time period where an awful lot of the people are on the drug to which you're trying to show equivalence. One would argue, then, that probably the best analysis is to censor at the time they went on the actual drug to show an equivalence.

So, this is a complex issue where it's

hard to make across the board general statements. But as a general principle, I think it is valuable, I agree, to follow up for endpoints as best you can after people discontinue study medication.

DR. CALIFF: Yes, I guess my point is we're cheated of the opportunity to deal with the uncertainty in the most rational way if we don't have all the data. I would recognize that the answer is somewhere in between.

DR. FISHER: And I certainly agree with that statement.

CHAIRMAN PACKER: We rarely achieve unanimity of opinion amongst the members of the committee or with the committee and sponsor. This is a special moment.

DR. FISHER: We haven't heard from Dr. Pritchett yet.

CHAIRMAN PACKER: Ed, is it okay if we just say it's hard or do you want to tell us how hard?

DR. PRITCHETT: Rob, I think that's the point, that it's hard. If you're following a mortality endpoint, you can get that always, even from

the national death registry if you need it. If you're following some non-fatal endpoint, particularly one like documentation of a symptomatic arrhythmia that required a certain amount of cooperation from the patient, it is much more difficult. And I think that that is one of the principles that has guided the design of these trials as we've worked on them over the past several years, along with the attempt that the outcome of the trial, the conclusions drawn from the trial, could mimic the way clinicians think. And I don't think that clinicians equate a recurrence of an arrhythmia with "I discontinued the drug because the patient didn't like it." Just like I don't think physicians equate a recurrence of an arrhythmia on the second day of therapy when the patient has only had a couple of doses of medication with one that occurs two or three weeks later when they're at steady state.

So, these trials were designed to mimics the clinical practice as well as to deal with the practical difficulty trying to document an outcome in patients who won't cooperate with you any more.

DR. CALIFF: But there are clinicians

don't, when a patient fails a drug, don't say I'm going to forget about you for the rest of your life. They actually follow the patients after that, maybe on another therapy. So, I think your analogy is actually flawed in that respect.

DR. PRITCHETT: I think that sometimes the physicians following patients in clinical trials are the physicians who follow the patients forever and other times they're not. So, I think we do see many patients in clinical trials that, once they're finished with the clinical trial, are lost to the investigator after they lose their ability to document the outcome.

CHAIRMAN PACKER: I think we're actually all saying the same thing. I think that we're saying that to systematically design the trial so that the information is not collected is not a good idea. That every effort must be made to obtain the information and we understand it would be hard to do so under some circumstances. And some trials may lend itself to more completeness, to greater completeness, of data than others. And certain indications might lend

itself to that.

But, I think we're -- it's really important to emphasize the principle. Having emphasized the principle, maybe we should go back to sotalol.

DR. KOWEY: Just one point about what could have been done in this study was with something that was like what we have done in 004, which was to allow a titration down on the dose for the patients who have been randomized for maximum dose. That's a much more conventional way of handling it. Then you do your first period analysis. You have your data. And the patient may be able to stay on this drug and you can follow forever its effects. And that probably should have been the design and unfortunately we all agree that it wasn't.

But it was -- Just to make sure that everybody understands that the intention of the study was a dose ranging study and patients report on a dose, and they had no option once they were at that dose.

CHAIRMAN PACKER: But, Peter, even in

normal, usual, conventional dose ranging studies, the dose to which a patient is randomized is not considered to be an all or nothing phenomenon. It's usually considered to be a target dose. It's the intention to achieve that dose, not the perfection of achieving that dose.

DR. KOWEY: I agree.

CHAIRMAN PACKER: So, this trial is doubly confounded in the sense that there was no follow up after discontinuation and that in fact clinical practice was subverted here. There would normally be down titration. One normally designs dose response trials with an intended target as opposed to, "gee, if you don't take this dose, you're out." So, there are lots of things that could have been done better with this trial.

DR. KOWEY: Which was really what was done in 9A, which allowed the people to have one or two doses in a titration mode trial.

CHAIRMAN PACKER: JoAnn, while we continue with comments on 05.

DR. LINDENFELD: This is just a point of

clarification. I think when drugs have beta blocker effects and we measure time to symptomatic recurrence, one has to wonder if that's because the -- when they recur, the rate is slowed and they have less symptoms, or in fact the duration is prolonged.

So, can you, just to clarify for me, show me the difference in this study in terms of time to symptomatic recurrence and time to EKG documented recurrence? Were those substantially different?

In other words, I believe when I look at this, that if one just takes the EKGs that were measured, I think by telephone line every two weeks, that the study was less significant if one measured the time to EKG documented recurrence irrespective of symptoms. But, I just want to be sure that's a correct statement.

DR. KOWEY: This is for the symptomatic. Can we have all ECG -- all A fib flutter recurrences for 05. I don't believe that we have that analysis in our back ups. We'll look for it, JoAnn.

DR. LINDENFELD: I just want to know if some of this beta blocking as opposed to the other.

DR. KOWEY: We do have that analysis for, you saw, for 04. And there was really no difference between the two analyses. That is, no real big differences.

DR. LINDENFELD: I thought 04 was less significant for the EKG as opposed to --

DR. KOWEY: We show you the two for 04 if you'd like.

DR. LINDENFELD: We can probably come back to that.

DR. KOWEY: Would you like to see those? Yes?

DR. THADANI: JoAnn, while on this point, this slide really shows the patient had a symptomatic and then were documented to be an A fib on ECG. I didn't see any data when I was reading that you might have that is data showing that repeat ECGs were done was recurrence rate. I didn't see that either. These are patients who complain of symptoms and they were collaborated to be an A fib and the ECG showed that.

Is that correct, Peter, or they were symptomatic and then you happen to do the ECG. And

I've not seen any in my reading. You might have seen it because you are the primary reviewer, but I didn't.

DR. LINDENFELD: No, I think that's really what I'm asking because I think that patients are less likely to be symptomatic in atrial fib if they're on sotalol than placebo. So, less likely to be picked up.

DR. KONSTAM: Could we get this clarified some more. So, if the patient was symptomatic, the first endpoint, symptomatic A fib, I assume, and maybe you can correct me if I'm wrong, that, then, was confirmed by ECG?

DR. KOWEY: Correct.

DR. KONSTAM: So, the symptoms, what we're calling symptomatic A fib was symptomatic, then confirmed by electrocardiogram?

DR. KOWEY: Correct.

DR. KONSTAM: Now, this is -- now, this one is different. How -- were you doing screening electrocardiograms? That's what this is.

DR. KOWEY: Right. That's in the 04 study which we already showed.

You have the slide number? Number 24.

DR. LINDENFELD: People need to use the microphone here so that we can get this.

DR. KOWEY: And go forward one.

DR. KONSTAM: Well, I guess I'm asking for clarification about what these endpoints mean.

DR. KOWEY: One more. And then one more after that. This is any atrial fibrillation, atrial flutter, even without symptoms. The patients were being periodically monitored in the absence of symptoms.

DR. KONSTAM: Can --

DR. KOWEY: We don't have the data for 05.

DR. KONSTAM: Well, wait a minute. Can you tell us more about that? In other words, tell us about these screening EKGs. Tell us whether there were additional EKGs done if the patients were symptomatic. I think I'm concerned about the same --

DR. KOWEY: Yes. We'll go through that methodology for you.

Ed.

DR. PRITCHETT: This study, this is the

one that was done in Scandinavia, Europe. It did not use trans-telephonic monitoring. It used -- patients were asked to come back periodically. If they had symptoms of atrial fibrillation, they could come back to the site to have an ECG recorded. They were also asked to come back at specific months of follow up. And if they were symptomatic and had an atrial fib, they went into the symptomatic. If they were asymptomatic or symptomatic, they wound up in this analysis.

DR. KONSTAM: So, this endpoint includes the time when patients showed up?

DR. KOWEY: Yes. This is any atrial fibrillation.

DR. KONSTAM: So, it's still, I think-- I think the concern that JoAnn raised still stays. I think that this is influenced by the fact that patients are experiencing symptoms. Then we have to get into interpretation about the implication with regard to heart rate.

But, it doesn't dispel the problem, I don't think, based on what I'm hearing about how this

endpoint was derived.

DR. GRABOYS: Can I --

CHAIRMAN PACKER: Yes, Tom.

DR. GRABOYS: Let me just comment on that.

Those of us taking care of large volumes of patients with AF realize that a large fraction of patient with this rhythm present with stroke. I think it's extremely soft data in terms of what the actual time from the recurrence of the arrhythmia is based on clinical grounds in which frequently we see patients, whether or not their rate is slowed or not by concomitant therapy or not, who present in atrial fibrillation having never had any kind of symptoms.

So, it's, to me, disquieting and very difficult that we're basing judgments upon data potentially coming from very soft sources.

CHAIRMAN PACKER: This -- let me see if I understand it. The concern, Marv and Tom, just so we can clarify this specifically, is indeed a sampling approach in the trials. Are you convinced that either the 05, and I hate to move into 04 because we're not quite there yet, but it's a related question, that

either 05 or 04 did it the way you think it should be done? In other words, in order to avoid the issue of bias?

DR. KONSTAM: I'm not sure what you're asking.

JoAnn raised the point that, the question is, are we actually -- if I may paraphrase, are we actually looking for -- looking at recurrences A fib or are we looking at something else, perhaps, and recurrence of a fib driven by the fact that patients had to be symptomatic to be identified. This drug has a beta blocker effect. It slows, we believe, it slows heart rate at time of recurrence. Therefore, a recurrence of atrial fibrillation may tend to be less symptomatic than if the drug were not on board.

DR. GRABOYS: And therefore, what may happen is if you've got a patient presenting who is now symptomatic but in fact had the onset of atrial fibrillation, a good bit of time prior to when they were symptomatic.

CHAIRMAN PACKER: But I don't understand how -- I understand the issue that you're bringing up

and I don't disagree with the issues. I'm just trying to figure out how would the sponsor have fixed this problem?

DR. GRABOYS: Well, short of continuous monitoring, there's no way he can -- there's no way that we can be assured that this data is in fact what it is.

CHAIRMAN PACKER: But specificity --

DR. GRABOYS: It is only dependent upon symptoms --

CHAIRMAN PACKER: No, I understand. But you can say this is a problem here with the approach, the sampling approach. But I'm just trying to figure out, is there an approach they should have used.

DR. KONSTAM: Let's, before answering that question, I mean, let me just point out. This isn't generic to all antiarrhythmics, necessarily, because this agent has a beta blocker effect. So, I think it's more important in this drug than perhaps in other drugs, first of all. And, secondly, it is a very important problem for the reasons that Tom raised.

Now, in terms of how it might have been

dealt with, I don't, maybe JoAnn had an answer to that.

DR. LINDENFELD: Well, didn't 05 look at monitoring every two weeks? Is that correct?

DR. MARROTT: Yes.

DR. LINDENFELD: And 004 was just symptomatic recurrence plus a much longer duration of routine follow up. So, if we could have the same data for 05, I think we all probably would give a couple of weeks as a reasonable time.

DR. KONSTAM: Well, I'm not sure about it but that's why I was asking about the nature of this ECG derived endpoint in 05.

DR. MARROTT: Mr. Chairman, if you don't mind, I would just like to clarify. In both studies, 004 and 05, there's a TTM when the patient was symptomatic. But there were routine TTMs performed every two weeks. In addition to that, of course, when the patient visited the outpatient clinic, there was an opportunity to see what the rhythm was.

DR. LINDENFELD: So, in 004, I thought you said earlier that this wasn't done every two weeks.

It was done every two weeks?

DR. MARROTT: Yes, it was.

DR. THADANI: One of the issues, I think, comes up even when you're just doing monitoring, the 05 trial is a paroxysmal method trial. And you know, to be confident, I realize that symptomatic isn't shown, would have liked to see at least 48 hours Holter data because these patients were in sinus rhythm from zero to three months before they were entered in the trial.

And it's possible, even if you're just doing a routine ECG, they could be in sinus rhythm and once -- even I realize Holter is not adequate because even 48 hour Holter will miss it unless you've got the now cardio-beeper device or something else.

DR. KOWEY: But with the information that you now know that the patients were monitored --

DR. THADANI: But we haven't seen any data on that.

DR. KOWEY: Well, no, we have it right here. We have Kaplan Meier for --

DR. THADANI: No, no. 05. This is 004.

DR. KOWEY: Well, we don't have the data, unfortunately. We can -- I'm sure we can get the data. We don't have it. But for 004, the Kaplan Meier values are exactly the same for any AF recurrence --

DR. KONSTAM: Peter, how often were ECGs done in 004 routinely?

DR. KOWEY: There was trans-telephonic monitoring, I'm told, every two weeks in 004. This is the European trial.

Is that true -- Every two weeks.

DR. THADANI: 004 is the chronic effort trial, right?

DR. KOWEY: That's correct.

DR. THADANI: And this is the paroxysmal --

DR. KOWEY: No, this is --

DR. THADANI: 05 is -- 05 is the paroxysmal.

The data we're discussing at the moment is 05.

DR. KOWEY: The data you're looking at