UNITED STATES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

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CARDIOVASCULAR AND RENAL DRUGS

ADVISORY COMMITTEE

87TH MEETING

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Thursday

January 28, 1999

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The Meeting took place in the Natcher Building, Main Auditorium of the National Institute of Health, 45 Center Drive, Bethesda, Maryland at 9:00 a.m., Chairman Robert Califf, presiding.

MEMBERS PRESENT:

DR. ROBERT CALIFF, Acting Chairman
JOAN C. STANDAERT, Executive Secretary
DR. RAYMOND LIPICKY
DR. CINDY M. GRINES
DR. JOANN LINDENFELD
DR. UDHO THADANI
DR. MARVIN KONSTAM

CONSUMER REPRESENTATIVES:

DR. THOMAS GRABOYS
DR. ILEANA PIÑA

A-G-E-N-D-A

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

(9:00 a.m.)

ACTING CHAIRMAN CALIFF: I'm Rob Califf, and I will be the Acting Chairperson today. We would like to start by asking if there is anyone who would like to give public comment.

Yes? Come forward and please use a microphone and identify yourself again.

MR. SASICH: My name is Larry Sasich, and I'm from Public Citizen Research Group in Washington, D.C.

Public Citizen had requested, on January 7th, through the Freedom of Information Act, access to the FDA and other data sent to your Advisory Committee concerning the safety and efficacy of Dofetilide.

Our request was denied, and we were deeply concerned about the evidence that this drug can cause potentially life-threatening heart rhythm disturbances, even though it may be approved to treat or prevent heart rhythm abnormalities.

Despite not being allowed access to this data, and the fact that peer review in medical

literature is not an adequate substitute for the FDA reviews of safety and efficacy, we do have serious concerns based on a brief review of the published literature about the safety of this drug, because of its proarrhythmic effects in association with Torsade.

We are also apprehensive about the use of an antiarrhythmic drug to prevent the recurrence of an arrythmia, after the increased risk of death was found with a class 1C antiarrhythmic drugs, and the cardiac arrythmia suppression trial in the early 1990s.

Several studies in patients with atrial fibrillation or flutter of normal volunteers, have led to our concerns over the potential of this drug to cause arrhythmias.

In the study of IV Dofetilide in 16 patients with recent onset atrial fibrillation, 2 of 15 patients, or 13 percent completing the study, suffered episodes of Torsade.

In a study of 10 healthy male volunteers given oral Dofetilide, one subject exhibited asymptomatic polymorphic ventricular tachycardia. When its corrected QT interval was excessively

prolonged.

The authors felt that this may have been due to a repolarization abnormality unmasked by the drug. These authors caution that the efficacy of drug for terminating an arrythmia is not necessarily equivalent to efficacy in preventing recurrence. And we would add that it may not be as safe, either.

They also pointed out that Dofetilide manifests electrophysiologic features that may predispose to apparent ventricular conduction during atrial fibrillation that may be difficult to distinguish from short runs of ventricular tachycardia.

Public Citizen is on record as being deeply troubled about drugs that have been approved by the FDA with known safety problems that were subsequently withdrawn from the market after many deaths and injuries.

The three most recent examples are dexfen Fluramine, Mibefradil, which three members of this Advisory Committee thought should not have been approved, and Bromfenex.

We are concerned that this trend is continuing with the recent approval of Cilostazol for the treatment of intermittent claudication, a painful but non-life threatening condition that is most effectively managed by a program of structured exercise, and the possible approval of this drug, Dofetilide.

We urge that this committee decide that Dofetilide, a drug that can cause potentially life threatening arrythmia should not be approved to prevent recurrent arrhythmias because, if approved, the tragic experience of the class 1C antiarrhythmic drugs will be relived.

Thank you very much for the opportunity and your attention.

ACTING CHAIRMAN CALIFF: Are there any other public comments?

(No response.)

ACTING CHAIRMAN CALIFF: Hearing none we will now proceed with our agenda. Joan, do you have announcements?

SECRETARY STANDAERT: Yes. This will be

the conflict of interest statement for January 28th, 1999.

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

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

In accordance with 18USC208 B3, full waivers have been granted to Dr. Marvin Konstam, Dr. Ralph D'Agostino, and Dr. Peter Kowey. A copy of these waiver statements may be obtained from the Agency's Freedom of Information office, room 12-A30 of the Parklawn Building.

In addition, Drs. Dan Roden, Milton Packer, and Lemuel Moye are recused from participating in all matters related to Tikosyn.

Further, we would like to disclose that Dr. Califf's institution was previously involved in research relating to Tikosyn, and we believe this should be disclosed.

FDA believes that it is important to acknowledge our participant's involvement so that his participation can be objectively evaluated. Dr. Califf's employer, the Duke Clinical Research Institute previously participated in two studies of Tikosyn.

Dr. Califf's only involvement in these trials was to ensure that the projects were being effectively conducted, and the results were disseminated in an academic form. He was not personally involved in any way in the conduct of these trials.

With respect to FDA's invited guest speaker, Dr. Arthur Atkinson, he has reported interests which we believe should be made public, to allow the participants to objectively evaluate his comments.

Dr. Atkinson has reported that he owns

stock in Pfizer, and Pharmacia, and Upjohn. In addition he is a former corporate officer of the Upjohn company that developed one of the competing products to Tikosyn.

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

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

That concludes the statement for today.

ACTING CHAIRMAN CALIFF: Thank you. We have a large amount of data to review today, and we have a number of guests. Just looking at the logistics of the room, it is going to be very hard for many of us to see the slides, unless we sit down front.

And for that reason and others, just for

the Committee, I would like to at least put forth a proposition that we very much limit the discussion until the presentation is complete, unless there are major issues of clarification of the data that is presented.

With that, Committee members who need to see the slides and can't, we will move down front, and we invite the sponsor now to come forward with the presentation.

DR. RYDER: Good morning, my name is Steven Ryder, I'm Senior Vice President of Clinical Research, U.S. Clinical Research for Pfizer Central Research.

Dr. Califf, Dr. Lipicky, members of the Cardiorenal Advisory Committee, ladies and gentlemen, on behalf of Pfizer I want to thank you for this opportunity to present the data on Tikosyn, which supported safety and effectiveness in the conversion to, and maintenance of sinus rhythm in patients with chronic atrial fibrillation.

In the time allowed for this presentation we will present the results of both clinical and

relevant non-clinical studies of Tikosyn more commonly known by its generic name, Dofetilide.

The clinical development program for Dofetilide was extensive, and has allowed Pfizer to characterize the potential clinical benefits and risks of Dofetilide to a degree that is uncommon for this class of drug.

The overall results of this program have led to the conclusion that the antiarrhythmic properties of Dofetilide have therapeutic benefit in patients with chronic atrial fibrillation.

We will present the results of two placebo controlled clinical trials that show that Dofetilide is effective in maintaining normal sinus rhythm after either pharmacologic, or electrocardial version from atrial fib.

The results of the same two placebo controlled trials, as well as other trials in supraventricular arrhythmias, and results from two large mortality trials in patients with significant structural heart disease show that individualization of the starting dose reduces the incidence of Torsade

de points to an amount equal to, or less, than that of approved agents.

The results of the two large mortality trials do not suggest an increase in mortality among patients taking oral Dofetilide. In addition we will show data that there are no significant non-cardiac risks associated with Dofetilide treatment.

This is the agenda for our presentation. Our presentation will begin and end with discussions of the current therapeutic environment for treating chronic atrial fib, and the potential utility of Dofetilide in this setting. These will be presented by Dr. Jeremy Ruskin.

Three presentations of Dofetilide clinical data will be given. One on its pharmacokinetic/pharmacodynamic properties by Dr. Craig Brater, one in clinical efficacy by Dr. Tilman Friedrich, and one on clinical safety by Dr. Craig Pratt.

With that I would like to begin the sponsor presentation by introducing Dr. Jeremy Ruskin.

DR. RUSKIN: Thank you, Dr. Ryder. Dr.

Califf, Dr. Lipicky, members of the committee, ladies and gentlemen.

I would like to begin by just offering some very brief comments as an overview with regard to the problem of atrial fibrillation. I will try to keep my comments very brief.

I will offer just a few words about the epidemiology and the clinical consequences of atrial fibrillation, and then say a few words about the current options available for the treatment of this very common clinical problem.

Atrial fibrillation is the most common arrythmia requiring therapy that the clinician faces. It is also, unfortunately, the least well understood from an electrophysiologic standpoint, and the most difficult to treat.

In addition, at the present time, our therapeutic options for the management of this problem are relatively limited.

Atrial fibrillation is a very common problem affecting more than two million patients in the United States alone. And while it is not terribly

uncommon in younger patients, it is far more prevalent in the older population, with six percent of people over the age of 65 having atrial fibrillation.

This slide is a composite slide showing you two different population age distributions. In pink is the age distribution of the U.S. population, and in blue bars is the distribution, or age distribution of patients with atrial fibrillation.

And the point that I wish to make from this slide is a simple one, and that is that as this baby boom becomes the senior boom, the absolute numbers of patients with atrial fibrillation is going to increase very significantly, and this is, at least to the best of my knowledge, the only arrythmia that we currently treat that is increasing substantially in numbers.

Atrial fibrillation also consumes a great deal of hospital time, and it generates enormous cost. This slide summarizes for you the number of hospital days in thousands per year, consumed by various arrythmia diagnoses, and as you can see atrial fibrillation swamps all other arrhythmias, consuming

about a million hospital days per year, at a cost of approximately a billion dollars.

And this refers only to atrial fibrillation as a primary diagnosis. Its contribution as a secondary diagnosis to prolong length of hospital stay and other situations, is also well appreciated.

The consequences of atrial fibrillation are also well known. The primary reason for treating the problem relates to symptoms. Perhaps less well appreciated is the very important contribution of atrial fibrillation to the development of congestive heart failure.

The problems of increased risk for stroke and death are also very widely and well appreciated. And, unfortunately, in 1999 we have no data for any form of antiarrhythmic therapy that control of atrial fibrillation reduces risk for stroke or death. Those data are simply not available.

It is also important to emphasize that patients with atrial fibrillation represent a broad spectrum with regard to symptoms, ranging from those who are entirely unaware of the presence of their

arrythmia, to those who are incapacitated by it.

And, obviously, any discussion of therapy directed at rhythm control must be involved with, and directed towards patients with significant symptoms.

This cartoon simply delineates for you differences between paroxysmal and chronic atrial fibrillation, and this distinction is important in light of what you will hear with regard to the data on Dofetilide.

Paroxysmal atrial fibrillation, which has been the commonest target of drugs which have been submitted for approval for an AF indication, have been studied largely in patients with frequently recurring, highly symptomatic discrete episodes of AF, in which symptoms of palpitations, dizziness, and dyspnea predominate.

And, generally, in patients in whom the onset and the offset of the event, both in terms of the rhythm, and the symptoms accompanying it, are very discrete and well-defined.

On the other hand, chronic atrial fibrillation which generally affects a somewhat sicker

population, more commonly is associated with dyspnea, fatigue, and weakness, and diminished effort tolerance. And it is often a lot more subtle and insidious, in terms of its onset, and a lot more difficult to measure precisely because of the chronicity of the problem, and its frequent association with other forms of heart disease.

This slide summarizes for you the available treatment options for the management of atrial fibrillation, and these are well appreciated by everybody here, and include the use of rate control in patients in whom loss of atrial transport is not the primary problem, but rapid rates are.

In the subset of patients, however, in whom loss of atrial transport is the primary cause of symptoms, antiarrhythmic drugs are used for maintenance of sinus rhythm, and the available options are listed here, and include the Class 1A and 1C drugs, the 1C being widely employed but limited by labeling to patients without structural heart disease, precisely because of the results of the cardiac arrythmia suppression trial, which you heard mentioned

in the public comment period.

Sotalol and Amiodarone, which are not approved for use in atrial fibrillation factor widely employed for this problem in patients with structural heart disease, and constitute important therapeutic options in this population.

Nonpharmacologic therapies are in their infancy at this point, and at present, and at least for the foreseeable future, applicable only to a very small percentage of patients with symptomatic atrial fibrillation.

I show this slide simply to emphasize one point, and that is that in 1999 we have nonpharmacologic treatment options in the form of curative catheter ablation techniques for every arrythmia listed on this slide, with the exception of atrial fibrillation, for which the mainstay of therapy remains drug therapy.

This slide lists for you the various agents currently approved for the treatment of atrial fibrillation, for conversion of atrial fibrillation to sinus rhythm, Ibutilide, and Quinidine are both

currently labeled for that indication. Ibutilide, as you know, available only for paretral use.

In terms of prevention of recurrent paroxysmal atrial fibrillation in patients without structural heart disease, the two available agents include Flecainide and propanol.

In terms of prevention of relapses of atrial fibrillation, the only approved agent is Quinidine.

This slide summarizes for you the total prescriptions written in 1997 for antiarrhythmic agents, and the vast majority of these are written for atrial fibrillation, as you will see on the following slide.

The only point that I want to make is that at the present time the two most widely employed agents are Quinidine and Amiodarone. Quinidine is still the most commonly prescribed drug for this problem. Amiodarone, the most widely used agent for atrial fibrillation in the setting of advanced structural heart disease, in particular congestive heart failure.

And this simply confirms the fact that the vast majority of these prescriptions are written for supraventricular indications, that is for atrial fibrillation. What this slide illustrates for each of the antiarrhythmic agents in blue is the percentage of prescriptions written for supraventricular indications, compared to other indications.

In conclusion atrial fibrillation is a problem of enormous public health significance. It affects a large number of patients, and is associated with very significant morbidity and costs to the health care systems.

Finally, at the present time our current therapeutic options for maintenance of sinus rhythm in highly symptomatic patients, particularly those with structural heart disease, are very limited.

Thank you.

ACTING CHAIRMAN CALIFF: Before you sit down, I think the order we would like to go in, if there are questions, would be to start with Dr. Grines and Dr. Kowey, who are the primary reviewers, and then come back to the others.

DR. ATKINSON: Jeremy, I just have a question for you, which is going to play into some things that come on later, but we still use drugs a lot for atrial flutter, even though I agree with you that ablation is a very realistic option for many of those patients.

Do you believe that drugs of this class, that we are going to talk about today, should be expected to have a differential effect on flutter versus atrial fibrillation in their efficacy?

And that plays in, obviously, to a risk benefit assessment, which you are going to come into later.

DR. RUSKIN: Well, I think that there are theoretical reasons why they might work better for flutter than fib, and you are as aware as I am of the reasons, since most flutter is a macro re-entrant right atrial rhythm, one would expect drugs that prolong action potential duration, and alter wavelength, would have a favorable effect on re-entrant rhythms, particularly macro -re-entrant rhythms.

So I would expect a differential efficacy there, with a dominant effect on flutter, or a more prominent effect on flutter.

That said, certainly, and I can only speak for where I work, our approach to flutter, when it is pure flutter, is largely an ablative approach at the present time. I suspect that is true of you, as well.

ACTING CHAIRMAN CALIFF: Other questions? Dr. Grines?

DR. GRINES: I have a question about the annual utilization of hospital beds, and I was just wondering if you knew the breakdown of patients who are just newly diagnosed with atrial fibrillation, that is why they were admitted, versus one with recurrent episodes?

DR. RUSKIN: Yes, it is a very important question, and I'm sorry, I don't have that data, and it was not available in the source that that slide was derived from, I just don't know.

ACTING CHAIRMAN CALIFF: We can start in this end with Dr. Thadani.

DR. THADANI: Regarding Amiodarone use, I

know it is not approved, but at least in my institution is used very often. And the fact one feels safe or even in a patient with pulmonary valve dysfunction.

So what do you -- you are using it in your institution for, say, 100 or 200 milligrams? I realize there are pulmonary toxicity of that, but it is a fairly safe drug, and realizing it is not approved for maintenance. So that is one question.

Other question is I'm not sure, in chronic AF, I realize the symptoms are subtle, a lot of patients don't have symptoms, and that will probably come up in the discussion, and NIH is, as you know, is doing a study to say the rate control is as good as controlling sinus rhythm. So how much emphasis you really want to pay just on conversion?

I realize some of the patients don't like Afib, so if you could address those two issues?

DR. RUSKIN: With regard to your first question the answer is yes, I certainly use Amiodarone, and I'm very glad I have it as an option. It is, in fact, the only option that I think we have

in patients with advanced heart disease, particularly congestive heart failure, and AF that requires therapy for maintenance of sinus rhythm. So it is a very effective drug, and we certainly use it.

It is not completely free of risk, as you know, particularly with regard to long term organ toxicity. But it is a very important agent, and in Europe it is the treatment of first choice, in many countries, for atrial fibrillation.

Unfortunately, at the present time, in the very sick group it is the only option that we have.

With regard to the question of whether or not to treat chronic atrial fibrillation I think is a very difficult one, but it has to come back to the question of symptoms. At least in my own practice I would only initiate a path of treatment and conversion, and long term suppression in situations where there are significant symptoms associated with the loss of atrial transport.

And I would not want to suggest, in any way, that the patient with chronic atrial fibrillation who is functioning at a high level, and not

symptomatic from the AF itself, should be treated with antiarrhythmic drug therapy.

DR. THADANI: So you are saying they should not be?

DR. RUSKIN: If they are asymptomatic for the AF, they certainly, in my personal opinion they certainly should not be treated.

DR. THADANI: So the rate control, and anticoagulation is pretty reasonable way to do it?

DR. RUSKIN: Yes, I think it is in that subset.

DR. TEMPLE: Would you agree that is a matter of opinion at this point, as Udho said, there is a randomized trial addressing that right now?

DR. RUSKIN: Absolutely. I think that everything we are talking about with regard to precisely when to treat is largely a question of personal opinion, and one has to make judgements about the level of symptoms that the patients present with. It is a clinical judgement.

In terms of data on outcome, as you've said, there is a large scale multicenter trial that

will, hopefully, provide some information about whether there is a mortality benefit to maintenance of sinus rhythm, compared to rate control, but we simply don't know that at the present time.

ACTING CHAIRMAN CALIFF: Dr. Temple, and then Dr. Cohn.

DR. TEMPLE: When you referred to symptoms, which ones do you think are most troublesome, and also respond to placement into sinus rhythm?

DR. RUSKIN: That is a critical question. What I'm offering now is just personal perspective as somebody who practices medicine, so I don't have data to support this, this is just a question of experience, and I would be interested in other people's thoughts.

But in the subset with long term atrial fibrillation, meaning months to longer than that, what I see most commonly is diminished effort tolerance, and exertional dyspnea with minimal activity.

And there are people with chronic atrial fibrillation who know that their lives are infinitely

in sinus rhythm than in AF. They may not be acutely, absolutely incapacitated by the AF, but they feel that they are very different people in terms of their ability to function and exert themselves in sinus, compared to atrial fibrillation.

DR. TEMPLE: Just one other question. When someone is converted would you, ordinarily, or would everybody ordinarily stop any anticoagulants, or do you keep that on just in case they recur?

DR. RUSKIN: I think that one of the highest risk periods for systemic embolism is immediately after conversion. So I think that most people would accept the need to be very aggressive about anticoagulation following cardioversion, in virtually everybody who can take an anticoagulant.

DR. TEMPLE: And is there some time after conversion when you breathe a sigh of relief and stop it?

DR. RUSKIN: The conventional wisdom, Dr. Temple, is that you can stop it if there is no recurrence at a month or so. I don't do that unless I'm absolutely sure. And there are many, many

situations where I feel I can't be sure, and I'm very aggressive about continuing anticoagulation in a large percentage of patients.

DR. TEMPLE: So you would not urge that one of the obvious benefits of prolonging the period of time before you recur, or anything like that, is that you get spared coumadin?

DR. RUSKIN: I generally don't -- I don't argue that point. There are some patients in whom the onset of AF is so clearly defined by symptoms that you can be quite confident that if they are not having symptoms that you can stop anticoagulation.

But that, by no means, applies to everybody.

ACTING CHAIRMAN CALIFF: Peter? You had another question.

DR. KOWEY: Jeremy, can I just clarify a little bit of a nosology, because it is going to happen all through the day. And I know that people have tried to put names on atrial fibrillation but I'm really kind of concerned about this term chronic.

Maybe we can agree that maybe John Camm is

right, maybe there is a persistent form of AF, which I think is the target for the clinical trials we are going to talk about today, and chronic is maybe atrial fibrillation that is fixed, and with no hope of reversion.

Do you think that is reasonable?

DR. RUSKIN: I think that is entirely reasonable, and your assessment of what we are talking about is accurate. I think we are talking about, in the Camm classification, what would be persistent atrial fibrillation, rather than permanent atrial fibrillation; persistent being longstanding, but convertible.

ACTING CHAIRMAN CALIFF: If we could try to keep discussion to pertinent things to the application, and not just interesting issues in atrial fibrillation. Udho?

DR. THADANI: Another question relevant, perhaps, to the discussion later on. When I was reading this, they say Afib has to persist for 24 hours, or whatever. That is something new to me. To me Afib recurs, it recurs, you know? You

cardioversion somebody, and two hours later the patient is in Afib, you cardioversional therapy didn't work.

And the definition in the two trials, let me hear it, I'm not prematurely emptying it, is one is one hour, one is 24 hours. To me, a patient goes into Afib, is that a risk of thromboembolic, so I'm going to anticoagulate him for a while.

What is your feeling on the review, when you are talking about maintenance, because a lot of patients, even what we call as a sustained afib, after cardioversion could be paroxysma. And that is why your rate at six months could be different at 12 months.

So just a short comment on that.

DR. RUSKIN: Yes, I agree with what you are saying. There are protocol issues around definitions of recurrence that you will hear about, and that I'm sure will be discussed.

ACTING CHAIRMAN CALIFF: Any questions on the right-hand side? Joan?

SECRETARY STANDAERT: Just a quick

question. You said the median age of people in the United States with atrial fibrillation is 75, and I assume that about half are women, is that correct?

DR. RUSKIN: Yes, it is roughly evenly distributed, although because there are more women alive -- excuse me, it is not evenly distributed. It is more common in males than females.

But because there are more women alive over the age of 65 it is roughly equally balanced in the population.

ACTING CHAIRMAN CALIFF: Okay, I think we are doing pretty well, let's move on to the next presentation.

DR. RUSKIN: Thank you. I would like to introduce Dr. Craig Brater who will discuss clinical pharmacology of Dofetilide.

DR. BRATER: Thank you, Jeremy. Dr. Califf, Dr. Lipicky, members of the Advisory Committee, ladies and gentlemen.

I'm Craig Brater, I'm from Indiana University, and I have been asked to present the clinical pharmacology aspects of this drug.

With all drugs it is important to understand the relationship between dose and response, as shown here. And this is particularly the case with cardiovascular drugs.

The sponsor has conducted an extensive clinical pharmacology program on Dofetilide in order to understand the relationship shown here, and the determinants of disposition and response.

In defining this relationship one must understand the variables shown here on the bottom that can permute the linkage between dose and concentration, and then between concentration and response.

In this presentation I will first summarize studies that examine the determinants of pharmacokinetics, and then pharmacodynamics.

In so doing I will show the derivation of a method for individualizing dosing that accounts, firstly, for pharmacokinetic variability, and secondly for pharmacodynamic variability, and then I will conclude with data showing the PK/PD relationship with Dofetilide to serve as a background for further

discussions of efficacy and safety.

Let's first turn our attention to the pharmacokinetic characteristics of Dofetilide. The absolute bioavailability is greater than 90 percent. As such there is no risk for drug interactions involving pre-systemic clearance.

And, moreover, this high bioavailability implies negligible metabolism at the gut wall by CYP3A4, and negligible intestinal secretion by P-glycoprotein.

There is no effect of food on bioavailability, although as one would predict, T-max, the time at which peak concentrations occur, was delayed by about one hour.

In pondering absorption one must also consider interactions of bioavailability that can decrease absorption. The lack of effect of the drugs listed here indicates limited risk therein.

There was an interaction of absorption with immediate release for Verapamil, which caused a 43 percent increase in peak Dofetilide concentration that was due to more rapid absorption. There was not

an equivalent increase in overall exposure.

This may be due to increased GI blood flow that has been reported to occur with Verapamil, whether or not this occurs with sustained release for Verapamil, or with potassium is unknown.

The majority of Dofetilide dose, approximately 70 percent, is eliminated by the kidney. The magnitude of Dofetilide renal elimination indicates that Dofetilide clearance is predictably affected by level of renal function, which also indicates a need for dosage adjustment based on renal function.

In a moment I will show you data assessing the relationship of Dofetilide clearance to renal function, and how it allows design of a regiment for dosage modification.

Dofetilide has a high renal clearance that exceeds GFR, approximately 250 milliliters per minute. Secretion is the dominant component of renal elimination, accounting for 85 percent of renal excretion.

This high degree of renal secretion

indicates a need to define the relevant secretory pathway, and thereby identify potential drug interactions that might occur therein. I will also discuss this issue subsequently.

The next slide shows the relationship between renal function, estimated by the Cocockroft-Gault equation, and Dofetilide clearance. On the X axis is creatinine clearance, estimated from the Cocockroft-Gault equation, on the wax, this is Dofetilide systemic clearance.

This relationship has been assessed as individual studies in patients with moderate and severe renal impairment in patients throughout phase 2 and 3, and in a renal substudy of the Diamond studies.

The slope of this relationship is consistent across all groups, and is approximately 0.2. The very high R squared value of 0.84, and consistent slope, indicate that the majority of variability in Dofetilide disposition can be accounted for by renal function, thereby allowing prospective dose adjustment.

These findings have also been confirmed in the patient population studies, or patient pharmacokinetic studies of over 1,400 patients. Subsequently I will show you the method for dose adjustment, and how it performs.

But before that let's address the question of renal secretion. There are three pathways by which the kidney secretes drugs. One is the organic cationian pathway, the organic cation pathway, or via P-glycoprotein.

The organic cation pathway is not a reasonable consideration because Dofetilide is positive charged at physiological PH, in fact it has three PKs, all of which are basic.

In terms of them sorting out whether or not this is an organic cation, or via P-glycoprotein, Cimetidine is used as the traditional probe of the organic cation pathway. It has been shown to inhibit secretion of procainamide, Creatinine, and other basic drugs.

Cimetidine caused an increase in the AUC of Dofetilide of 58 percent. And this, as I will show

you, this was due primarily to a reduction in the renal clearance of Dofetilide.

This effect on Dofetilide renal clearance supports that the pathway is via the organic cation secretory path.

Theoretically other actively secreted organic cations could also affect Dofetilide secretion. This possibility was examined in the phase 3 patient pharmacokinetic data base. This data of 1,445 patients included 219 who were receiving organic cation substrates, and 20 who were receiving organic cation inhibitors.

There was no evidence of an interaction with substrates, but even with a small number of concomitant inhibitors, a decrease in clearance of 14.6 percent was suggested.

Targeted studies of commonly used organic cations should be considered to be performed.

This slide shows the data, these are the data from the Cimetidine study showing the inhibition of Cimetidine on Dofetilide clearance. There is a total decrease in clearance of 36 percent from a value

of 484 to 308. There is a minor effect on non-renal clearance, and you will see that the substantial effect is on renal clearance, as is shown in the blue column here.

Let's now address the question of whether the P-glycoprotein pathway might be involved.

P-glycoprotein transport seems unlikely since Dofetilide was not transported by Caco 2 cells. In addition Verapamil, a potent P-glycoprotein inhibitor had negligible effects on overall clearance.

These comments notwithstanding, this area may warrant further study with other P-glycoprotein inhibitors.

Ketoconazole inhibited renal clearance, and I will show you those data in a moment. And though Ketoconazole is conventionally thought to inhibit P-glycoprotein, in addition to inhibiting CYP3A4, there is also evidence that it, and fluconazole can inhibit organic cation secretion.

Thus the Ketoconazole data are still consistent with organic cation secretion, though this area may also warrant further study, assessing the

effects of Ketoconazole on other organic cation substrates.

The phase 3 pharmacokinetic data were also queried to see if there was a signal for interactions with P-glycoprotein substrates or inhibitors. In this data base were 658 patients receiving P-glycoprotein substrates, and 239 patients receiving inhibitors. There was no evidence of a clinically important interaction with either group of drugs.

Let's now turn to the component of the -- the metabolic component of Dofetilide's elimination on the next slide.

Metabolism is a minor pathway of elimination compared to the kidney, accounting for about 30 percent of a dose. The metabolites are at such low concentrations that they have not been quantifiable in plasma, they have negligible intrinsic activity, the potency is less than 5 percent, and therefore they do not contribute to activity.

Dofetilide has negligible affinity for CYP iso enzymes, other than CYP3A4. A variety of in vitro and in vivo studies indicate that CYP3A4 is the iso

enzyme of interest in Dofetilide metabolism.

The low affinity of Dofetilide for CYP3A4 predicts lack of inhibition of the metabolism of other substrates of this iso enzyme. This has been confirmed by a variety of clinical trials, and I will list those subsequently.

Ketoconazole, a very potent CYP3A4 inhibitor, and I presume we would all accept the most potent inhibitor available today, caused a 55 percent increase in exposure to Dofetilide. Part of this was attributable to inhibition of metabolism, and part attributable to decreases in renal clearance. The data are shown on the next slide.

This slide shows the effect of Ketoconazole on both renal and non-renal clearance, and the data are shown in the table incorporated in the slide.

As discussed previously, the effect on renal clearance, which is the dominant component here, appears to be via inhibition of organic cation secretion.

The potency of Ketoconazole means that the

magnitude of effects seen here likely represents the maximal inhibition of CYP3A4 that might occur with any other interactants via a metabolic pathway.

Ketoconazole decreases non-renal clearance, shown here on the table, by about 50 percent. Since non-renal clearance represents about 30 percent of total clearance, this amounts to an approximate 15 percent decrease in total clearance that can be attributed to the metabolic effect.

This value serves as a reasonable frame of reference when considering the potential impact of other drugs that might inhibit CYP3A4 to a lesser degree.

We also queried the phase 3 population pharmacokinetic data for -- to see if there was a signal for interactions with drugs that are either substrates or inhibitors for the CYP3A4 pathway. There were 108 patients receiving substrates, 27 patients receiving inhibitors. There were no signals of a clinical important interaction in that data base.

The next slide summarizes these interaction data. On the left grouping is a group

disappointing.

One of the things that one could speculate about, and this is pure speculation, is that there are probably mechanistic differences between paroxysmal and persistent atrial fibrillation. At least in a substantial percentage of patients.

And there is now increasingly impressive data on the role of focal tachycardias from the pulmonary veins as the primary triggers of paroxysmal AF. And if that is the case one might not expect them to respond to a class 3 agent.

But that is very highly speculative, and I don't think it provides a comforting or absolute answer to that. I just don't have an answer.

DR. KOWEY: It really is a very important issue in labeling because physicians have to be warned that they don't have a hope of having this drug work for a population of patients they are used to treating.

DR. PRATT: I think that is correct, I think we have to go with the data, and the data that we have, that demonstrates efficacy is in people with

SGE CONSULTANTS:

DR. RALPH D'AGOSTINO
DR. PETER R. KOWEY

GUESTS:

DR. ARTHUR ATKINSON
DR. J. THOMAS BIGGER

ALSO PRESENT:

DR. STEVEN RYDER
DR. JEREMY RUSKIN
DR. TILMAN FRIEDRICH
DR. CRAIG BRATER
DR. GLEN ANDREWS
DR. BRADLEY MARSHANT
DR. CRAIG PRATT
DR. ROBERT TEMPLE
MR. LARRY SASICH

where there is no effect of Dofetilide on this list of drugs, and that would be as is predicted from the in vitro studies.

In the middle are a list of drugs where there has been no effect demonstrated by them to have an effect on Dofetilide, and in addition the population pharmacokinetic analysis indicated no effect on these concomitant drugs.

On the right are the three drugs for which a significant interaction has been identified. Again, Cimetidine occurs through an effect on renal secretion, Ketoconazole through an effect on secretion plus inhibition of metabolism, and Verapamil, by affecting the rate of absorption.

A study of hormone replacement therapy has been completed in terms of all of the patients have been enrolled and completed the study, and the data are currently being analyzed.

The sponsor has also explored the influence of patient demographics and concomitant disease on pharmacokinetics. As noted previously, there is an extensive data base for doing so. There

have been pharmacokinetic evaluations in more than 1,500 patients in phase 2 and 3, with over 10,000 plasma concentration measurements.

Analysis of this data base indicates that neither age, heart disease, type of arrythmia, nor hepatic impairment are independent predictors of Dofetilide clearance after accounting for renal function.

What about a gender effect? Dofetilide plasma concentrations were about 12 percent higher in young healthy female volunteers compared to men.

In one study specifically designed to assess gender differences in pharmacokinetics the gender difference could be completely explained by differences in body weight. However, in contrast, gender related differences were still seen in the larger population of pharmacokinetic data base collected in phase 3.

The concentration differences shown here would translate into a two to four millisecond higher QTc value in women than in men.

The next slide summarizes the

pharmacokinetic features of Dofetilide. Dofetilide pharmacokinetics are predictable. This is reinforced in particular in the population studies.

In phase 3 variability among patients in clearance was 24 percent, after accounting for renal function. Again, after accounting for renal function.

That volume of distribution was 28 percent after accounting for body weight, and the residual variability was 27 percent. These values are small.

The pharmacokinetics are linear, and the multiple dose pharmacokinetics are predictable from single doses.

Consistent with a half-life of 10 hours, steady state is achieved within two to three days. As stated, between patient variability, and the pharmacokinetics is low after adjustment for renal function. It is clear that the dependence they are in is such that doses need to be adjusted in patients with decreased Creatinine clearance.

Following is a scheme to individualized dosing that was implemented in the phase 3 trials. As indicated, treatment is initiated in hospital with

continued CG monitoring, a serum Creatinine is obtained, and by using the Cocockroft-Gault equation, creatinine clearance is estimated, and then dose is adjusted as shown here in this middle box.

This scheme adjusts doses in a fashion to account for the main determinant of the pharmacokinetic variability. Subsequently I will discuss considerations in pharmacodynamic variability.

The next slide shows how this dose adjustment performed in patients. This figure shows the average state plasma concentrations observed in patients in phase 3 studies, for the patients with normal on the right, and reduced renal function.

It includes patients in a renal substudy of Diamond, who were dosed according to the dosage algorithm, and patients in the two pivotal chronic atrial fibrillation studies who were randomized to receive 500 micrograms twice a day, some of whom received lower doses due to the reduced renal function.

The concentrations in patients with low renal function are within the range of values for

those with normal renal function, so these bands are pretty much the same.

The dosing adjustment was introduced after the start of study 120, so a few patients with low Creatinine clearances received 500 micrograms twice a day. These are marked in blue in the middle column.

It is apparent that these concentrations were at the upper end of the range of concentrations. If dosing adjustment had been applied, these values would be half those that are shown, which would drop them down into the range with all of the other patients.

So it appears from this data that the dosing individualization scheme works as it should.

We now turn to the pharmacodynamic aspects of Dofetilide effects. Firstly, some of its hemodynamic effects. As a PRKR blocker, Dofetilide would not be expected to have a negative anatropic effect.

This has been demonstrated in two invasive clinical studies of patients with left ventricular impairment. Study 127, which is shown across the top

of this slide, was performed by Dr. Risseau in Belgium. These investigators randomized 32 patients with heart failure, and LVEF's less than 35 percent, to Dofetilide or placebo given intravenously.

Study 105, which is shown across the bottom, was performed in the U.S. In this study 29 patients were randomized, they had ventricular tachyarryhtmias, and left ventricular ejection fractions between 20 and 30 percent.

They received either Dofetilide 250 micrograms three times a day, 500 three times a day, or placebo.

All patients were in sinus rhythm in both of these studies. There is no negative effect on cardiac index, small increase in left ventricular ejection fraction, and no change on the right, in systemic vascular resistance.

Data from study 120 in patients with atrial fibrillation show the effect on hemodynamics when patients are converted to sinus rhythm. Cardiac index is preserved, shown on the left panel, despite a reduction in heart rate, shown in the red line,

associated with the conversion from atrial fibrillation to sinus rhythm.

Since Dofetilide is an IKR inhibitor, it is predictable that it will affect the QTc interval. And, indeed, there is a direct relationship between QTc and plasma Dofetilide concentrations shown here.

So on the X axis we have mean Dofetilide concentration. On the Y axis we have change from baseline and QTc.

After a single dose, which is shown in blue, the slope is approximately 15 to 20 milliseconds, and this relationship has been confirmed in the population studies.

Attenuation to sensitivity occurs during the first few days of dosing, where in a steady state, shown in red, the slope is about 10 milliseconds per nanogram, per milliliter.

Of note, the horizontal bar shown in this graph is white, it may be a little difficult to see, is that it represents the concentrations achieved with a 500 microgram BID dose.

Despite this good relationship some

patients are likely to have greater sensitivity. As such, incorporated into the dosing regimen is a step to account for pharmacodynamic variability, as shown in the next slide.

The top part of this slide I've shown you before, and after dose adjustment occurs on the basis of renal function, patients are -- again have consideration for dose adjustment based on their own response.

So if the QT/QDC is prolonged greater than 15 percent, or goes to a total duration of greater than 500 milliseconds, then the dose is, again, decreased to half over and above any reduction that was based on changes in renal function.

Since concentration correlates well to QTc, one might also predict a correlation with response. Our last slide examines this relationship in terms of looking at the effects of QTc and how they relate to efficacy.

So in the columns we have the probability of remaining in normal sinus rhythm at six months, and in the lines, the vertical lines, are the change in

QTc interval from base line.

And you can see that each has approximately the same slope indicating a relationship here.

I hope that these last couple of slides, in particular, will serve as the basis for your thoughts in terms of thinking about the efficacy and safety of this drug.

And that concludes my comments about the clinical pharmacology of Dofetilide.

ACTING CHAIRMAN CALIFF: Thank you. This is a lot of information. Again, I would like to give Dr. Kowey and Dr. Grines a chance to ask the first questions, and then we have Dr. Atkinson as a special consultant, who I think will -- we are going to look to for a lot of help here.

DR. KOWEY: Craig, the reason why this is such an important discussion, it seems to me, is that there is this linear relationship between plasma concentration QT effect, efficacy, and Torsade.

And so I think this is really a critical part of the discussion. One of the things I'm having

some difficulty with is drug interactions, and maybe you can help me.

What you've said is, basically, that if you take the most potent inhibitor, CYP3A4, that we know of, which is Ketoconazole, and you estimate its renal effect vis a vis its non-renal effect on metabolism, as a gross estimate, that it is somewhere in the vicinity of 15 to 20 percent, maybe closer to 15 percent of its potentiating effect of Dofetilide is hepatic, or likely to be, non-renal.

And then if we then go backwards we could say that there is lots of other inhibitors of this enzyme system that we wouldn't expect them to be as potent.

Do we have to worry about that? I mean, do we have to go back and actually look at some of these drugs, antibiotics for example, that might influence that enzyme system? Because it is an assumption which I think is probably correct, but I'm a little concerned about it, because the stakes are pretty high here.

DR. BRATER: I guess you could approach it

in two ways. You could either say, if you indeed believe that Ketoconazole is the biggest effect you are going to see, you could say, okay let's be ultraconservative and say, all the other things that inhibit that iso enzyme, let's just presume that they are going to have a similar effect and label accordingly.

Alternatively, you could go back and try to define, with more precision, by individual trials with some of those different drugs, and try to map out the degree of effect that is going to occur.

And I think that, in turn, is probably going to boil down into the thought process that you all have about the width of the therapeutic margin here, and how that leads you down either of those paths.

DR. KOWEY: You see, I don't think there is a whole lot of room, and that is why I'm having this problem, and we are going to be faced with -- and if you look down through the questions, you always do that to find out what the bottom line is going to be here, we are going to be asked a question, at the end

of the day, are there other studies that need to be done.

DR. BRATER: Right.

DR. KOWEY: And my concern is that if we don't have studies, I think you are absolutely correct, that if we don't have a study of a drug interaction, and a drug which is in the category of a drug that blocks that enzyme system, and a drug that has a fairly narrow margin for safety, that we are going to have to make the worse case assumption, and label the drug so that every single drug on that long, long list is put into the labeling as being a problem, and the drug needs to be dosed accordingly.

Is that -- I may have paraphrased what you have already said.

DR. BRATER: I'm saying the same thing you are. And the same thing, it goes to the cationic secretory pathway. We have data with Cimetidine. There are -- that is a short list of potential inhibitors there, but so the question is, do you take Cimetidine as the worse, and then presume everything else is -- and lump everything else in that category

or do you do specific studies.

So it is exactly the same thought process.

ACTING CHAIRMAN CALIFF: Dr. Grines?

DR. GRINES: A couple of questions on the hemodynamic effects. And one is on the bar graph you showed for ejection fractions. I wondered if you knew the sample size?

DR. BRATER: Is this the hemodynamic data?

DR. GRINES: The hemodynamic effects of normal sinus rhythm.

DR. BRATER: No, I don't know the sample size, approximately 25 patients.

DR. GRINES: 25 patients. Yes, because it seems like there is a huge increase in ejection fraction, and that is hard to --

DR. BRATER: That is percent of a percent, I believe. That is not an absolute -- all the changes on that graph are percent changes.

DR. GRINES: It looks like an absolute ejection fraction, actually, the way it was plotted.

The second question on the dosing

individualization, there is recommendations for cutting to half dose if the QT interval is prolonged. But in the study actually several patients were completely discontinued due to QT prolongation, and I wondered, with regard to these QT intervals, at what level of prolongation would you recommend completely discontinuing the drug, and how often does one have to measure this?

DR. BRATER: I can't answer the first part of your question, you are going to have to depend on your cardiology colleagues, I think, to answer the -- you know, where you would absolutely quit the drug in terms of what QT. I'm a poor country clinical pharmacologist, so I don't know that.

But the other question, you had another part to your question, which was --

DR. GRINES: I guess I'm just a little confused.

DR. BRATER: The stability of the QT. I haven't seen the data myself, but I'm told that the QT is very stable in terms of its relationship to plasma concentration throughout the course of therapy.

ACTING CHAIRMAN CALIFF: Will we have a chance to see that data later on about the stability of the QT? Okay.

DR. BRATER: I see people nodding their heads yes.

DR. GRINES: It is my recollection that in the studies the QT interval was measured just after the first dose, is that correct? And so, therefore, does that mean you don't have to measure it subsequently if it is stable?

DR. BRATER: My recollection is that the greatest prolongation is, as one might predict, which is about the peak time after the first dose, which is when you have your greatest sensitivity, and thus your plasma concentrations are coming up, so it is two to three hours after the first dose.

But I think the dosing recommendation is to monitor throughout this three day period, and make sure that if there are others that exceed that, that those are ones that are taken into account in terms of changing the dose.

DR. KOWEY: Can I just follow up on that

a little bit, Craig, because it will come into some practical concerns with a poor country cardiologist using the drug.

If you start somebody on the drug at a dose level that is calculated based on the creatinine clearance, and you have the patient in the hospital, monitoring their rhythm, and their QT interval, is it three whole days before you can say that you don't have to do anything more with the dose because the QT interval didn't prolong, or can you get away with a shorter period of time?

DR. BRATER: My bias is that they ought to be in there for three days of therapy on Dofetilide. And one of the reasons for that is from a pharmacokinetic -- a lot of these patients are going to have decreased renal function, and their half-lives are going to be longer, and so you want to make sure that they are in there long enough to get the steady state.

So in that group of patients with the lowest level of renal function, 20 to 40, their half life is about 21.7 hours. And so the three days will

get them like 90 percent to steady state.

So if for no other reason they ought to be in for three days just to make sure you capture that group of patients.

DR. KOWEY: And then after that, let's say for the sake of argument, I've cut the dose based on a QT prolongation that is protocol defined, and you are now down at a lesser dose level, do you keep them for three more days to make sure that at that steady state plasma concentration their QT is going to go back; or do you say, that should be enough, I can send them home now?

DR. BRATER: Well, I hadn't thought about that, but I -- just off the cuff, I would say that like most things it is probably going to be a clinical judgement, which might impart, do you know how long did it go out, did it go out 16 percent? And that triggered it, or did you -- you know, did it go out further and so you are more worried and you make sure you want to really follow that patient more closely.

So I guess you would have to dial that into the individual patient. I don't know if

recommendations have been thought of in terms of that scenario.

DR. KOWEY: This is -- it occurred to me in the middle of reading this, I was trying to go through, well what is, as I said, try to just be an old country cardiologist, and I'm in the hospital, and I have a patient, I put them on the drug.

I think we have to be a little bit more definite about what the recommendations are going to be, as we dial back the dose. Because this is a very novel way of dosing, as you know, with an antiarrhythmic drug. We don't dose antiarrhythmic drugs this way. We do with Amiodarone, but nobody knows what the right dose is there, anyway, so that doesn't matter.

But here we do think we know what the right dose is, and we are going to be giving very specific instructions about a very novel way of dosing the drug to people who aren't used to using this drug, and doing it this way.

So I guess what my question is, do we have to maybe do some studies, or do we have to think about

this some more to come up with a way of approaching this?

Because I'm very uncomfortable not being able to tell people how to do this. Does anybody else, on the panel, because I haven't been able to figure this out. Or does anybody else from the company want to respond?

ACTING CHAIRMAN CALIFF: Peter, let me suggest that we -- I mean, I think when we hear the efficacy data wed be a better time to discuss this.

DR. KOWEY: It is not in there, Rob. I mean, you can wait until the end of the day if you want to, but I'm telling you that we don't have those kinds of data in the -- I haven't seen it, maybe they are going to present something. If you want to wait, that is fine.

ACTING CHAIRMAN CALIFF: I really would rather wait, because if we get into this discussion now, we are going to have to repeat it at the end of the day anyway, about the practical. Okay?

AUDIENCE MEMBER: Dr. Kowey, just some information. The clinical trials, what was done, when

dose adjustment occurred, you want to be sure that the patient is in sinus rhythm so you would keep the patient at least one day in the hospital while the patient is in sinus rhythm.

DR. GRINES: I have one other question. You showed a graph, it is titled the concentration relationship in young volunteers over 24 days. And in that graph I think you described an attenuation of the QT interval?

DR. BRATER: Correct.

DR. GRINES: Basically the QT was longer on day 1 than it was on day 23. And my question is, are we going to be able to safely monitor the chronic effects looking at the QT interval? Because on the bar graph you see that now we have much higher doses of drug with the shorter QT interval.

Now, is the incidence of Torsade related to that QT interval, or is it related to the dose of the drug?

DR. BRATER: Well, when you -- let's flash that slide back up there, that is slide number 19. Just as a frame of reference.

I think one of the questions that you are asking, and make sure if I'm going in the wrong direction you correct me, is that basically I think one of the questions will be, how quickly does that occur, and how stable is it once you get down there?

If we call back up 96, this shows the time course of this decrease, so in black is Dofetilide and you see, and these are the same patients from which that previous figure is derived.

You see that basically you start getting this decreased sensitivity by the second dose, and you come out here and you plateau out very quickly, and it is very stable.

So I guess it is the stability of this plateauing effect that I think would -- isn't that the answer to your question?

DR. GRINES: Well, I guess my real question is, how confident are we at decreasing the dose, or discontinuing the drug based on the QT prolongation, if the QT interval is going to change over time?

DR. BRATER: I guess that gets back to the

question, again, of what is the stability of the QT throughout the time course of therapy, say six months, or something. I don't personally have those data, but I saw nods that that was going to be addressed by somebody else.

DR. GRINES: Because the dose can be -- the dose for a given QT interval, you can have a much higher dose, chronically. And if the Torsade is related to a high dose, then perhaps we could be having some late arrhythmias, even though the QT interval may look relatively normal.

DR. BRATER: Say that again? I'm not following --

ACTING CHAIRMAN CALIFF: Maybe I could try to -- I think what you are asking is, is the risk of Torsade more closely related to the QT interval, or to the concentration?

DR. GRINES: Correct.

DR. BRATER: Well, my cardiology colleagues tell me that the main reason for following QTs is because of -- is because the Torsade risk, that you wouldn't be following it as an efficacy predictor,

but basically as a safety monitor.

And I guess what we are saying is, that the concentration seems quite tightly linked to the QTc interval, so then for example, if you are going to think about monitoring the patient, it makes more sense to monitor the QT than it does to, say, monitor the plasma concentration.

ACTING CHAIRMAN CALIFF: Dr. Bigger, do you have a comment on that?

DR. BRATER: Because that is closer to the end point of adverse effect.

DR. BIGGER: I have a question right along that line, on that slide 19, in that very nice slope of the QT change on the dose, or the concentration of Dofetilide. If you are in a steady state, and you alter the serum potassium substantially, say with diuretics, or something else, in a current diarrhea, or whatever, does that slope shift up or down, or is it sensitive to changes in potassium that might occur in the usual course of events in people with heart failure and so forth?

DR. BRATER: I don't know that that study

has been done. I didn't see it in anything that I reviewed, but it could have escaped me. The best I can say is that there, I think in the supplement that went out, there was a pretty detailed analysis of risk of Torsade and of mortality according to a whole lot of concomitant medications in substantial numbers of patients, as you would expect, who were on diuretics, both thiazides and loops.

And my understanding of those data is that there was no -- that is epidemiological data that there was no signal that there might be an increase in mortality, or Torsade. But that is not a direct answer to your question, of course.

DR. BIGGER: The pharmacokinetic question I have, in Diamond CHF, I think over 90 percent of the people who are taking diuretics. But it didn't differentiate which kinds, and I wondered, since the different diuretics posited in different segments, and tubal, if there is any relationship to particular diuretics, or diuretic combinations that might affect the renal clearance of Dofetilide?

DR. BRATER: Well, the potassium sparing

diuretics, ameloride and triamterene, not spermalactone, but ameloride and triamterene are organic cations that are secreted by the nephron.

So there is a potential for -- and a pharmacokinetics interaction there. But I wouldn't suspect a pharmacokinetic interaction with thiazide or loops.

ACTING CHAIRMAN CALIFF: I want to give Dr. Atkinson a chance. And what I would urge, based on what I've heard so far, would it be correct to say that, Dr. Brater, you are not going to answer clinical cardiology questions, but renal questions of pharmacokinetic, or pharmacodynamic questions you are prepared to answer?

DR. BRATER: That's correct.

DR. ATKINSON: Thank you, Dr. Califf. I would like to ask a few questions, because I probably will be silent for the rest of the presentations.

I think, Craig, first of all you have summarized an awful lot of very interesting data very elegantly for us today.

DR. BRATER: Thanks.

DR. ATKINSON: But, really, all the nuances of drug interactions, and variability, and pharmacokinetics, have an importance, really, that relates only to the therapeutic index of the drug.

And I think we've heard from the floor,earlier today, that there is general concern between the therapeutic, the levels or dose that may cause therapeutic efficacy, and those that cause toxicity.

And I wonder if you have, or the company, has any data on therapeutic index, not necessarily relating to the QTc interval prolongation, but Torsade which is the main concern here.

DR. BRATER: It is clear, from the data I have shown you, that there is a good relationship between concentration and QT, and if QT is the predictor of Torsade, you might expect that well gee, we ought to see a good relationship here than between concentration in plasma and Torsade.

The problem, I guess, is that there are so few patients in the data base with Torsade, that you can't really do that analysis now. There has been an

attempt to look at analysis between relating concentration to efficacy in terms of maintaining normal sinus rhythm.

I showed you the relationship between QT and normal sinus. That is also a difficult one because it is, in my simplistic approach to things I thought, well, we can just do some sigmoid max plot of CP versus response, but I was shot down by biostatisticians and said, you have to do a Kaplan-Meier approach, because these are categorical data which makes that much more difficult.

That analysis has been done. To me that shows a relationship. I can show it to you, if you would like.

DR. ATKINSON: I would like to see it.

DR. BRATER: That is backup slide 203. So here on the X axis we've got these categorical data of different serum concentration values, probability of remaining in normal sinus rhythm, similar to what I showed you with the QTc normal sinus rhythm thing.

And at least to my eye, you see this coming up and plateauing out.

DR. ATKINSON: Thank you. From my calculations I would estimate that the sponsor intends to recommend the dose that would achieve effective concentrations for maintenance.

DR. BRATER: Well, if we could have that slide back, I guess we could put a frame of reference where the 500 microgram BID would be out in this range.

DR. ATKINSON: Exactly, and that is with appropriate adjustment for renal functional status?

DR. BRATER: Right. So patients who had decreased renal function, if they were supposed to get 500, and you down titrated it, I think I showed you data that shows that that keeps those patients in the same kind of concentration range, so they would be in the same kind of bar.

DR. ATKINSON: Is there evidence to suggest that the levels required for initial cardioversion from atrial fibrillation might be different than those required for maintenance? Or is that not --

DR. BRATER: I don't know that that

analysis has been done. That is not been looked at.

DR. LIPICKY: Before that slide goes away if you would show that slide again? If you believe that data, where would you put the EC50 for the therapeutic effect?

ACTING CHAIRMAN CALIFF: For the audience, could you define AC50?

DR. LIPICKY: The concentration at which about 50 percent of the efficacy effect occurred, or about 50 percent of the patients would have a good effect from the drug.

DR. BRATER: Well, that is why I wanted them to do a sigmoid max kind of thing, but they said you can't do that. But if I look at my eyeball, and subtracted out placebo, and looked at that curve I would say, maybe you are in the 1.3 to 1.7 bar.

DR. TEMPLE: No, it is below .4, it is below .4, the lowest concentration gives you the easy 50, obviously. To the extent you believe all that, anyway. If you are going from 50 percent to 60 percent, or 30 percent to 60 percent.

DR. THADANI: The mode will be between the

first three lines.

DR. BRATER: Well, I don't know, this plot looks to me to be up around 65 or 70, right?

DR. TEMPLE: Well, that is the plateau that goes after .4, but most of the action is between zero and .4.

DR. BRATER: Well, but if you are do an easy 50 you map out the whole curve, right? And then you say how long does it take to get -- where do you need to be to be 50 percent up there.

DR. TEMPLE: But the lowest concentration is more than 50 percent of the effect.

DR. LIPICKY: And where is the EC50 for the QT? You know that very well.

ACTING CHAIRMAN CALIFF: This is, I think, going to be the central discussion, and I hate to think we are going to be left with us all eyeballing this bar graph and coming to conclusions.

So during the course of the day we need to come to some better resolution of --

DR. ATKINSON: Having raised the specter of therapeutic index can I focus now a little bit on

pharmacokinetics?

You've shown a very good relationship between overall clearance of the drug, and estimated creatinine clearance. And I believe your correlation coefficient squared was .84.

There are other equations that appear, as different studies, as you might expect. One point I would like to make is that although you emphasized that normally non-renal elimination is minor, it accounts for only 30 percent of elimination, obviously as renal function becomes impaired, non-renal function becomes more important.

And what seems to be unusual, at least from my calculations here, is that this is a drug in which not only renal clearance declines with decreasing creatinine clearance, but non-renal clearance declines with decreasing creatinine clearance.

And I wonder if you or the sponsor have data that actually separate out? I know you've done the renal clearance of the drug versus creatinine clearance. Can you show us the variability in non-

renal clearance now, as creatinine clearance declines?

DR. BRATER: If we bring up backup slide 11. Went back to some of the previous studies and calculated total clearance, renal clearance, and non-renal clearance at the different levels of renal function.

The patients on the far right would be recommended to be excluded from therapy. So the ones in the middle, which would be the lowest, non-renal clearance drops from 7.8 to 5.6. But, as you point out, becomes a substantial component of the overall clearance, probably three quarters or more of overall clearance.

So there is, clearly, a decline in non-renal clearance with decreasing renal function. That is not unprecedented, as you know, that is seen with other drugs. We don't know the mechanism for that, but it certainly does occur with Dofetilide.

And you can also see that by the slope, the intercept of the slope of those relationships if you look close.

DR. ATKINSON: That brings me to another

point. By looking at the intercept of the slope we are, in fact, extrapolating from a curve that has been incompletely characterized.

And one obvious deficiency that I saw in an otherwise detailed kinetic package is that there is no study, at least that I'm aware of, of Dofetilide kinetics and functionally nephric subjects.

I mean, here is the population where non-renal clearance accounts for 100 percent of elimination, and I think I may have seen, in fact, a draft package insert where the recommendation for patients with creatinine clearance less than 20 is to individualize the dose.

And I submit that if you don't have an estimate of what the clearance is for those patients, it is awfully hard to individualize the dose, using the paradigm that you recommend.

DR. BRATER: I think that gets to one of the questions that you all will be faced with later in the day.

DR. ATKINSON: Okay. Another question that I think is germane to the proposed strategy of

individualizing dose based on creatinine clearance is the extent to which creatinine clearance is determined, or estimated, if you will, from the Cocockroft-Gault equation in hospitalized patients.

I wonder if you could give us an estimate, from your medical center in Indiana, as to how many patients in the hospital really have their creatinine clearance estimated?

DR. BRATER: I guess it depends on who is your attending that month. When I'm attending, every one of them.

I think that is a rhetorical question, but you are asking about the awareness of the potential users of this algorithm. And I think that is an issue that needs to be considered in terms of how that kind of education is going to occur, and even questions like should it be -- you try to get people to remember an equation like that, or should you develop a little nomogram that we've all seen, where you just have to lie a straight edge across something, and that helps give you the dose.

There are a lot of different ways to

slice, to try to slice that cake. But the bottom line is that you are going to have to educate people on how to estimate renal function in patients who are going to receive this drug, and adjust the dose.

DR. ATKINSON: I would submit to you that educational efforts are not terribly effective. I mean, this may be that I'm a poor teacher, but I haven't had much success with it. And, in fact, it seems -- and I will pass this on to the company, it seems inappropriate in this day and age of computers to expect busy physicians and pharmacists, and nurses, to do these trivial calculations themselves.

The real problem here is that clinical chemistry laboratories report serum creatinine measurement which in many cases is frankly misleading. There are patients with grossly abnormal renal function that have normal serum creatinine values.

Someday, hopefully, we will get the hospital data systems to bring the patient age, and body weight, and gender together with the serum creatinine number, and actually calculate the creatinine clearance or estimate it automatically.

But that may work better for the company to focus on, than trying to continue educational efforts. And I think, Craig, you and I both will say have largely been futile.

DR. BRATER: Yes, well, and we have electronic medical record that we can actually feed that to our doctors, and that is the ultimate solution.

DR. ATKINSON: Those are the questions that I have at this point.

ACTING CHAIRMAN CALIFF: Thank you. What I would like to do is give the right side of the table a chance to ask some questions, to start with, and work back around.

DR. LINDENFELD: I have a question. The relationship you showed between QTc and Dofetilide concentration, is that slope the same in the elderly with age, and with women versus men?

DR. BRATER: So the question is both gender and age?

DR. LINDENFELD: Right. Which I think is particularly important in the population of patients

we are considering here.

DR. BRATER: Yes. There is data on that. Let's first have the backup slide that shows it according to gender. I'm trying to find the number here. How about backup slide 99.

This looks at the slope. Now, this is single dose slope, so it would be the higher value that I mentioned. And so here is the slope in young men, young women, elderly as opposed to young.

And this was noted in the elderly study, that they might have, actually, a decreased sensitivity. But you see all of the numbers are reasonably consistent.

DR. LINDENFELD: I know this might be difficult, but can you give me some idea of what this elderly population consists of, the age range, or the median age, or something, and what was considered elderly?

DR. BRATER: Yes, we actually have that. Backup slide 73, I think, would show that. I don't know if this is the graphical presentation. How about 74? That is the graphical presentation, I believe.

So here is the age distribution, it is pretty broad, a lot of elderly people.

DR. LINDENFELD: Second question, in pharmacodynamics. Do you have any data on the -- we had some concerns, I noticed, in the packet, about blood pressure, and heart rate in patients on beta blockers, and also patients on diltiazen.

DR. BRATER: I don't on Diltiazen. Well, pharmacodynamics data on it. We've queried the population data base in terms of interactions with things like Diltiazen, and Diltiazen also fits in the 3A4 category of potential inhibitor substrate, and did not see a signal for any interaction.

But there is a propranolol study.

DR. LINDENFELD: Right, and the blood pressure and heart rate dropped substantially on one of the patients.

DR. BRATER: Let me show you that.

DR. LINDENFELD: Let me show you that. So I would be concerned about Diltiazen, as well, with that.

DR. BRATER: Let me show you the

Propranolol stuff, because that is -- I think it is important to see what happened there. And we can do that very quickly.

Backup slide 54 shows the heart rate data with Propranolol. And this is subtracting out the base line, so this is changed from base line and heart rate. I mean, you see, it looks like there is a Propranolol effect.

I guess it depends on how you want to slide and dice this cake, because backup slide 55 shows that if you just look at absolute effects on heart rate, absolute heart rate in these studies.

And so, clearly, what you are seeing on the first one was a different baseline. The same thing is true of blood pressure.

So whether or not there is an interaction here, it probably is debatable.

DR. LINDENFELD: Just my last question. Someone else may want to address this. How are QT and QTc intervals measured in this study, in atrial fibrillation? And I guess I want to comment --

DR. BRATER: You are going to have to have

one of these other folks --

DR. LINDENFELD: -- both on how are they measured in terms of heart rate, and then how often could QTc actually be measured.

DR. BRATER: Well, in terms of heart rate, a bazetts correction was used. But in terms of the mechanics of how it was actually done in the studies, I think --

DR. LINDENFELD: I mean in atrial fibrillation the heart is often very irregular, that is what I'm getting at.

MR. MARSHANT: Brad Marshant, Pfizer Central Research. The QT interval was measured by instructing the investigator to select the most appropriate lead, and to use the same lead continuously throughout the study, and they were given guidance as to how to measure the end of the T-wave, and that was defined as the end of the T-wave, unless there was disturbance, abnormal T-wave morphology, in which case they were instructed to draw a tangent to the steepest portion of the T-wave, and where that tangent crossed the itroelectic line, that was the end

of the T-wave.

In study 120 we gave careful instructions as to how the QT interval should be corrected for heart rate, and investigators were instructed to measure at least 10 beats of atrial fibrillation, and then work out the heart rate from there.

DR. LINDENFELD: So, in other words, in patients with atrial fibrillation you will be asking physicians to average the QTc interval over ten beats?

MR. MARSHANT: Correct.

DR. LIPICKY: And that has to include beats where the QT was measured?

MR. MARSHANT: Certainly, it would be important that the QT was measured during the interval that -- over which you are measuring the heart rate.

DR. LINDENFELD: Which in many cases there are not ten consecutive beats on our average current 12 lead EKGs, depending on the heart rate. Just as a practical matter many 12 lead EKGs, which have all the beats right in a row don't have ten beats.

ACTING CHAIRMAN CALIFF: I know we are going to get back to this, but I guess the

recommendation of the sponsor that all patients be continuously monitored for three days would probably give you a rhythm strip.

But, then again, the question of which lead, it is an interesting set of issues.

DR. LIPICKY: You have left me with the impression, from the last slide you showed in your talk, that there is no safety margin. That is, if I look at the relationship between dose and QT, and dose and probability of being in sinus rhythm, if I want to be in sinus rhythm I have to have the QT go up.

And if I want a little better chance of being in sinus rhythm I have to have another increase in my QT. Is that the impression you want to leave, that I have no chance of having a beneficial drug effect without having a significant prolongation of the QT, and that there is no safety margin associated here?

DR. BRATER: Well, I think this is going to be discussed in agonizing detail with Craig Pratt's discussion, but I guess maybe this is an oversimplification of what you are saying, Ray, or

asking.

If you are asking, is there a dose at which you can get efficacy and completely avoid risk, the answer is probably no. So like everything else, it is a ratio thing.

ACTING CHAIRMAN CALIFF: We will come back many times to this question, I'm sure. Other questions over here?

DR. LINDENFELD: Just quickly. Were many patients excluded because the QT could not be reliably measured in atrial fib, were there many patients excluded for that reason?

DR. BRATER: Brad is shaking his head no.

MR. MARSHANT: No, there weren't.

ACTING CHAIRMAN CALIFF: Dr. Konstam?

DR. KONSTAM: Yes, thanks. I wonder if you could put back up the slide labeled interaction studies? I think it is your number 11.

DR. BRATER: Slide number 11, please.

DR. KONSTAM: Yes, there it is. I guess I'm going to be looking for any help you can give us here, because this is another area where we are going

to be concerned, given our past experiences with drug-drug interactions, and particularly here where there is going to be such a significant potential adverse effect if concentrations go up.

Can you just explain, again, what it took to get a particular drug in one of these boxes, what does it mean that a drug got into that second box with no effect on Dofetilide?

DR. BRATER: These are where studies were actually performed. So a focused interventional drug interaction study was performed where patients received Digoxin plus Dofetilide, and the effect of Dofetilide on Digoxin pharmacokinetics was examined. That is the same for all on this list.

So these are the result of directly performed studies addressing those questions.

DR. KONSTAM: What are the ends of such studies?

DR. BRATER: I don't know. What are the ends of those studies, on average? 24, maybe. Usually these studies are about 24 people.

DR. KONSTAM: Then is this the universe of

drugs on which these studies were conducted?

DR. BRATER: So that we have no useful information on any other drug besides the ones that are in this list, or definitive information?

DR. BRATER: Only indirect through the -- what is a very rich population data base. These 1,400 patients have had over 10,000 blood concentrations.

And let me stress that that should not -- there is often a tendency, certainly I have it sometimes, to dismiss that kind of data. But there was clearly a Ketoconazole interaction, right, I showed you that.

If you take the patients from those Ketoconazole study, the end of 16, and if you dump that data into the data base of the 1,445, and then you do the population analysis and say, does it pick up a signal for a meaningful drug interaction, it does.

So that, you know, you get a signal that hey, Ketoconazole has an effect, and in turn that the effect on clearance, estimated by that population analysis is in the same range, 30 some percent, as in

the interventional study.

So I do think that the population data base does, indeed, add some information.

DR. KONSTAM: Well, I mean, are we going to see that? In terms of negative -- so there are other drugs that you could draw up on that population to say that there is no effect on Dofetilide concentrations by the presence of that drug?

DR. BRATER: Yes, through the population data base. Now, does that mean, for example, we know that there is a cation pathway here. Does that mean that we would want to base our comfort level solely on that population analysis? My bias would be no.

I would say that, yes, we probably need to do another study or so with some other organic bases and map that out in a little bit more detail. And similar to where I think Peter was going with the 3A4 inhibitors, do we need to do some specifically targeted studies there.

DR. KONSTAM: Okay, just a couple of specific questions, then, about it.

So you mentioned with cimetidine an effect

on renal clearance, and you mentioned with Verapamil an effect on absorption.

DR. BRATER: Correct.

DR. KONSTAM: Can we anticipate that there are other drugs that would fall into those classes of interaction?

DR. BRATER: Being able to answer that question may require another, definitively, may require another study.

So, for example, one would presume, just from what we know about Verapamil and the way that interaction looked, that it is probably an effect of increasing the rate of absorption.

How might that happen? Well, it could be through increased blood flow to the gut. So then you would ask yourself the question, okay, what is another drug that we might look at that has the same pharmacologic effect and see if it does the same thing.

And then if it did not, then you would say, maybe this is because it was immediate release, and we need to look at sustained release, and maybe it

is a non-issue. Or, alternatively, it could be an issue with drugs that affect GI blood flow.

DR. KONSTAM: So are there other drugs that we have to worry about this --

DR. BRATER: Yes.

DR. KONSTAM: How many, and also with regard to the Cimetidine effect? I mean, is this a very unusual interaction?

DR. BRATER: No, it is nothing like you saw with Mibefradil. This drug isn't even close, at least in my opinion, I would be interested in what others have to say in terms of its potential as Mibefradil.

DR. KONSTAM: What other drugs can you think of that would have the Cimetidine effect?

DR. BRATER: Organic cations that are actively secreted are Metforman, Triamterene, Ameloride, Trimethraprine. Those would probably be the main ones. There are a few others, but they -- Ethambutol, Amantadine, they are not used very much.

But that is a pretty short list.

DR. KONSTAM: Well, what will you

recommend that we do about even that list? I mean, should we do more studies on it, should we have --

DR. BRATER: I would.

DR. KONSTAM: But if we were to approve the drug, if the drug were to get approved, what would you be saying about that list of drugs right now?

DR. BRATER: Well, I think again you can take two approaches. One would be to say it is highly likely that the Cimetidine effect is the biggest that you are going to see, so you could basically say, we are just going to assume that all those other things maybe have the same magnitude of effect as Cimetidine, and just lump them all together, and label accordingly.

Or one could go back and recommend some specific studies. And I'm sure that is why that is a specific question that the Agency is going to ask you to address.

DR. KONSTAM: Just one last thing. Oral contraceptives, I came across something in the data that there is an interaction. And I didn't hear you, really, talk about it in any way.

DR. BRATER: Yes, I think that is worth actually spending a minute on. Let me first how you the data that triggered that question, backup slide 52.

And this is a study that was not designed to address the effect of oral contraceptives on Dofetilide, it was the converse. In effect to see, does Dofetilide affect oral contraceptives.

But Dofetilide concentrations were obtained, and lo and behold the seam axis were quite high, even relative to this larger dose. So then the question was raised, my goodness, do orally contraceptives potentially inhibit the metabolism of Dofetilide.

To try to get a handle on that, the first step was to go back and look at the phase 1 studies in the U.S. and essentially merge data and look at women on oral contraceptives, as opposed to not on oral contraceptives. And those data are in backup 50.

And, again, this is basically a retrospective analysis, taking data from individual study reports. And so here women on no oral

contraceptives, females on oral contraceptives, if you look at AUCs, they are pretty much the same in the seam axis. So they don't look nearly like what was seen before.

Now, so that then raises several questions. Why were those Dofetilide concentrations as high as they were? One thing, and if you want me to show you the data I will. The assay, the quality controls on Dofetilide assay were running abnormally high that day, with that run, about 18 percent high, so there could be an assay thing.

But I think most importantly this stimulated a study to specifically address the question. A little bit variation of the theme, and that was hormone replacement therapy in elderly patients.

And I can show you some preliminary data in that, in 12 of the patients that have been analyzed. So let me show you that, that is backup slide 45.

So this is single dose. Again, in equal 12, emphasizes the preliminary data. The end is going

to be about -- this is about two-thirds of the patients. And you see this little shoulder here, but otherwise basically the plasma concentrations are quite comparable.

The next slide, which is backup 46, shows it at steady state. That was single dose, here is at steady state. And the area in the curves here are really quite similar.

So there doesn't seem to be an effect of hormone replacement therapy. And, parenthetically, you wouldn't expect one. If you look at -- let me see backup 39. If you look at in vitro studies, and you look at the ability of ethinylestradial to affect metabolism of Dofetilide, which is on this axis, you see, you have to get way over here before you start seeing an effect.

Well, circulating Ethinylestradial concentrations are basically back here at the Y Axis. So from in vitro data one would not predict an interaction, and the HRT data, that was a study specifically designed to address the issue.

And so I think those are probably the most

definitive that we have on that question.

DR. ATKINSON: One comment on your slide, Craig, that you showed. Although the total area in the curve between the HRT and the controls wasn't perhaps significantly different, it did appear that the peak levels were higher in individuals getting HRT.

Now, do you ascribe that to an increase in blood flow getting back to the same mechanism that you've used for verapamil, or not?

DR. BRATER: Well, it could be from maybe some slight change in volume of distribution. If you look at C peaks, at least in the preliminary data, again, those -- there aren't any statistically significant differences.

But, again, the end is only about two thirds of what it is going to be.

DR. ATKINSON: Also, in terms of gender, there does seem to be a difference in the response of males and females to the Ketoconazole interaction, and it appears to me that the non-renal clearance in females is impaired, to a greater extent, by

Ketoconazole than in males.

DR. BRATER: Yes, I think that the data from the Ketoconazole study would indicate that the non-renal component of elimination in women, in that study, is about 40 percent, and that the Ketoconazole effect is to decrease that by, and my recollection is the number is 53 percent, so basically cut it in half, which would mean that in that group, if you are just looking at that group, your effect on total clearance is a decrease of 20 percent.

That is going to extrapolate, it is an inverse relationship. That would extrapolate to a change in the area under the curve of maybe 25 to 30 percent.

ACTING CHAIRMAN CALIFF: Dr. Graboys?

DR. GRABOYS: I know you want to move along, but I want to ask the sponsors, they have to really help us out here, in terms of how to manage patients with this drug chronically. I mean, I think it is a horrendous problem right now.

First of all, in terms of the QT, I don't know what to make of the QT data when you have

patients in atrial fibrillation with varying cycle lengths, and you are telling them to measure ten beats, and then make a judgement on the QT on that basis.

Other problems with the QT we have patients who are on 1A drugs, who on quinidine will display their QT way out, and never have a problem, and those with minimal changes will have a problem, and then you look at Amiodarone, in which you may see the longest QT, and nothing ever happens with those folks.

So the QT issue is, from my point of view, in a hospitalized patients a real problem.

Secondly, and as the point has been made, no one is going to be looking at creatinine clearance. And what happens when the patient is discharged from the hospital and now you want to increase the dose? Are you going to bring him back into the hospital?

So all of these -- I mean, you are going to have to be a rocket science to figure out how to orchestrate management of these patients. But the way the current suggestions are simply doesn't appear to

me to be satisfactory.

ACTING CHAIRMAN CALIFF: I think, again, that is going to get to the clinical portion, and we have a lot of time devoted to that.

DR. THADANI: Yes. One comment, and a short question, I will try to restrict myself. I thought I was smart enough, and try to remember creatinine clearance on the one out of two studies, which I memorized, and on the tenth patient I forgot, and I couldn't convert kilograms into pounds.

So I think it seems easy, and yet I can assure you, when I'm standing in the unit nobody does it. It seems very simple, I think it can work toxicity is more complicated than you think. Now I can tell you 140 minus A multiply it, then you have to correct for the females .85, so it is easy, but it is difficult.

Now the -- when I'm treating Afib a lot of the patients are rapid rates, even if they are in chronic, and a lot of them are going to be. And as in the suggestion, we now talk about Diamond study, which is probably dysfunctional. A lot of them have a good

LB function.

And they are either on Verapamil, or Diltiazen to control their rates. And Verapamil is a major issue of interaction here. And if you are going to give doses above 500 micrograms you run into trouble.

So does one have to stop Verapamil while you are worried about the rate, and watch the patient 3 days, he is having palpitations?

And the other question is, what about any interaction between Diltiazen, because you showed in L-Dopamine there is no interaction, but Diltiazen you did not show any pharmacokinetic, or pharmacodynamic data.

And the last one is related to your over the counter antihistamines, which are also -- can cause Torsade, and I know it will come in the protocol. They were excluded. Have you looked at any interaction, either on the QT or just your pharmacokinetics?

DR. BRATER: In terms of the Verapamil question, I mean, Verapamil should contraindicate a

patient having the drug. So then by definition that would mean if you wanted to use Dofetilide you would have to stop Verapamil and get them well adjusted and get --

DR. THADANI: For how long? Some of them are once a day 240, 320, long acting. So you suggest to stop it for two days, one day, and then start your drug, prolong hospitalization for another day, or what?

DR. BRATER: Well, the half life of Verapamil is pretty short. The sustained release preparations mean that it persists for a while, but as soon as you stop it goes away quickly. So you don't have to have them off for a prolonged period of time before you did that.

DR. THADANI: So you recommend another day before you start, if you were to approve to start this drug?

DR. BRATER: Well, I don't remember the half life of Verapamil, but my recollection is that a day would be certainly four times a half life, and that ought to be enough, unless there is something in

the patient that prolongs the half life.

You would have to look, I mean that --

DR. THADANI: So none of the patients were given the drug in question on top of Verapamil in the studies, am I right?

DR. BRATER: I'm sorry?

DR. THADANI: So that you have to stop the drug before you actually give them the first dose, that is what you are saying?

DR. BRATER: Yes, I would worry about the magnitude of this effect. I would -- yes.

DR. THADANI: What about Diltiazen, is there any --

DR. BRATER: Diltiazen there are no data, and I think if another study is done to probe that issue, that would be a logical one to do.

DR. THADANI: And the reason I'm asking is because is because Diltiazen is used pretty often than you think, you know, patients are on Digoxin, I'm talking about relatively good function, we see also post-op patients that come on IV Diltiazen.

DR. BRATER: I think you said there is no

data.

DR. THADANI: So are you suggesting we should do a fairly large study to look at that?

DR. BRATER: Well, I'm not so sure it has -- I think the first cut would be to basically do a very rigid interventional trial, in a tightly controlled group of patients to see, and then that would drive whether or not you needed a very large study after that. That could be readily addressed.

ACTING CHAIRMAN CALIFF: Bob?

DR. TEMPLE: I think this is right. Verapamil's half life changes with time. So that by the time you've been on it for a few weeks it is probably more than half a day.

DR. BRATER: Okay, then they need to be off two days.

DR. TEMPLE: Right. What is the half life of Dofetilide? I thought there was a reference to 20 some odd hours, but the other data I've seen here, in one of your slides says it is closer to seven. So --

DR. BRATER: Yes, seven, ten, somewhere in that range. And people with decreased renal function

down to like 20 mills per minute, it is about 22.

DR. TEMPLE: Okay, then it gets longer. Is the Verapamil data, at least for the AUC, a reasonable test of drugs with intermediate levels of 3A4 inhibition, or do you actually think you have to go and look at erythromycin and things like that?

DR. BRATER: Well, see, I don't think you know because Verapamil probably also inhibits P-glycoprotein. So is it a renal -- would it be a renal secretory effect, or a metabolic effect.

And, so, you would have to again do some more specifically targeted studies to tease that out.

DR. TEMPLE: I guess you could form the impression, from all of this, that there is so many different things showing up. I mean, with alteration of renal function, as well as possible 3A4 effects, at least in people with diminished renal function, early versus late, that it is hard to conclude anything without actually looking at it?

DR. BRATER: Well, I guess if you are saying there are some specific, at least in my domain, of drug interaction stuff, are there a few specific

studies that would offer additional information that might be helpful? I don't think there is any question about that.

DR. TEMPLE: I guess I was struck by the Verapamil data, where you think you are doing okay, because it doesn't do much through its 3A4 inhibition, and then sort of unexpectedly you get a 50 percent increase in C-max, which is probably the thing you are worried about more.

DR. LIPICKY: I have gotten confused as this discussion went on, and just want to return to the population pharmacokinetic study. And you said when you dropped the Ketoconazole plasma concentration data into that data base pool, that that signal that came from Ketoconazole was fairly well obvious, and was able to be picked out.

How many other signals, one, two, three, four, were picked out of that pharmacokinetic screen, and how many different drugs were people on during the course of the trials, did you ever say that?

DR. BRATER: I said, as I went through, in terms of groups of drugs, and that are 3A substrates,

3A inhibitors, P-glycoprotein, potential P-glycoprotein inhibitors, cation, substrates, cation inhibitors, I enumerated those values as I went through those parts of the presentation.

DR. LIPICKY: Pretty many?

DR. BRATER: In the hundreds. Well, it depends, on the cation, cationic inhibitors it was 20.

DR. LIPICKY: 20?

DR. BRATER: But there was a -- there was a -- it depends on how you define it. That analysis suggested a 14.6 percent decrease in clearance with those. Is that clinically significant or not? It depends on how you define that.

DR. LIPICKY: Well, I understand, but the thing is that in fact you could identify drugs that had some of those properties, and they were fairly large numbers, and you could actually identify that there was an effect, and sort of have a feeling for what its magnitude is, and how worried you need to be about it.

DR. BRATER: Right.

DR. LIPICKY: And you want to leave it

from the vantage point of would the biggest sort of population kinetic change you saw was in the 10 to 15 percent range?

DR. BRATER: Well, when we put these Ketoconazole data in there it was -- I think it was 33 percent.

DR. LIPICKY: And that was the biggest thing you saw?

DR. BRATER: Right.

DR. LIPICKY: So is that a reasonable characterization of that stuff? I mean, if I were to say that from the population kinetic data base the worst actor that was seen in a definitive drug interaction study that changed things by 35 percent, that just popped out like a sore thumb, and that other drugs you would expect to do something, in fact were identifiable, but the changes were in the order of ten percent, and that although all of this is important to think about studying more, because there is lots to learn, that is what academics like to do.

Would I be improperly characterizing the circumstance?

DR. BRATER: I guess it really depends a lot on, you know, would you want to put all your money on -- invest all your money in the bank of the population analysis is what you are asking, really.

DR. LIPICKY: And I know you don't like population analysis, but it seems to me that there is -- that some of the questions that people have been asking are in there.

DR. BRATER: Right.

DR. LIPICKY: And it is not like this is totally unknown and at sea. It might be that you wouldn't want to put all of your money on that, but in fact there is something there, and some people would put some of their money on that.

DR. BRATER: Right. Well, I can show you the data, if you want to, it is backup slide 29.

DR. LIPICKY: That would be nice.

ACTING CHAIRMAN CALIFF: Dr. Ryder wants to make a comment, I think.

DR. RYDER: I just want to be sure that there was an addendum to the briefing document that covered the population pharmacokinetics, and it has a

lot of tables, and lists of medications, including Diltiazen, including Verapamil, and the hundreds of patients that were on different medications, because one of the -- one of the items that I would like to point out is that it is a very large data set, and the population PK and the pharmacodynamics of that, the QTc change, and as Dr. Pratt will get into later, the various safety cuts were looked at, according to the concomitant medication.

I just want to make sure that the Committee had the addendum.

ACTING CHAIRMAN CALIFF: Thank you, I think that is -- we did get the addendum, and it is helpful. I agree with the sentiment of several people that we should go ahead and look at that data, then.

DR. BRATER: And what I'm going to show you is the PK data. In the supplement that was described there is also an extensive analysis of population Torsade relationship and mortality. It is backup slide 29.

So here is the peak inhibitors, a cationic transport. So an N of 20, in first visit, and this is

a signal of 14.6 percent. And you see the ends on some of these are pretty healthy, okay?

The only other one that really pops up is Thiazides.

ACTING CHAIRMAN CALIFF: Craig, just because we haven't seen much of this kind of data, in this panel recently, could you just describe how the study was done?

DR. BRATER: Well, this is basically, again, this is a data base with these 1,445 patients, and throughout the course of their therapy they had serum sampling at different times, a total of about 10,000 samples.

And then what you can do from that is you can estimate the pharmacokinetics using non-linear mixed effects modeling. You can estimate the pharmacokinetics on each one of those patients, and then you can do essentially a multivaried analysis and see how other things going on in that patient, be it demographics, concomitant disease, or concomitant medications affect the different pharmacokinetic parameters.

So this is concomitant meds, and here is the signal that was picked up in terms of effects on clearance.

Why Thiazides might jump out, I don't know. But that might warrant further study as, Ray, you are basically saying, maybe this kind of targets you down where you are going to do those additional studies.

ACTING CHAIRMAN CALIFF: Were the concentrations drawn in a particular relationship to the dose?

DR. BRATER: No, actually, what you want in these kind of studies is you want to have -- you don't want things drawn consistently at a time in relationship with the dose. You want to know when the dose was given, and when the sample was drawn, but you want that to be different at different times, and that is how you use this technique to then go back and construct the individual patient's PK.

DR. KOWEY: I'm Peter, over here. This sort of runs both ways, and I think it is going to be very important for Craig to spend some time on this,

because one of the things that really stood out in this analysis, this addendum, was the Digoxin, and the fact that there was a higher risk of Torsade with concomitant Digoxin use, despite the fact that it didn't show up as an interaction.

DR. BRATER: Yes, so what that says is that that is not a kinetic interaction.

DR. KOWEY: I know that. I'm saying, that is exactly right, that is exactly my point. It did not show up as a kinetic interaction, and yet in the population study -- maybe the reason you don't like population studies, and I don't like them either, is because it doesn't have any precision.

And one of the problems with precision is explaining interactions which are maybe not PK interactions. Obviously that has to be some kind of pharmacodynamic interaction, if it is true.

But one of the -- it does work both ways. I mean, you can use these things for some comfort, but it also raises a little bit of anxiety in my mind, because now we have an interaction that we weren't supposed to have on a real true endpoint, which is

Torsade.

So we have to deal with that somehow, and maybe that will come up in Craig's presentation.

DR. KONSTAM: If you could clarify, if you look at, for example, thiazide diuretics, minus 16 percent, but we don't know whether that is not being driven by one particular thiazide diuretic that has particular drug/drug interaction that may or may not be characteristic of all thiazide diuretics.

So there could be something hiding in there. Well, I guess I will ask the question, couldn't there be something hiding in there that has a dramatic effect, and so therefore, how reassured am I that because 95 patients were on thiazides, but maybe 10 of them were on a certain drug? We don't know.

DR. BRATER: No way to sort that out.

ACTING CHAIRMAN CALIFF: I want to register a difference of opinion with Peter. I love these studies because they are less precise, but they do reflect what actually happens to patients. And although there are problems with them, there is more

to interactions than just the kinetics.

DR. KONSTAM: I agree. And that is why I don't -- I'm not going to ask Craig to do it now, but he is going to have to do it to look at the other aspect of this, which is the pharmacodynamics, and true effects, not just focusing on the PK data.

I agree with you Rob. I think the part I don't like is this part. The whole global picture is actually very helpful.

ACTING CHAIRMAN CALIFF: Well, we have both FDA representatives I guess Bob, you are next, and then Ray.

DR. TEMPLE: I think there is a lot of reason to like these analysis, too, apart from the fact that they touch on far more things than you can reasonably be expected to study intimately.

They give you numbers that small studies often don't, even if you don't have as much precision.

Is there some reason not to think that thiazides are just working by decreasing creatinine clearance? I mean, they do that a little.

DR. BRATER: I mean that would be my first

hypothesis, that that is the logical thing that would happen. But I think what you are leading to is that these kind of data lead to hypothesis generation, that will lead you to that next step.

DR. TEMPLE: Yes, that is commonly said. I'm not sure these aren't just as believable as the typical small interaction studies we see. There are some examples that suggest that sometimes you get better data from these.

But these could certainly be looked at individual diuretics, if you wanted to. You would reduce your number, but someone could certainly do that if that was of interest.

And a lot of the effects are the ones you would expect. 3A4 inhibition gives you a sort of minor effect, just what you would imagine with only 20 percent of the clearance being due to that.

So there is a certain -- I like these things. The other point that I guess you were making is, this is a pharmacokinetic analysis, it is not supposed to predict that Digoxin has a pharmacodynamic interaction, that is another problem, that is why you

look at what people are on when they get their Torsade.

ACTING CHAIRMAN CALIFF: Ray?

DR. LIPICKY: I just want to echo what Bob just said, in that it isn't a matter of like or unlike. I think I object to the word of imprecise. You know, I don't know what that word means.

The point, I think, and it is right there on the slide, is that with observational data, and that is what you get when you grab a blood sample, and you write down what time the drug was given, and when the drug sample was gotten.

And that you get the drug sample, any time, at midnight, or at 2 a.m., or at 12 o'clock noon. And you dump it into something that can do something with that kind of data, you really can distinguish stuff.

That is not imprecise to me. It will only find stuff in relationship to plasma concentrations. It isn't going to find stuff in relationship to others, although it will, if you plug other information in.

So it isn't a matter of precision, but it is a matter of hypothesis generation. That is, you know, you don't know exactly what is going on, you -- it identifies signals that might require greater study, but the thing that is missing from here is the Ketoconazole guide.

That is the guide that the last study that was done, and it is sort of the biggest pharmacokinetic interaction. That resulted in a 43 percent change in clearance. That is a very big number compared to any of these other numbers that are there.

And the only reason I think we are looking at these, is these are mean changes, obviously, and some of the people had big changes, and some people had little changes.

The only reason for looking at this is this gives a feeling for magnitude. How big a problem is this. And on average it is in the 10 to 15 percent range in plasma concentrations.

Now, that has to be put into the equation with what the relationship between plasma

concentration and QT is, and what one knows about the relationship between QT and Torsade, which we will get to.

But I wouldn't want to leave this in an imprecise term. I think that is bad, just, semantics.

ACTING CHAIRMAN CALIFF: Joan, do you have another question?

DR. LINDENFELD: Just quickly. Can we assume that these changes in clearances are additive, as you add on drugs; is that a fair assumption?

DR. BRATER: No.

ACTING CHAIRMAN CALIFF: You took the question I was going to ask, which gets to an analytical issue which I don't think was presented in the packet.

Another thing that this type of analysis should allow you to do is to look at combinations. It is essentially a multivariable problem. And we know that since this is going to be an elderly population, most of them are on multiple medications.

And one reason I like this kind of study is that your typical 24 patient study of interaction

is looking at one thing at a time, whereas here you have the opportunity to see if combinations of drugs are additive, multiplicative.

Was this looked at?

DR. BRATER: Well, I think whether or not they are additive or multiplicative is probably going to depend on the pathway that they are affecting. So, for example, if you had a drug that had Ketoconazole like effect on the metabolic component, and then you added another drug that affected only the cationic secretory component, then those are going to be additive, no question about it.

But if you put two organic cation inhibitors in a patient, as opposed to one, will it be? It is, you know, it may be -- it is going to depend on the doses, it is going to be dependent upon the intrinsic activity of each of those towards affecting that pathway, etcetera.

ACTING CHAIRMAN CALIFF: But it wasn't looked at as to whether, for example, if one was on nitrates and thiazides, there was a minus 25 percent, or a minus 50 percent?

DR. BRATER: No, but that ought to be able to be done.

ACTING CHAIRMAN CALIFF: Okay. I had three or four questions. If we could just put back up the slide that says QTc efficacy relationship by dose?

DR. BRATER: That is core slide, I think it is 21.

ACTING CHAIRMAN CALIFF: The first question is if you -- and I think this is really a key, at least from my perspective, is a key plot. If you plotted probability of Torsade alongside the probability of remaining in normal sinus rhythm, would the slope be exactly the same as the normal sinus rhythm plot, or would it be deviant from that?

DR. BRATER: I'm not -- well, I think you would have to -- if you took each, I don't know if you can do that. I mean, the numbers are so small. It is what I've been told. I mean, I asked people to do that, and they told me the numbers are so small you can't do that.

ACTING CHAIRMAN CALIFF: Well, if we don't look at the numbers then we are left with having to

just guess about it. I would think at least seeing the data would be better than -- and I guess maybe we will.

DR. BRATER: Well, I know that -- I don't know if it is out in other pieces of the data that are coming forward, but --

ACTING CHAIRMAN CALIFF: I mean, there is a plot in our briefing booklet about the probability of Torsade as a function of QT. So it seems like we could do it by trying to put one on top of the other in our briefing books, but it would be nice if there was some way to get a more definitive picture.

DR. BRATER: I don't know who has that slide. Is that yours, Craig?

ACTING CHAIRMAN CALIFF: Well, maybe that is something we can come back to when you have a chance to think about it.

The second question is, do we know what the same slide would look like for Quinidine, or Amiodarone?

DR. BRATER: I'm not the expert, Ray is the expert, he says no.

DR. LIPICKY: From my point of view, I will say absolutely not, not the slightest perception.

ACTING CHAIRMAN CALIFF: Dr. Atkinson?

DR. ATKINSON: I think an essential assumption here is, is QT interval prolongation a reliable surrogate for Torsade? And I don't know, I would like to pool maybe other members of the committee here, but my impression is that I have to at least see some patients who have had minimal QT prolongation at a time when they've had Torsade.

And so even though both QT interval and risk of Torsade may increase with increasing blood level, and I'm not sure that QT prolongation necessarily lies on the causal path to Torsade.

DR. LIPICKY: We could spend three days talking about this, and so my summary statement that I will make, from my vantage point is, summarizing three day's worth of debate, and I have absolutely no data, whatsoever, to support the statement I'm going to make.

The QT interval, any drug that has caused an increase in QT interval, has also caused Torsade.

Torsade occurs in the absence of a drug that causes increases in QT. Torsade probably occurs in the absence of an increase in QT, although you can't make the diagnosis, because you can't call Torsade, Torsade, unless you have an increased QT.

But people certainly see multiform ventricular tachycardia, which is what Torsade de points is, plus a long QT somewhere identifiable before you see the episode.

So the thing that makes it Torsade is seeing the QT somewhere. And if you don't see a QT somewhere, you call it multiform ventricular tachycardia. I don't know that those are different, all right?

So if you believe Torsade is a special entity, then indeed it doesn't occur without a long QT. But if you think Torsade is just a certain thing that happens, then it could be multiform detach, you don't need a long QT.

So that is point number one. Point number two is that at doses that -- at plasma concentrations that give you longer QTs, on average, you have a

greater incidence of Torsade on average, and that certainly is true.

But that -- but the incidence of Torsade in people that have long QTs, like people who have long QT syndrome, is an incident -- their QT is long all the time, is they have Torsade once every five years. But every bloody beat for those five years has a long QT.

So it isn't the long QT, it is something else. But the long QT is associated with whatever it is. And we can talk about this for three days, and not get to an answer.

And that is my summary of three day's of debate.

ACTING CHAIRMAN CALIFF: You just said that life is multivaried, and I think you and Dr. Atkinson probably agree. Bob?

DR. TEMPLE: I don't want to add to three days, either. The fact seems to be, though, that the mechanism of this class of antiarrhythmic and its benefit comes, at least partly, because it delays repolarization.

So you are never going to have effectiveness without some effect on that. What isn't completely clear, however, since QT intervals vary throughout the day, is whether when you are looking at a drug that causes an average change, the problem really arises, for the small fraction of people that spend a little time over 500, and you just -- there isn't any way to really know that.

So here they have tried to exclude anybody who has a really robust increase, and maybe that is why you don't see so many cases. If you hadn't done that, and just had an average increase with a fraction of people going over 500 you might have more trouble.

So there is, as Ray says, I don't think there is any doubt that the two are related, but what exactly triggers it isn't clear, and it seems modestly clear that things like hypokalemia can make the same QT interval dangerous when it wasn't -- when it wasn't before.

But the implication here, I think, that is important is that you are not going to get effectiveness without some increase, and you have to

look at the rest of the data to see how dangerous that increase was, and how variable it is going to be with all these attempts to minimize extreme values.

I don't think there is any doubt, either, that a value over 500 is more trouble than a value of 440.

ACTING CHAIRMAN CALIFF: I have one final question, and then we will take a break, which looks to me like it is sorely needed for some Gatorade, or something.

And this, again, is a relative question compared to other alternatives for these patients. If you look at the interactions that we've just gone through, would you say that these are more complex, or less well characterized, either one, than what we know about Quinidine and Amiodarone, and Sotalol for these patients, and the drug interactions, and their consequences on QT interval, or Torsade?

DR. BRATER: Well, again, Ray may be in a better position to answer that than I. It seems to me we know a lot more about this drug in terms of its PK than we do most others.

And that is in part, in my own mind, a function of this big population data base that was gathered that is impressively entirely consistent with what is seen in the shorter term studies.

So I think from a pharmacokinetic point of view that probably more is known about this than most that I've seen.

ACTING CHAIRMAN CALIFF: Dr. Atkinson, you are saying a lot of these -- and it is a two part question, one is the characterization itself, and the second is, looking at the characterization, is the use of this drug, with its interactions you think more complex than say, Quinidine or Amiodarone?

DR. ATKINSON: Well, one disadvantage, obviously, is that it hasn't been in the marketplace as long as other agents, so we really don't know. But I would say that the company has done an elegant job.

I particularly think that the PK, population PK study is extremely well done. And for those of you that wonder whether population PK studies always turn up the important signals I will tell you that Lou Shiner's first study on population PK of

Digoxin completely missed the fact that Quinidine, on average, doubles Digoxin levels.

So that the ability to pick up the Ketoconazole signal here I think is most impressive, as a positive control.

I think there are holes in the sponsor's package, and I think Dr. Brater has certainly suggested some that might be corrected. But I would say that we know a lot more about this drug than Amiodarone.

I would say with regard to Quinidine that there have been a number of, you know, that drug was approved long before we had ever dreamed of population PK studies. I don't know of anything on Quinidine that could approach the kind of study that has been done here.

There have been ad hoc studies by academic investigators on Quinidine, but nobody has really done detailed interaction studies across the whole gamut of drugs that patients are on.

DR. KOWEY: I think Art is right, I think we do know more about this drug than we know about any

other, and maybe I can defend a term that I used earlier about precision rate.

But one of the reasons why I'm concerned about that kind of an analysis is because we have never seen a drug, at least had a drug considered for approval for atrial fibrillation, which is not necessarily a lethal disease, in which the upper end of the dose of the drug is abutting so closely to a toxic effect.

And, therefore, drug interactions have never in my mind, at least, for AF? We are -- I'm talking about Torsade -- I'm sorry?

DR. LIPICKY: Weren't you part of saying Flecainide should be approved?

DR. KOWEY: No, I'm talking about Torsade risk right -- I'm talking about --

DR. LIPICKY: Weren't you part of the panel that said Quinidine should be approved?

DR. KOWEY: Flecainide.

DR. LIPICKY: Quinidine for atrial fibrillation?

DR. KOWEY: Yes, that is right.

DR. LIPICKY: You think that is different?

DR. KOWEY: No, but I don't think we have ever -- no, we are looking at pharmacokinetic data that we didn't look at for Quinidine, because we didn't have it.

DR. LIPICKY: No, that is correct, so you know a lot more about this guy, and you were ignorant for Quinidine?

DR. KOWEY: That is right.

DR. LIPICKY: Okay.

DR. KOWEY: Just because you were ignorant of one drug, and smarter about another one, doesn't mean you can't look at the data.

ACTING CHAIRMAN CALIFF: I think it is time for a break, but I would just point out, probably the most amazing statistic, in light of this calculation that I saw this morning was that Quinidine is still the most frequently prescribed drug for this indication. After all this time we still don't know any of this data about Quinidine.

It is break time, 15 minutes we will be back.

(Whereupon, the above-entitled matter went off the record at 11:08 a.m. and went back on the record at 11:30 a.m.)

ACTING CHAIRMAN CALIFF: What I suggest that we do is we go straight through the efficacy and safety presentations without stopping, because they both deal with the body of clinical trial evidence, and if we ask questions about one, and then the other, we are going to go over the same trials again and again. Is that acceptable?

And then we will save the balance presentation at the end, until after we've discussed the body of the clinical trial evidence.

Let's get started.

DR. FRIEDRICH: Dr. Califf, Dr. Temple, Dr. Lipicky, Members of the Advisory Committee, ladies and gentlemen.

I will present evidence for the Dofetilide efficacy in the maintenance and conversion of atrial fibrillation and atrial flutter to normal sinus rhythm.

I will begin by reviewing maintenance of

sinus rhythm, then I'm going to present data on dose response, subpopulations, and secondary endpoints of symptomatic benefit and quality of life improvements.

Finally I will review the Dofetilide effect on conversion to normal sinus rhythm in patients with chronic atrial fibrillation/atrial flutter.

Throughout my talk I will use the term chronic atrial fibrillation in the sense, as it is defined by the term persistent atrial fibrillation.

The entire Dofetilide clinical program included nearly 8,500 patients, 6,800 in the oral program, and 1,700 on the IV program.

The support for the clinical efficacy of Dofetilide comes from the oral program. Specifically I will be discussing the results from studies of approximately 1,100 patients who were included in the chronic atrial fibrillation trials.

All of these trials were double blind and placebo controlled. Patients enrolled in other parts of the program, including over 3,000 patients from the Diamond mortality trials, are discussed at the safety

presentation by Dr. Pratt later this morning.

Entry into the trials was limited to those patients where document target arrythmia, no excessive QT prolongation, AV block, or body cardia.

Patients were excluded if there was evidence of acute myocardial infarction, unstable angina, unstable congestive heart failure, reversible causes of the target arrythmia, or history of polymorphic ventricular tachycardia associated with QT prolonging drugs.

In all clinical trials treatment with Dofetilide is always initiated in the hospital, under continuous electrocardiographic monitoring. Consistent with the primary renal excretion of Dofetilide, the dose of Dofetilide is adjusted downward, if renal function is compromised, in order to maintain equivalent serum levels.

After the initiation of therapy, the dose is further reduced if QT or QTc is excessively prolonged.

Here is an example of how the algorithm works. After assessing the EKG to exclude patients

with prolonged baseline QTc or QT, creatinine clearance is then calculated using the Cokcroft-Gault formula.

Note, this only requires a routine measurement of serum creatinine, and covers other important factors like age, weight, and gender.

For example, a patient randomized to 500 micro on BID with normal renal function receives 500 micro on BID Dofetilide. While this dose would be reduced by half, to 250 micro on BID, if creatinine clearance was between 40 and 60 milliliter per minute.

Patients below 20 milliliters per minute were excluded from the trials.

Two to three hours after the first dose the QT or QTc will be checked again, and in case of a 15 percent increase, or an increase beyond 500 milliseconds, the dose would be reduced by half.

This dose reduction is needed in those few patients with increased sensitivity to the drug's QT prolonging effect.

These dosing principles were implemented at various time points during the development program,

as shown on page 17, figure 2, in your briefing document.

However, more than 70 percent of patients in the atrial fibrillation, atrial flutter trials were randomized to 500 micron on BID were dosed according to the creatinine clearance algorithm.

Let me now turn to the clinical trials that provide evidence of efficacy in the maintenance of normal sinus rhythm in patients with chronic atrial fibrillation or flutter.

In the dose finding studies, 311 and 320, doses ranging from 250 micro on BID to 750 micro on BID were explored.

A positive dose response relationship was identified and this led to the design of the confirmatory efficacy studies 120 and 345.

Study 345 was a large clinical trial in 671 patients which showed unequivocal efficacy of evidence of efficacy by meeting the pre-specified endpoint with high statistical significance.

The result of the second large study in atrial fibrillation or flutter, study 120, are

strongly supportive of the findings in study 345, as I will discuss shortly.

Please note that all chronic atrial fibrillation trials were designed to measure time to first recurrence of the target arrythmia. Relapses beyond the first reoccurrence of chronic atrial fibrillation were not captured.

Studies 345 provides evidence of efficacy of Dofetilide in patients with atrial fibrillation/atrial flutter. This is a trial conducted at 79 centers that involved a total of 671 patients with chronic atrial fibrillation or flutter of duration ranging from one week up to two years.

Study 345 is a twelve months randomized parallel group, double blind, placebo and active control study. The active comparator is Sotalol.

The primary analysis of the trial compares the efficacy of Dofetilide with a placebo in maintaining normal sinus rhythm once a patient is successfully converted.

Here is a design for study 345. During the running period of up to 14 days, where atrial

fibrillation or flutter is documented by electrocardiogram the patients are anticoagulated. Patients are hospitalized for the initiation of blind therapy and are closely monitored during this phase.

All patients are considered to be at steady state by day three. Patients who did not convert pharmacologically to normal sinus rhythm, up to one hour after the day three morning dose, underwent DC cardioversion.

Patients who did not convert to normal sinus rhythm were discontinued from the study at this time point. During the maintenance phase regular visits occurred.

Patients were randomized to one of five treatment groups, 500, 250, and 125 microgram BID Dofetilide, placebo, or Sotalol, 80 milligram BID. Calculated creatinine clearance was used to adjust doses downward.

The actual numbers of patients who received lower doses are shown on the bottom of the slide. For example, of the 129 patients who were randomized to 500 microgram BID, 96 received their

dose, and 33 were dose adjusted to achieve an equivalent serum exposure.

This is a predominantly male population, average age 65. About 50 percent of structural heart disease and approximately 45 percent have neurochord association function at less two or three.

Ninety percent of the patients have atrial fibrillation, ten percent have atrial flutter. Overall the mean duration of atrial fibrillation or flutter is 144 days. There are no clinically meaningful differences in the baseline characteristics between the Dofetilide and placebo treatment course.

The concomitant medications, Digoxin, diuretics, and ace inhibitors are typical of this patient population with mild to moderate concomitant cardiovascular disease. Use of concomitant medication was comparable between the treatment arms.

Let's now look at the pre-specified primary endpoint. Using point estimates from the Kaplan-Meier curves at 12 months, maintenance rate are 66 percent, 51 percent, and 39 percent on Dofetilide, compared to 21 percent on placebo.

Differences between Dofetilide and placebo at 12 months are highly statistically significant.

So the vastness of efficacy in this study is confirmed by an intention to treat analysis wherein patients that did not convert to normal sinus rhythm were included as treatment failures at the zero.

The initial drop in the Kaplan-Meier curve represents these patients. Retaining these patients in the analysis does not change the overall outcome of the trial.

Dofetilide in this analysis is more effective than placebo, and the dose response relationship is preserved with high statistical significance.

Study 120 examines the efficacy of Dofetilide in 325 patients with atrial fibrillation or flutter and is supportive of the findings in study 345.

The primary endpoint of this trial is the proportion of patients in normal sinus rhythm as estimated by the Kaplan-Meier method. The primary analysis is the intention to treat comparison of the

maintenance of normal sinus rhythm among the four treatment groups at 6, 9, and 12 months, by the Locarin test, noting that the sample size estimate was based on the six month's time point.

This analysis is repeated for all data through to the 12 month study visit. Kaplan-Meier estimates for the proportion in normal sinus rhythm at 6, 9, and 12 months are examined. The study design is similar to the design used in study 345.

Patients who are randomized to one of four treatment groups, 500, 250, 125 microgram BID Dofetilide or placebo. And the dose could be adjusted for both baseline creatinine clearance and QT prolongation.

The actual doses received, and patient numbers, are shown in the lower half of the slide.

The baseline characteristics for this population were similar to those of studies 345, with the exception of structural heart disease, which is more prevalent in study 120. The majority of patients are functional and record functional class 2 and 3.

In contrast to study 345, more patients in

this study are treated with Digoxin, 80 percent; diuretics, beta blockers and ace inhibitors.

These findings reflect the population with more advanced cardiovascular disease in this study, relative to studies 345.

The primary pre-specified analysis of this 12 month study is the comparison of the proportion of patients maintaining sinus rhythm across the four treatment groups at 6, 9, and 12 months.

All randomized patients are included, with patients never achieving normal sinus rhythm considered treatment failures at times zero. This is represented by the initial drop in the Kaplan-Meier curve.

The curve show clear trend of increasing efficacy with increasing Dofetilide dose. The pre-specified overall Locarin test across treatment groups, up to six months, is non-significant, with a P value of .125.

Applying the identical test to all data from the start of the study through 12 months demonstrates a difference across all treatment groups

with a nominal P value of .035.

Not surprisingly, assuming linear dose response, and applying a statistical test for trend using nominal P value for 6 and 12 months, of .02, and .006, respectively.

At 12 months 47 percent of patients assigned to 500 microgram BID, and 20 percent of the placebo patients are in sinus rhythm. This difference has a nominal P value of .008.

A pre-specified secondary analysis of the maintenance population including only those patients converting to normal sinus rhythm is shown here. This is discussed in more detail on pages 50 to 52 in your briefing material.

This analysis is comparable to the primary analysis of studies 345. It shows 58 percent of patients assigned to 500 microgram BID in normal sinus rhythm at 12 months, compared to 25 percent on placebo. This difference has a nominal P value of .001.

To examine dose response we looked at the four atrial fibrillation trials. As shown here, we

found a positive dose response relationship across all four clinical trials in chronic atrial fibrillation.

This was first demonstrated in the dose ranging studies 311 and 320, and subsequently confirmed in the large clinical trials 345 and 120.

Now I would like to discuss subpopulations and maintenance of normal sinus rhythm. This is best done by pooling two large trials, studies 325 and 120, into a combined atrial fibrillation or flutter data set.

The justification for this pooling is that both trials are similar in design, and as shown here, had similar results. For example, about 60 percent of patients remained in normal sinus rhythm on 500 microgram BID in both trials at 12 months in the maintenance population.

The hazard ratios derived from this combined atrial fibrillation/atrial flutter data set, demonstrate reduced risk for relapse shown here for patients assigned to 500 microgram BID.

These data are discussed on page 54 to 56 in your briefing material.

Superior efficacy for Dofetilide, compared to placebo, in maintaining normal sinus rhythm in the following subgroups is demonstrated in patients with atrial fibrillation or atrial flutter, in males, or in females, or in patients below or above the age of 65.

We examined the effect of our dosing algorithm on efficacy in the maintenance of normal sinus rhythm in the same combined data set. The first group represents patients randomized to 500 microgram BID, whose dose is not adjusted.

The second group represents patients adjusted for creatinine clearance at baseline, compared to placebo patients.

While efficacy is estimated to be less than what is observed in unadjusted patients, it cannot be determined whether this is due to dose adjustment, or differences in the underlying patient characteristics of these two populations.

A hazard ratio cannot be determined for those few patients with dose adjustment for excessive QT or QTc prolongations, because a matching group of placebo patients predisposed to excessive QT or QTc

prolongations cannot be identified.

These few patients are not shown here on the slide. However, I can tell you that nine of the thirteen patients in this group remained in normal sinus rhythm at 12 months.

Overall, of the patients randomized to 500 microgram BID Dofetilide in studies 345 and 120, 72 percent were treated according to the proposed treatment algorithm.

Let me summarize the results presented so far. Evidence for efficacy in the maintenance of normal sinus rhythm in chronic atrial fibrillation or flutter was demonstrated in a large double blind placebo control trial, with a pre-specified endpoint was reached with high statistical significance.

These findings were corroborated by another large placebo control trial, study 120, that was clearly supportive of efficacy at the 500 microgram BID dose, with statistically significant nominal P values at 12 months.

Furthermore, a positive dose response relationship in the early dose ranging studies 311 and

320 was confirmed in trial 345 and 120.

Finally, in a combined atrial fibrillation/atrial flutter data set efficacy was demonstrated when examined by arrythmia type, gender, age, and renal function.

Pre-specified secondary endpoints in trials 345 and 120 included measures of quality of life and symptoms. Although not powered for this endpoint, analysis from these studies might provide some insight into the expected benefits of maintaining patients in normal sinus rhythm.

In studies 345, multiple validated instruments such as SF36, psychological well being and perception of symptoms were used to collect quality of life data.

In study 120 symptoms, severity, and frequency data were collected using symptoms previously established as relevant in patients with atrial fibrillation or flutter by the Duke group and others.

The analysis shown here is a percentage of patients with improvement from baseline symptoms

across the eight quality of life instruments, by rhythm status at month one.

All of these quality of life instruments, I explained in detail in your briefing material, in appendix 4 pages 9 to 13. These exploratory analysis is no longer randomized, but might give some insight into the association of quality of life outcomes with being a normal sinus rhythm.

Each column contains a mixture of patients on Dofetilide and placebo. Of the 269 patients in normal sinus rhythm, 217 were on Dofetilide, and 52 were on placebo, whereas 136 patients in atrial fibrillation included 85 patients on Dofetilide, and 51 patients on placebo.

Looking at the SF36 physical function, 67 percent of patients in normal sinus rhythm show an improvement, compared to 49 in atrial fibrillation.

The improvement seen in 6 out of the 8 instruments suggests an association between normal sinus rhythm, and improved quality of life.

Having established the plausibili-y of an association between normal sinus rhythm and quality of

life we examined quality of life by treatment group.

The analysis shown here is a percentage of patients with improvement at one month from baseline values across the eight quality of life instruments.

Patients randomized to 500 microgram BID in blue are compared with patients receiving placebo in red.

You can see that six of the eight instruments show various degrees of improvement for patients on Dofetilide compared to those on placebo. Similar trends were observed at six and twelve months, with data from month one as showing you the greatest effects.

This difference was more pronounced for instruments which may be considered more relevant in patients with atrial fibrillation. The SF36 physical function, the psychological well being score and design symptom score, with nominal P values less than .05.

In study 120 we use a questionnaire to assess arrythmia related symptoms of fatigue, worry, chest pain, lightheadedness, shortness of breath, and

palpitations.

Both frequency and severity were recorded using the point scale system. All symptoms were collected at two week's intervals to the end of the trial. For patients who had missing data or who dropped out of the study, the last observation was carried forward in this analysis.

This slide shows reduced frequency for system for patients in normal sinus rhythm as compared to atrial fibrillation. In this graph bars moving downward represent reduction in symptom frequency compared to baseline, whereas bars moving upwards represent an increase in symptom frequency.

For example, patients in sinus rhythm experience less frequent worry than those in atrial fibrillation. The trend toward frequency reduction was observed across all symptoms in patients who maintained normal sinus rhythm, with the most noticeable effects seen for worry, shortness of breath, and palpitations.

Similar trends were seen for symptom severity. Analysis of symptoms by treatment group,

shown here for the Dofetilide 500 microgram BID patients in blue, and for placebo patients in red, demonstrates an overall trend in symptom severity and frequency reduction in favor of the Dofetilide treatment group.

This favorable trend is apparent despite the delusional effect of mixed rhythm status within each treatment group, although no differences reached statistical significance.

In the frequency and severities cause the benefits of Dofetilide is most apparent for the symptoms of fatigue and shortness of breath. These data suggest that there is symptomatic benefit in patients treated with Dofetilide, possibly through the maintenance of normal sinus rhythm.

The FDA reviewers, Dr. Ganley and Dr. Hung analyzed 120 symptom data setting a different way, as is shown in table 120.21 of FDA's medical and statistical review of the efficacy data.

Using a categorical approach of symptom improvement, no change, or worsening, they confirmed the finding that patients in normal sinus rhythm

experience an improvement in symptoms.

Now I will discuss conversion to normal sinus rhythm. Patients in studies 345 and 120 entered the trial with chronic atrial fibrillation or atrial flutter. All patients were initially given the opportunity to pharmacologically convert to normal sinus rhythm on randomized study treatment.

Both of these studies, 345 and 120, provide clear evidence for efficacy in conversion of atrial fibrillation and flutter to normal sinus rhythm with strong statistical significance.

This slide shows pharmacological conversion of atrial fibrillation to normal sinus rhythm in studies 345. The Ye axis represents a probability of converting to normal sinus rhythm, and the X axis is a time to pharmacological conversion in hours.

There is a significant difference between the proportion of patients in sinus rhythm at day 3, which is a pre-specified endpoint for conversion.

For patients on Dofetilide 500 microgram BID 29 percent converted compared to 1 percent on

placebo, statistically significant was the P value of .001.

Seventy percent of the patients that converted did so within the first 24 hours. Patients that did not convert pharmacologically were subsequently DC cardioverted.

Here is the conversion data for study 120. There is a significant difference between the proportion of patients converting to normal sinus rhythm between Dofetilide 500 microgram BID, 30 percent; and placebo 1 percent. Statistically significant was the P value of less than .001.

As in studies 345, approximately 70 percent of the converted patients did so within the first 24 hours.

This slide demonstrates a positive dose response relationship across the two trials, with 500 microgram BID being the most effective dose.

To summarize, two large double blind placebo control trials showed efficacy and conversion of normal sinus rhythm with high statistical significance.

Similar to the dose response relationship seen in the maintenance of normal sinus rhythm there was also a dose response relationship in conversion of atrial fibrillation.

The data that I've presented show that Dofetilide is efficacious for maintenance of chronic atrial fibrillation or flutter, as shown in two placebo control trials, with more than 1,100 patients.

More than 70 percent of patients randomized to 500 microgram BID have been dosed according to the proposed treatment algorithm.

Efficacy is also demonstrated in subgroups and in patients whose dose was adjusted by the treatment algorithm. Maintaining patients in normal sinus rhythm was correlated with decreased arrythmia related symptoms, severity, and frequency, and increased quality of life.

Furthermore, two placebo control trials demonstrate that Dofetilide is superior to placebo for conversion of atrial fibrillation and atrial flutter.

Thank you very much.

I would like to introduce the next

speaker, Dr. Craig Pratt, who will talk about the safety presentation.

DR. PRATT: Dr. Califf, Dr. Lipicky, Dr. Temple, and members of the Committee, and ladies and gentlemen, good morning, almost good afternoon now.

The next topic is safety, and I would like to begin with the next slide, please.

What I propose to do is to go through in sort of a logical fashion, issues relating primarily to survival, because I think where we are all going with this, is there a mortality signal that translates from the Torsade that is inevitable in a drug that causes QT prolongation, as Dr. Lipicky has pointed out in his three day dissertation.

And I'm going to focus on proarrythmia with mostly talking about Torsade, other potential proarrythmias and other adverse events.

Now, as we pointed out, this was a large program, of over 6,000 patients, of which over three thousand were in clinical trials of SVA. I'm going to focus, repeatedly, on four populations comprising a wide spectrum of risk.

I will repeat this sequence throughout each safety category. The first will always consist of the SVA trials relevant to the pivotal trials you've just heard about. The second will be the very important 3,228 patients in the Diamond trials comprising patients at high risk, and it will include a look at the group of patients, over 500 of them, in these trials, with LV dysfunction, and atrial fibrillation at baseline.

This survival analysis, I think, is quite relevant in establishing the safety of Dofetilide in treating atrial fibrillation, and we will move on.

As you have heard, from previous speakers, in the whole issue of safety revolves around the appropriate use of the algorithm which was derived through the experience in this entire program.

The renal function algorithm was added, and you can see that time course on figure 2 page 17 of your document, and it reflects QT prolongation adjustment, as well as the renal function adjustment.

And as a result of this individualized approach, emphasizing safety, it is clear that many

patients randomized to receive Dofetilide 500 micrograms BID actually received lower doses.

So let me first now, focusing on survival, turn to the dosing algorithm in the ten placebo control trials.

Listed here are the reasons for dosage adjustment or discontinuation in these trials. Page 88 in your document has a lot of details about this information.

You can see that ten patients had discontinuation of Dofetilide due to Torsade. An additional 37 required discontinuation due to QT prolongation.

Then we have dosage adjustment, and I think this is really pivotal in understanding the survival data because a large number of patients had their dosage decreased for creatinine clearance, or QT prolongation.

And this is a fact, I believe, really contributes to long term safety, and you will see the same data in the Diamond set.

So turning first to survival in the SVA

analysis. This compares placebo to Dofetilide with reference to total mortality in the relatively low risk patients in these placebo controlled SVA trials.

Analysis is by intention to treat, and this is evaluated by the Kaplan-Meier estimate with one year follow-up.

If you look at the baseline characteristics here there are no significant differences in Dofetilide and placebo assigned patients relative to risk for mortality, including the gender, age, structural heart disease, and other issues that you see listed on this slide.

You've seen the Kaplan-Meier analysis in your document, it reveals no significant mortality difference between the groups, but we acknowledge the fact that there is a small number of events, and whatever we say about this group, wide confidence intervals surround the attempt to make a point estimate of mortality.

So let's show you four such attempts on the next page. So here we have four analysis. The pooled survival analysis, these first two analysis

were actually conducted at Duke by Dr. Pritchard and associates, and these represent all patients in the pivotal placebo controlled SVA trials, and it revealed the relative risk of 1.4 unadjusted, and 1.1 adjusted when the analysis was adjusted for baseline imbalances.

Now, I just want to mention what those imbalances are. It is important to realize that the proportion of Dofetilide patients who had chronic or persistent, as Peter said today, atrial fibrillation were randomized three to one, in 120 and 345, and therefore there is an excessive number of those patients, and there are also differences that were adjusted for age, gender, and structural heart disease. So those were the adjustments made, and these two point estimates were obtained.

There are many other described looks at this data with point estimates that range in this area. And you have them in your document on pages 90 through 93.

If one wants to look at subgroups with so few deaths, one can look at subgroups like gender,

presence or absence of structural heart disease, and those are the point estimates that one obtains with those, with obviously extremely wide confidence intervals.

What I want to do now is turn to supporting safety mortality that the committee has not previously experienced in terms of evaluating an antiarrhythmic drug for atrial fibrillation. And the population strongly supporting this safety are the Diamond trials, whose background is presented in detail in section E of your document.

All patients had structural heart disease and LV ejection fraction equivalent to, or equal or less than 35, based on the wall motion index. Both these trials are randomized, placebo controlled, double blind studies, with most patients assigned to either placebo or Dofetilide 500 micrograms BID.

More than 80 percent of the patients were treated with the dosing algorithms similar to the SVA approach and the primary endpoint was all-cause mortality evaluated by the Kaplan-Meier analysis, and the analysis was by intention to treat.

Obviously the original trial was designed to show superiority of Dofetilide over placebo.

The two trials differ in that the heart failure trial focuses on patients with clinical congestive heart failure, and this trial focuses on patients very early after myocardial infarction, both whom have LV systolic dysfunction.

The baseline demographic characteristics for both the Diamond CHF and Diamond MI trials known to be associated with mortality risk, are similar for Dofetilide and placebo assigned patients.

I won't go through the laundry list there, you've seen it. Patients in the Diamond CHF clearly had worse LV function, more severe functional impairment, than patients in the Diamond MI trial.

All-cause mortality, the primary endpoint of both of these trials are presented by the Kaplan-Meier plots. Placebo mortalities at one year in Diamond CHF is 28 percent. For Diamond MI 23 percent, emphasizing the high risk in these populations.

And as you can see, there is literally no mortality difference in either of these trials,

between Dofetilide and placebo assigned patients. The hazard ration in Diamond CHF is 0.95, and 0.91 in Diamond MI.

Fairly narrow confidence limits are seen because of the fact that there are 1,101 deaths in these two trials. Overall there are 19 more placebo related death than there are Dofetilide associated deaths.

Since the issue of proarrythmia is important, a separate analysis of arrhythmic death is an important category. Now, these deaths are all classified by a committee, blinded by the drug assignment, and as with total mortality, there is no excessive arrhythmic death in either of the groups, with a total of six more patients classified as having an arrhythmic death on placebo, than on patients assigned to Dofetilide.

As in the SVA trials, safety was a principal motivation for requiring, number one, in-patient initiation, and ultimately, after about 400 and some patients, the dosage adjustment algorithm that we've presented today.

In the same format as in the SVA trials is a summary of the in-hospital dosage adjustments that were performed in the Diamond trials.

Now, a large percentage of Diamond patients had adjustment for creatinine clearance, and that stands to reason, given they had LV systolic dysfunction, and reduced renal function.

Some had adjustments for QTc, the discontinuations for Torsade, and excessive QT prolongation are listed.

While efficacy and safety are analyzed as intention to treat, they include almost 50 percent of patients, therefore, who had their dosage adjusted. The individualization of this dose is, really, I think a critical component in the long-term safe use of Dofetilide.

Now, since there is a total of 1,101 deaths in the combined Diamond trials, exploratory analyses of clinically relevant patient subsets is, I think, potentially quite informative.

Presented here are hazard ratios and point estimates of such relevant subsets in Diamond CHF

including gender, neo heart class, and the other ones that you see here, there were no subsets which showed a statistical difference in mortality between Dofetilide assigned and placebo assigned patients.

Quite similar results are seen in Diamond MI, with no significant differences between Dofetilide and placebo assigned patients.

Now, in the FDA questions the panel has been asked to consider the effect of ischemia. The Diamond MI population, in fact, is an early post-MI population of over 1,500 patients.

A subset of Diamond CHF and MI patients had clinical angina. If you look at that subset of patients with angina, which comprised over 800 patients, the point estimates of mortality are 0.84 and 0.98 for Diamond MI and CHF, respectively.

I want to turn now to this Diamond AF population, and I think the people that do care for atrial fibrillation patients frequently do appreciate the fact that this is a unique population.

These 506 patients are a little bit different than the rest of the Diamond patients, other

than atrial fibrillation at baseline, they have a one year mortality of 32 percent, as compared to 24 percent overall.

We think this represents a very robust sub-analysis, it is the largest long-term experience in patients with atrial fibrillation and significant structural heart disease in a randomized trial.

One important difference that we need to remember from the remainder of the Diamond patients, is that the initial Dofetilide dose for patients with atrial fibrillation was 250 micrograms BID, further modified, if necessary, by the treatment algorithm on an individual basis.

Now, this analysis is a predefined population, but this was a retrospective analysis. The total mortality was compared in those patients assigned to Dofetilide or placebo. All-cause mortality, again, by intention to treat, evaluated by Kaplan-Meier method, the one year estimate of mortality, as we mentioned, was nearly 32 percent.

Baseline characteristics in these two groups, as in the previous groups, are matched for

risk with not statistically significant differences between treatment assignment.

The Kaplan-Meier analysis of the two atrial fibrillation treatment groups reveals identical mortality. There are five more placebo assigned than Dofetilide related deaths.

I want to call your attention to the fact that approximately 35 percent of the AF patients in Diamond were entered into a substudy, and that substudy has been presented and discussed in appendix 6 of your document.

So this figure summarizes Dofetilide survival experience in these various trials, the SVA patients, the individual trials that were the pivotal trials for efficacy, with the advise that we did one year follow-up on every patient, regardless of whether or not the patient was still taking the study drug.

The Diamond CHF MI and AF populations, and these are the point estimates mortality, and their confidence limits for all those populations.

We believe that these overall results are reassuring, and they are closely related to the in-

patient initiation in individualized dosage adjustment algorithm.

The next topic is proarrythmia. Sudden cardiac death, although listed here, we've mentioned some issues related in sudden cardiac death in the Diamond trials.

I'm going to turn to the most important clinical issue concerning the committee, concerning an you of us as clinicians, and that is Torsade de points, ventricular tachycardia.

Now, the observed incidence of Torsade ventricular tachycardia in the same main patient peoples that I previously discussed, including the SVA trials, Diamond CHF, Diamond MI, and Diamond AF, are presented here.

It is important to realize that these include both pre and post-algorithm results.

There were no cases of Torsade in clinical pharmacology studies of 909 healthy subjects. Doses up to 1,250 micrograms BID. They are not included in the slide.

Now let's turn to the fact that 442

Dofetilide assigned patients were entered prior to the initiation of the renal algorithm, and therefore one has the opportunity to observe the importance of adding renal function algorithm in these trials.

For instance, before adjustment of dose using creatinine clearance, the rate of Torsade in the Diamond trials was 3.1 and 4.7 percent, respectively. And this was reduced, after that algorithm was initiated, to 2.9 and 0.6 percent, respectively.

In the placebo controlled SVA trials you can see that 11 Dofetilide assigned patients developed Torsade des points ventricular tachycardia. Of these, ten were identified in the in-patient initiation phase, days one through three, and none of these patients died.

In the Diamond trials there were 32 patients that had Dofetilide associated Torsade. Of these 23 were identified in the first three days. This doesn't necessarily result in in-patient or out-patient, because some of these patients had a longer hospitalization, but 23 of the 32 were first three days, of which 3 of those patients did die.

Let's look at a little more detail about what happened to these patients. In the SVA trials 9 of the 11 had symptoms, 8 required intervention, and no patients died.

For the Diamond trials 29 of the 32 were symptomatic, 23 required intervention, and 3 patients died.

In the Diamond AF trial you can see the same information as contained in the other parts of that slide.

A total of 8 cases of Torsade in the SVA program occurred in females, and 15 cases of Torsade in Diamond were female. 2 of the 3 deaths due to Torsade were female, the other was male. All patients developing Torsade had study drug immediately discontinued.

There were univarient and multivaried analysis done to look at the associations, and I think Dr. Kowey and others would tell you that, in fact, these looked to be similar to other drugs that are calcium blockers, that is there is an association, definitely, with female gender in the elderly,

prolonged QTcs, obviously a reflection of dose, and the use of diuretics.

Now, in multivaried analysis gender, QTc, dose remain predictors of Torsade.

Let me briefly go to issues relating to other proarrythmia. In addition to Torsade there were other -- four other documented proarrythmia events, new sustained VT of VF in the SVA data base. However, we need to call your attention to the fact that these are, three of the four are double counted. That is, patients had Torsade, and they were also circled to have ventricular fibrillation, so all four of these represent only one new patient. The other three episodes occurred in patients that had Torsade. The only new one was a patient who was on Dofetilide 750 micrograms BID, not a recommended dose.

In summary, Torsade is the primary clinically relevant proarrythmia, and the whole discussion this morning has reflected the fact that it is the committee's principal concern.

The occurrence of Torsade can be minimized, not eliminated, but minimized by the dosing

algorithm. We feel the clinical consequences of Torsade are minimized by in-patient initiation of Dofetilide, and the insistence of three days of monitoring.

The results of this cautious dosing algorithm for Dofetilide is no increase in mortality over a wide range of risk groups.

Let me turn briefly to other adverse events, the focus being on the SVA placebo controlled trials. You've seen many versions of this in your document around page 124. I only present one of them, we could present many others.

Listed here are the 10 SVA placebo controlled trials, the most prevalent adverse events, occurring at any time, adjusted for years of exposure.

Although there are small numerical differences observed, none are significant. There are also no differences in a similar table on page 124 of adverse events requiring discontinuation.

I think it is relevant to look at issues that are morbidity issues, like total hospitalizations for heart failure. It is certainly a relevant long-

term measure of safety, and we are looking at this in the Diamond trials presented here.

Dofetilide assigned patients, as you can see, had fewer hospitalizations than placebo assigned patients. Similar results would be observed if we shoed you the same curves for total hospitalizations.

I'm making no claim at this time, I'm just saying, at the very least, there is no evidence for increased Dofetilide associated morbidity as assessed by two measures of hospitalization, either for CHF or all-cause hospitalization.

I would also like to say, though, that I think you will find some intriguing results in the Diamond AF population that will be discussed by Dr. Ruskin in his risk benefit assessment.

Now, myself, Dr. Ruskin, everyone involved with the Dofetilide program realized that the appropriate clinical concern with an antiarrhythmic drug is the risk of Torsade, and it may be associated with mortality.

So we really have to look at the relationship to address this. Please allow me to

narrate this busy slide.

The data come from the Diamond population combined with the 10 SVA populations. On the left-hand side is a summary of the univariate analysis that we've already presented for some of the relevant issues that relate to risk of Torsade.

On the right-hand side is an analysis of the identical subgroups to examine whether we see an increase in mortality in Dofetilide compared to placebo.

For instance, taking gender, which is extraordinarily important, the relative risk of having Torsade is definitely increased if you are female, but the mortality analysis in females, in all the populations we've looked at shows a relative risk estimate that is less -- at least at one.

Similar results demonstrating the absence of increased mortality in Dofetilide compared to placebo are seen for the elderly population, QTc at baseline, and the presence of structural heart disease.

Now, I'm going to just go back, this is on

figure 2 page 17 of your document. This is just a list of all these trials. I know that most people can't really read those, except those sitting up very close, and this is when the creatinine clearance algorithm was initiated.

And so I think it is pretty relevant that realizing there was a learning curve in this development program over 8 years, that one could look at, an additional safety analysis focusing only on those patients who are put in the trials, after the initiation of this algorithm.

These populations being evaluated are identical to those previously represented, that is the SVA and Diamond trials.

Now, the more than 3,200 patients are included in this analysis, including SVA patients, randomized after creatinine clearance algorithm to the 500 dose, the dose which we intend to use.

The Diamond CHF and MI populations for all then non-AF patients randomized to the creatinine clearance, after the creatinine clearance amendment, and then very importantly, we take the group in the

Diamond AF population, randomized after the creatinine clearance amendment, that would have received 250 BID or less because of this creatinine clearance.

So I think it is all the populations clinically relevant to the way we intend to use the drug.

The results of this analysis are essentially they emulate the proposed clinical use of the drug. The SVA trials are 550 Dofetilide assigned patients, the Torsade rate is 0.8 percent, and the hazard ratio is less than one.

For the Diamond trials a total of 1,722 patients there is the Torsade rate overall, there is the point estimate of mortality, and you can go to Diamond trials alone, or you can go to the Diamond AF population, and those are the point estimates of mortality, as compared to the risk of Torsade de points ventricular tachycardia, and used correctly there is no mortality signal.

Now, Dr. Califf, I was going to make this a concluding slide, but you've asked me to go ahead with a couple other slides, so let me just say that I

was going to conclude, but based on what you've seen, there is no adverse effect on mortality, even in patients with severely compromised cardiovascular disease or function.

In patient initiation the dose individualization is very important in identifying and either lowering the dose, or eliminating these patients from further therapy.

And we think that the adherence to the dosing algorithm minimizes the consequences of the proarrythmia that is clearly there.

And in terms of other adverse events, there is no other differences that are clinically relevant from placebo.

Now, where I would like to take you from there, because of the previous conversation, and a discussion I had with Dr. Califf at the break, is the drug interaction document.

And you did have that as a supplement to your many documents that you had, and we apologize they didn't all come at identical times.

But that drug interaction document is

important, and let me just remind you, before we get any slides on, why don't we just take that slide off right now.

This is an analysis, then, of all the SVA and all the Diamond patients, 5,051 patients, in whom there was a great deal of long term follow-up, because it includes over 3,000 Diamond patients.

If you want to start reading about the concomitant meds these patients were on, you can start on page 11 of that document. But you will see that over 2,300 of these patients were on Digoxin, over 900 patients were on calcium blockers.

And there was a lot of long-term follow-up since, in fact, Diamond contributed 3, 028 of these patients. And we are looking at a data base in which there was 43 cases of Torsade de points ventricular tachycardia.

You know, before I show you the data, I think it is fair to say there is some real world data here, and I would like to tell you why. First of all, in Diamond the average age of the patients was 70 years old.

These patients were treated in local hospitals in Denmark. In fact, over half the population in Denmark was involved in the 37 general hospitals.

Many of the doctors there were internists and general practitioners, they were not all cardiologists, and certainly not all electrophysiologists.

In fact, the QT was often measured by junior physicians, and even nurses. So I think this does, in that respect, reflect some of the real world issues that we would like to know about.

The drugs weren't supplied some way special. They were put in bottles, and there was very extensive concomitant medication use not only at baseline, but during the trial. In fact, almost half of the patients had between one and five new concomitant medications.

So, with that, let me go to backup slide 18, and we will follow that by 22 and 21, just for your information.

So this is the population, and I don't

think it is insignificant. It is a lot of information, and it is the best information we have to try to address the questions which were very appropriately being the item of concern earlier today.

And we are going to examine the relationship between the occurrence of Torsade and mortality. And I think you've already seen that some of these drugs do have a relationship, albeit somewhat confounded by indication.

Here is sort of the top list of drugs. We have a number of patients. This is actually incorrect, we have almost 400 patients on Diltiazen, almost 425 patients on Diltiazen, another couple hundred on Verapamil, a total of about 900 in calcium blockers. You can see the number of people that are taking Digoxin, it is a very large group of patients.

So that is the concomitant medication. That is just baseline medications. Just to let you know, 93 percent had at least one concomitant medicine added or subtracted during the trial, 48 percent six to ten -- 25 percent, six to ten new concomitant medicines. So there is a lot of medicine changes

going on, all the things that we would be concerned about.

And this is the bottom line for the data that we have. Here is mortality, and here is the relative risk in these population, including Digoxin, including Verapamil, including all the other fairly complicated metabolic groups that Dr. Brater so elegantly discussed earlier. And that is the result of that analysis.

And with that, Mr. Chairman, I will stop.

ACTING CHAIRMAN CALIFF: We have seen a lot of data, we don't need to see the same data over and over, but if you have new perspectives to add, we would certainly like to hear it.

DR. RUSKIN: Dr. Califf, Drs. Lipicky and Temple, members of the Committee, ladies and gentlemen, I will do my best to stick to that 15 minute limit, and share with you some thoughts about the benefit risk evaluation of this agent.

What I would like to do is offer some comments about the therapeutic benefits of Dofetilide in treating atrial fibrillation, and share with you a

little bit of additional data, offer some comments on the risks of Dofetilide, in low and high risk patients.

And to the extent that the data permit, attempt to place in perspective the benefits and risks of this drug, that is its efficacy and its safety, in relation to currently available therapeutic agents.

As you've heard, Dofetilide results in conversion of atrial fibrillation to sinus rhythm in approximately 30 percent of patients with chronic atrial fibrillation, and among those patients converted to sinus rhythm, either pharmacologically, or electrically, about 60 percent remained in sinus rhythm, on the drug, at one year of follow-up.

This maintenance of sinus rhythm is associated with symptomatic benefit.

This slide summarizes for you average efficacy rates for a variety of agents reported in the literature, specifically with reference to maintenance of sinus rhythm after conversion of persistent atrial fibrillation.

And as you can see, for Dofetilide, as

you've heard, Quinidine, Disopyramide, Flecainide and Sotalol, the efficacy rates at one year are roughly comparable, that is, in the range of 50 percent.

And I think most people would agree that their clinical experience fits with that number. It is likely that Amiodarone is somewhat more effective, with an efficacy rate in the range of 70 percent at one year, compared with these other available agents.

Now, you've heard from Dr. Pratt about the subset of patients in the Diamond AF trial, these are 506 patients drawn from Diamond MI and Diamond CHF who had atrial fibrillation at the time of entry into the study.

You've also heard that the survival analysis in this population showed no difference between Dofetilide and placebo for all-cause mortality.

Among these 506 patients, 234 converted to normal sinus rhythm at some point during the trial. And this slide summarizes for you the time to recurrence of atrial fibrillation among the 234 converters.

And as you can see there were 148 convertors on Dofetilide, versus 86 on placebo, and that time to recurrence was much later on Dofetilide than it was on placebo following recurrence, yielding an 80 percent preservation of sinus in convertors on Dofetilide versus 42 percent on placebo at 12 months.

You've also heard about an analysis that was performed in the Diamond trials. This was a pre-specified endpoint examining time to hospitalization for congestive heart failure, for worsening congestive heart failure.

And what you see on this slide are two sets of Kaplan-Meier curves displaying time to hospitalization for CHF in Dofetilide versus placebo treated patients. In the CHF trial, versus the MI trial, there was a significant difference here in hospitalization rates for heart failure on Dofetilide versus placebo, yielding a hazard ratio of .75. This effect was not seen in the Diamond MI study.

The obvious question that arises here is whether or not this effect on heart failure has anything to do with rhythm status, whether it may in

fact be mediated by an effect on cardiac rhythm, since there is no other obvious way that the drug should improve hospitalization rates for heart failure.

And so similar analysis was performed among the patients in Diamond AF. The 506 with AF at entry into the Diamond trial. And as you can see this benefit that was observed overall in the Diamond CHF trial is in fact more prominently evident in the Diamond AF subset, that is time to first hospitalization for worsening congestive heart failure is significantly reduced in the Dofetilide compared with placebo treated patients, yielding a hazard ratio of .69.

TO further asses the relationship between rhythm status and impact on heart failure hospitalization, the same analysis was performed for time to hospitalization for heart failure in all the Diamond patients, excluding those who had atrial fibrillation at the time of entry into the trial.

And you can see that this impact on heart failure hospitalization is largely lost.

So what we see here, then, is similar to

what you observed in the SVA trials. That is, Dofetilide is associated in this very sick population with a higher conversion rate from atrial fibrillation to sinus rhythm, a higher maintenance rate of sinus rhythm, compared to placebo, and an associated reduction in hospitalization rates for congestive heart failure.

Because of the concern that this effect might be mediated by hospitalization for other causes, or drop outs for other reasons, or mortality, the same analysis was performed, that is time to all-cause hospitalization in the Diamond AF population, as well as a composite analysis of time to all-cause hospitalization death and withdrawal.

And you can see that the salutary effect of Dofetilide compared to placebo is maintained in this analysis, and in this composite analysis, although the effect is attenuated by including mortality.

You've heard that Dofetilide is, in fact, a well tolerated drug, and that it is not discontinued at a rate in excess of that of placebo for non-cardiac

side effects.

The primary risk of Dofetilide is proarrythmia, Torsade de points, and you've heard a detailed discussion of that by Dr. Pratt. I would like to just offer a few comments with regard to rates for this drug in relation to other agents.

The overall rate of Torsade in the SVA placebo controlled trials was 0.8 percent, which is quite comparable to what has been seen with other antiarrhythmic agents which affect repolarization, and you've also heard that the risk of Torsade can be minimized by the dosage adjustment algorithm, and its consequence is limited by in hospital initiation, both critical cornerstones to the safe use of this agent.

These are data from the literature on Torsade rates with other agents. The Dofetilide data are shown here for the SVA population, these are in placebo controlled studies, and this is for all patients receiving Dofetilide, the remainder of these are drawn from the literature, Sotalol, with a 1.4 percent rate in an SVA population, and Quinidine, Procainamide, and Disopyramide shown here.

And I think one can conclude, that to the best that one can compare these, and there are certainly some differences in populations, there is no obvious glaring excess of Torsade in this drug in relation to other agents known to cause the problem.

Amiodarone causes Torsade de points very rarely, as emphasized by Dr. Graboys, and I should emphasize that this represents only a single case in an AF population.

In the CHF Stat trial, which I will mention in a minute, which was a large heart failure trial with Amiodarone there were no cases of Torsade reported.

I will spend only ten seconds on this to reemphasize the point that Dr. Pratt made, and that is the univarient predictors of risk for Torsade are known for this drug, and they apply to virtually all drugs that cause Torsade, and they include gender, age, baseline QT, and the presence of structural heart disease.

But in this large very rich data base, these factors, which are known to predict Torsade, did

not predict mortality in patients receiving Dofetilide.

The next several slides will address the issue of mortality and again to attempt, to the extent that the data permit, to place it in perspective in relation to other available antiarrhythmic agents.

These are data from the SVA trials, and I won't belabor this point, because you have seen these presented in Dr. Pratt's talk. The point that I do want to make is that what we are talking about here are very small numbers of events, so that it is difficult to place any confidence in the hazard ratios that are -- in the point estimates of the hazard ratios that are obtained, and the lack of confidence is expressed in this very wide confidence intervals.

This is a problem with all data bases of this type, that is a relatively low risk population with a very low mortality rate. This is an issue that has been faced with every antiarrhythmic drug that the Agency has seen.

One of the analysis that was done, and again, it doesn't definitively answer the question, by

any means, but I show it to you because I thought the data was important to present, was an analysis of survival in all patients in the two pivotal AF trials, 120 and 345.

That is a 12 month mortality assessment in every patient in both trials. And there was 100 percent follow up.

This analysis obviously is limited in the sense that most patients on placebo either end up on something else or nothing, because they recur, and many patients on Dofetilide, throughout the course of this study, end up either on nothing, or some other drug.

But it is a real world look and one of the only real world looks we can get at one year, in an SVA population. And when that was done for these two studies, and as I mentioned with 100 percent follow up, there was no strong signal here of an excess mortality risk.

Now, I must emphasize that it is not possible, based on this data, to exclude some excess mortality risk associated with the use of Dofetilide

in this low risk population. One simply cannot exclude that possibility from these data.

In the past this is pretty much the limit of what the Agency has seen in reference to antiarrhythmic drug applications. And the concern has always been how do we know we are not missing a much bigger signal, and yes we have a drug that looks as if it has efficacy, but you are looking at a low risk population,a nd we know that this agent is going to be used in much sicker patients.

How can we possibly asses the risk benefit ratio in that group, and how do we know that there will not be an enormous increase in mortality when the drug is given to higher risk patients.

And I would like to just offer some comments specifically addressing that question in the next several slides.

Let me -- this is simply a reiteration of what you've seen for Dofetilide in the SVA data base showing an all-cause mortality rate of 1.3 percent, versus .9 in the placebo control population, compared with the Quinidine beta analysis with a 2.9 percent

one year mortality rate, with what appears to be a roughly comparable control group.

The arrhythmic date rate on Dofetilide was not different from that seen with placebo, and in the Quinidine meta analysis it was 1 percent versus .3 in the controls.

And I think all one can say from these data, again, in a group with a low event rate, is that there is no obvious signal here that Dofetilide is associated with a markedly increased risk compared with a drug like Quinidine, which remains the most commonly prescribed drug for atrial fibrillation.

Now, let me get beyond this because my comments on the previous slide related to the question of what happens with sicker populations.

And I think for the first time, and with the exception of Amiodarone, the only time that we have these kinds of safety data are in this data base.

This is a composite slide showing you hazard ratios for all-cause mortality as a function of antiarrhythmic drug class in post-infarction patients. And I show this because we have data in these

populations. That is extensive data, with many different classes of antiarrhythmic drugs.

And you are all familiar with the fact that the data on class IA drugs is quite limited, but it is not encouraging in terms of safety. Certainly a trend in most of the studies to an adverse effect on mortality.

As discussed in the public comment period the cardiac arrythmia suppression trial established a very substantial excess mortality rate when the class IC drugs are used in a patient population with coronary artery disease, and recent myocardial infarction.

The beta blockers are the only class of drugs that have very clear and definitive evidence of a mortality benefit in this population.

The calcium blockers are neutral effect. Amiodarone in the European trial, a neutral effect. A slightly favorable trend in CAMIAT, and if one were to pool these two, one would end up with a hazard ratio of just over .9, almost identical to what is seen in the Diamond MI trial, a 1,500 patient post-MI

mortality trial in patients with recent infarcts and impaired ventricular function.

I should also contrast this data with the D-Sotalol trial, the Sword study, this is a pure class 3 agent that was also studied post-infarction in which there was a clear demonstration of harm with regard to excess mortality.

One of the concerns that comes up, whenever you see a neutral effect on mortality in a sick population is whether or not the drug may, in fact, be having two effects; an antiarrhythmic effect in some subsets, and a proarrythmic effect in other subsets, resulting in a neutral impact on mortality.

And while there is no way to deal with that question definitively, I thought it would be interesting to just take a quick look at the Sword data, in which there was at least an adverse effect in a very select subset of patients, and to compare that with the data that we do have available for the Diamond MI trial.

These are Kaplan-Meier curves from the D-Sotalol mortality trial in which the drug was compared

to placebo in post-infarction patients who were stratified either by recent myocardial infarction versus remote, or by severe LV dysfunction versus moderate LV dysfunction.

And the only point that I want to make is that there was no subgroup here that showed benefit, but there was a striking adverse effect in patients with moderate left ventricular dysfunction, and remote infarction, in whom there appeared to be unmasking of a proarrythmic effect in a subset that had a very low placebo event rate, accounting presumably for much of the adverse mortality effect, although there was certainly no favorable effect in these other groups.

In analyzing the results of the Diamond MI trial, stratified by moderately severe and severe LV dysfunction, there was no evident difference in terms of a subset in which Dofetilide appeared to be having an adverse effect on outcome.

Now, what about congestive heart failure? Fortunately we have some comparative data, and I apologize for the imperfection of this part of the curve, this was scanned.

What it shows you are Kaplan-Meier curves for all-cause mortality in the CHF stat and the Diamond CHF trials, two very similar trials; the CHF stat study being carried out with Amiodarone in patients with severe LV dysfunction and congestive heart failure, and frequent ventricular premature beats versus the Diamond CHF study which you've heard about.

And I emphasize this, the importance of this study, because at the present time Amiodarone is really the most widely used agent for the treatment of symptomatic atrial fibrillation in patients with congestive heart failure.

What was seen in the CHF stat trial was virtually an identical, that is neutral mortality effect to what was seen in the Diamond CHF trial, and the mortality rates were very similar in the two studies.

In addition, analysis have been performed in both trials for patients who entered the trial with atrial fibrillation. And you've heard about the Diamond AF trial. In the CHF stat trial there were

103 patients who entered the trial in atrial fibrillation, roughly 15 percent of patients in both studies.

In looking at the efficacy of agents in converting atrial fibrillation to sinus rhythm, there were significant differences in placebo efficacy rates between the two trials. And I don't know whether this reflects differences in populations, or in the ways in which presence or absence of AF was determined.

But if one examines the placebo subtracted efficacy rate for conversion of AF to sinus rhythm, the effects of Amiodarone and Dofetilide in this very sick population are virtually identical.

This is the next to the last slide, and it represents a modification of a figure published in the recent review of therapeutics for atrial fibrillation, and emphasizes the fact that in patients without structural heart disease and symptomatic AF we have a number of therapeutic options available from virtually all classes of antiarrhythmic drugs.

In patients, however, with ischemic heart disease and in particular those with congestive heart

failure, the therapeutic options are relatively limited.

Some people would include some of the class 1A agents in this category, others would not. But I think most people would agree that the 1C drugs are contraindicated in these subsets.

And in thinking about where Dofetilide might provide an additional option, while it shows efficacy in all three categories of patients, perhaps the most crying need, in terms of an additional agent, are in the groups of patients with advance structural heart disease.

In summary, then, maintenance of normal sinus rhythm is a necessary goal in some patients with symptomatic atrial fibrillation in whom the symptoms are due to the presence of AF, that is the loss of atrial transport.

Our current therapeutic options, particularly in patients with advanced structural heart disease are limited, and all of them are associated with measurable risk.

Dofetilide is effective in the conversion

of atrial fibrillation, and in the maintenance of normal sinus rhythm, to an extent that is comparable to that seen with other currently used agents for the treatment of this problem, and the drug is well tolerated.

The risk of Dofetilide is proarrythmia, as it is with most other antiarrhythmic agents, and in this case specifically Torsade de points. And as you have heard, both the occurrence and the consequences of Torsade can be minimized with the use of the proposed treatment algorithm, and in hospital initiation.

And I would reemphasize that these two features constitute a critical cornerstone to the safe and appropriate use of this drug.

Finally, there is no evidence to suggest a mortality risk in patients with advanced structural heart disease treated with Dofetilide, and with the exception of Amiodarone, these are data that do not exist for any other antiarrhythmic drug that is currently being used.

As a result of the foregoing, Dofetilide

would provide a useful addition to our pharmacologic armamentarium for the treatment of patients with symptomatic atrial fibrillation.

Thank you.

ACTING CHAIRMAN CALIFF: Well, let me suggest that we take a break for lunch, and that we come back and have Pfizer identify a captain of the team to preside, because I know there are many consultants who may be called on in the discussion.

If we could reconvene, then at 1:15?

(Whereupon, at 12:53 p.m. the above-entitled matter was recessed for lunch.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:30 p.m.)

ACTING CHAIRMAN CALIFF: I want to thank the people for making a valiant effort here to get through lunch. Probably a fair amount of indigestion in the crowd.

What I think would be most effective would be to now launch into the questions, and if the Sponsor has a team captain who wants to come up to the podium?

There is a lot of material that we've been through, and a lot of issues. It would be fun, actually, to spend a couple of days just discussing the issues around atrial fibrillation, and all the implications that this data brings up, but we obviously have a different job to get done today.

So what I would like to do is start with our two primary reviewers, and then go to Ralph D'Agostino to ask whatever questions you have about the data that has been presented.

DR. GRINES: I have a series of questions related to the last two talks that were done.

My first question relates to the 14 day run in period, and exactly what was done during that 14 day period?

DR. RYDER: The 14 day run in period? Dr. Friedrich?

DR. FRIEDRICH: This was -- I take it you refer to the studies 345 by a running period of 14 days?

DR. GRINES: Yes.

DR. FRIEDRICH: Was in place. During that period patients who were not anticoagulated were anticoagulated, and also it was established that they were in atrial fibrillation, so an EKG was done, and the patients were in atrial fibrillation that had least passed this entry criteria.

But mainly, the main reason is that patients were anticoagulated, and if local practice was such that you would have a longer period of anticoagulation, then that was done.

DR. GRINES: Additional questions that I have relate to the proportion of patients who can actually start the trial, and that finish it. And,

for example, in the 345 and 120 studies, patients were enrolled acutely, and then if they cardioverted, either by drug, or by electrocardioversions, they went on to the maintenance phase.

And I would like you to go through, perhaps, a hypothetical 100 patients that were enrolled and tell me how many of them ultimately were cardioverted if one adds electricity to the drug, did the drug increase the cardioversion success rate? That is my first question.

And then secondly how many of them were able to continue on the drug for the one year follow up period.

DR. RYDER: I believe that Dr. Friedrich has the specific data from the clinical trials.

DR. FRIEDRICH: In both studies 345 and 120, the two studies that I have shown you, those patients that did not convert pharmacologically were cardioverted, as I have shown. This is -- in different treatment group it was a little bit different, but on average 20 percent of patients that were enrolled into this conversion phase did not

convert either pharmacologically, or when a cardioversion attempt was made.

So on average about 20 percent of patients did not get in sinus rhythm, and was stopped at that time.

DR. GRINES: Did the drug enhance the ability to be cardioverted? Say, for example, if I have a patient with atrial fibrillation, and I want them cardioverted, the question is, should I spend three days worrying about this patient, or should I just electrically cardiovert them? Does this drug add anything to my cardioversion?

DR. FRIEDRICH: We have not specifically designed a study to look, for instance, if different protocols of DC cardioversion would be more effective with Dofetilide on board, or not on board. So we can't answer this question.

DR. GRINES: But you know the proportion of patients in the placebo group, and the treatment group that were ultimately successfully cardioverted, correct?

DR. FRIEDRICH: And that was no different.

DR. GRINES: No different, okay.

DR. FRIEDRICH: In essence 80 percent of the patients that entered the trial made it into the maintenance phase.

DR. RYDER: I believe that the difference was restricted to the 30 percent that got pharmacologically converted in the Dofetilide 500 microgram BID group, compared to very few in the other dose groups, and very few in placebo.

DR. GRINES: Right, that was clear, but from a clinician standpoint we won't just stop at administering -- if we are bent on cardioverting somebody we are going to add electrical cardioversion.

And so then, from my standpoint the ultimate success rate does not differ depending on whether they are treated or not.

DR. FRIEDRICH: What you say, basically, is these 30 percent that pharmacologically convert, these patients do not need to undergo electrical cardioversion, that is the net result, really.

But, I mean, if you take 100 patients, 20 percent of these patients, or 20 patients, would not

be cardioverted by either pharmacological or electrical means, and at least 30 percent of these 100 patients that pharmacologically convert, and 50 percent that would need to be cardioverted.

DR. GRINES: So once they are started into the maintenance phase then how many of them either drop out or ultimately go back into atrial fibrillation?

DR. FRIEDRICH: I best show you the Kaplan-Meier curve again, because that is the answer right there, if I may. Efficacy core slide number 13, please.

This curves show the probability of remaining in normal sinus rhythm for different treatment groups, starting from the top 500 microgram BID Dofetilide, 250 the next line, 250 microgram BID, the green line Sotalol, and below that 125 microgram BID Dofetilide.

So you can estimate how many patients stay throughout the trail in sinus rhythm through the end of the trial. So if you go across you see about 70 percent of patients on 500 microgram BID in normal

sinus rhythm at the end of the trial.

DR. GRINES: Am I supposed to be looking at the curves, or those numbers?

DR. FRIEDRICH: At the curves.

DR. GRINES: But the numbers at the bottom say that your sample size is only 31 patients at 12 months. What does that number represent? Below the 12?

DR. FRIEDRICH: That is the actual number of patients still in the trial at this point.

DR. GRINES: See, that was my question.

DR. FRIEDRICH: The curves give you a probability.

DR. GRINES: Yes, that was my question, how many patients are -- say, for example, if you have 100 patients how many are cardioverted, can continue on the maintenance, and at 12 months are still on the drug?

DR. FRIEDRICH: It is right there, compared to the placebo group it is 31 patients on Dofetilide versus 7 patients on placebo.

DR. GRINES: So out of 100 patients --

now, this is a different question. Out of 100 patients who successfully converted only 31 remain on drug at 12 months, is that correct?

DR. RYDER: Do you have the slide showing the proportion of patients discontinued during the trial, and for the various reasons?

DR. FRIEDRICH: Backup slide number 19. This slide is from study 345, it shows you discontinuations related to study drug, split up by the different treatment groups, Dofetilide 125, 250, 500, Sotalol and placebo.

On the top you see the number of patients randomized. Total discontinuations is the yellow line, during the course of the trial.

DR. GRINES: But these numbers look different than -- this is randomization at the beginning?

DR. FRIEDRICH: That is correct.

DR. GRINES: Prior to cardioversion?

DR. FRIEDRICH: Was that your question? I mean, how many patients entered the trial, in other words were randomized, and then were discontinued

during the trial?

DR. TEMPLE: That doesn't include for failure.

DR. FRIEDRICH: This doesn't include relapse, this is discontinuations.

DR. GRINES: So basically 30 percent might be discontinued due to a drug side effect, and then another 40 percent might have relapse and atrial fibrillation?

DR. RYDER: No, I think that is misreading the slide. The number is for 500 micrograms BID, the first yellow line is the total number of patients discontinued, and then that is segregated below, and on the following slide, it is continued, so that that number will be 6, plus 7, plus 2, if you could show the following slide.

DR. TEMPLE: But that does not include people who discontinued because they failed?

DR. FRIEDRICH: That is correct. That information you get from the Kaplan-Meier curve, because that shows you exactly how many questions --

DR. TEMPLE: Yes, but that is the question

Dr. Grines is asking, at 12 months, for all the reasons that people left, how many are still in normal sinus rhythm at the end?

DR. FRIEDRICH: That is in the Kaplan-Meier curve, so if we could go back to --

DR. GRINES: So out of 100 patients that entered the maintenance phase, only 30 of them are going to be taking the drug in sinus rhythm at 12 months?

DR. RYDER: To get to the real heart of the matter, no pun intended, I would like to ask Glen Andrews, who is the statistician who actually ran the Kaplan-Meier curve to speak to the issue.

DR. ANDREWS: Essentially I would like to draw your attention to the briefing document, table 12 of the briefing document which deals with this in a bit of detail.

There are, essentially, a couple of issues, really, although 12 months was the specified end of the study, some investigators chose to have their patients come in prior to 12 months, and there was a two week window specified in the protocol.

So the 31 patients you see for the 500 group are those that made it to 12 months in total. In the briefing document in table 12, then, the number completing the study is 49, so it is approximately 50 percent.

DR. FRIEDRICH: Can I make one more point? Those discontinuations that occurred because patients relapsed were protocol driven, of course, because a patient who relapsed, the study -- the protocol prescribed that these patients were discontinued.

In the real world you would probably go on with these patients. I will ask Dr. Ruskin to talk to that issue, what really happens in atrial fibrillation treatment when you consider patients that are in need of treatment.

DR. GRINES: Another -- did you want to say something?

DR. RUSKIN: I just wanted to make one brief comment, and that is if we could look at the primary analysis for 345, the Kaplan-Meier curves, because another way to look at this, in terms -- I think you are getting at a practical question, which

is, what is the clinical impact here.

Another way to look at it is what is the median time to recurrence. And on that curve you can see that on 500 BID, even out to a year, you haven't hit 50 percent recurrence rate, whereas on placebo you've got a median type to recurrence of about a month.

So another way of thinking about it is that if you are on the drug, your chances -- if you are maintained on the drug, your median time to 50 percent, or time to 50 percent recurrence is more than a year, versus one month off therapy.

In this protocol people were dropped out if they had a single recurrence at anywhere along that route. And from a clinical perspective, I think that most of us would agree that if a patient went six months on a drug without a recurrence, had a recurrence at six months, we would probably cardioverted discontinue to treat them, and there is no way to evaluate that from this trial, which is not designed to look at things that way.

DR. GRINES: Well, the reason I bring it

up isn't because of the efficacy question, it is more related to the safety issue. And if we only have a proportion, and my calculation about 40 percent of the patients completed this study on a particular drug regimen, then how sure are we of its safety analysis?

You know, unfortunately all the safety data that was given to us incorporated these very low doses which, presumably, will not be marketed.

And if one looks at the number of patients who actually received the 500 BID it is only about a, I think we calculated here about 106 patients in the total -- in the 345 and the 120.

And although a lot of emphasis was placed on the Diamond study, they received a half dose, they received 250 twice a day for atrial fibrillation. Is that correct?

DR. RYDER: That is correct, but I think there is an important point that I don't want the committee to miss, and that is, there is no dose of Dofetilide. Dofetilide is a treatment regimen, and the dose that you are administered from the inception onward is dependent upon your creatinine clearance.

And so the randomized dose group that was shown you received 500 micrograms BID or a lower dose specified according to their creatinine clearance. And the intent was to get a common systemic exposure.

And the specific analysis that Dr. Pratt referred to, was one where he had us go into the data base and say, after this learning was obtained, during the clinical program in early 1994, and you realized that you should down-titrate, or administer, I should correct myself, administer from day one a lower dose if your clearance of creatinine is less, what does the safety look like in patients who would be getting the recommended regimen?

And that is what Dr. Pratt presented.

DR. GRINES: Right, but according to our calculations, and actually it is data from your slide number 24, if one combines the 345 and 120 studies, that is only 157 patients who received either the 500 dose, or the reduced dose for creatinine clearance.

DR. RYDER: From the two pivotal trials I think that that is correct. But I would offer the committee that I think that to dismiss safety data

from other patients, for example, take Diamond AF. Patients who are in Diamond AF were typically in their 70s, they had lower creatinine clearances, and they were receiving 250 micrograms BID.

Today, if we were to administer Dofetilide the way we were going to recommend it, if their creatinine clearance was less than 60, that is what we would say to start them on, 250 micrograms BID.

So I would offer the committee that that data may be relevant, and that is what Dr. Pratt included -- had us include in his analysis.

DR. GRINES: But how many additional patients would that be, would have been treated at the recommended dose?

DR. PRATT: You are referring now, Dr. Grines, to the Diamond AF study?

DR. GRINES: Right, the Diamond atrial fibrillation.

DR. PRATT: So let's go to backup 35 please. That is safety backup 35, please. And there is your answer, all but 85 of Dofetilide assigned patients would have received that.

Now, the question of safety then, might be best asked -- by the way, the overall analysis that I showed you after the algorithm included all those patients below that 85, okay? So they were included in the analysis that I showed you on my -- on your slides, about 38, 39 and 40.

But if we go to the next one, backup 36 --

DR. GRINES: So you have 100 extra patients here?

DR. PRATT: No, go back please, go back to 35. We have 85 from 249. So we have about 160.

DR. GRINES: So that was a protocol amendment to drop the dose? Because it was my -- maybe I missed something in the presentation.

DR. PRATT: Let me go back, because a decision was made by the sponsor in this trial to treat all patients with this sever LV systolic dysfunction with 250 micrograms BID as the maximum dose they would give, a decision made years ago.

It was a decision made even before the algorithm was initiated. What we did was to go back and say, were all these 249 to be put in a trial now,

how would we treat them? And the answer is, all but 85 would have received 250 or less, based on the renal algorithm.

Now, I can show you the safety data associated with that, that is in backup 36. And backup 36 says that they look pretty much the same in terms of mortality, as all the patients did.

So we've eliminated those 85 because they would have received 500 BID, and we can never guess, or intimate what they might have done.

So that was our closest approximation of that very good question.

ACTING CHAIRMAN CALIFF: Bob, you had a comment on this issue, or a question?

DR. TEMPLE: Yes, I guess my question would be why would only the people with AF from the Diamond study be relevant? Wee are interested in whether the people are susceptible to Torsade.

So you might also have people from the rest of the trial who at least are relevant, in some way, to the question. It is not just the people with AF.

DR. PRATT: Absolutely, and Dr. Temple, we've shown that analysis in that everybody else in Diamond was randomized to 500 BID until the implementation of the renal algorithm. That is why the Torsade rate was quite high.

I showed you that before and after, and it is in your document, where we really go down in Diamond MI, for instance, from 2,9 to 0.8 percent using the algorithm.

So there was a learning curve in how to use this drug, or if you will, how to not use it, and those were corrected, and all those patients are included, all the patients randomized after 500 are included in that analysis that begins on slide 38.

Would you like me to go through a little more detailed version of that? I think maybe it is pretty important, it is the real life use of this drug.

Dr. Grines pointed out something very important, that is that when we first developed a look at things we were certainly combining pre and post-algorithm, such as this kind of slide.

So the idea was to make a more detailed analysis, and that starts on core slide 38. And that includes all the patients to the right of that vertical line, all the patients in the SVA trials, the ten trials, to document a safety, and the Diamond trials, every patient, Dr. Temple, in those trials.

And if we could go then, to safety backup 3. And those are the actual numbers of the people that are in the trial, that were appropriately dosed according to the algorithm that is being proposed.

And that is, we have a total Dofetilide and placebo, of about 33, or nearly 3,400 patients, and they include 900 patients in the SVA trial.

So these are all dosed at 500 at randomization.

ACTING CHAIRMAN CALIFF: Marv, you had a question about --

DR. KONSTAM: Craig, can I just follow on that?

DR. PRATT: Yes. Unfortunately I'm sort of in a hole here, but I hear you.

DR. KONSTAM: But with the Diamond AF you

started automatically at a lower dose, right? In the Diamond trial with the AF patients?

DR. PRATT: Right. So we included in this analysis, at Diamond AF, are just the 139 Dofetilide, and 135 placebo assigned patients whose creatinine clearance was less than 60, so they would have received 250 BID or less.

DR. KONSTAM: Well, just clarify that a bit more. If you had a normal creatinine clearance, and you were in Diamond AF --

DR. PRATT: You are one of those 85 that would not be included here.

DR. KONSTAM: Okay, but then if you had -- if you were in Diamond AF and you had a low creatinine clearance, and you were randomized to the 500 group, what dose did you wind up getting?

DR. PRATT: Could you repeat it? I'm sorry.

DR. KONSTAM: Well, I think it needs a little clarification so that -- the AF patients in Diamond automatically started at 250 BID?

DR. PRATT: And that was true even before

the algorithm.

DR. KONSTAM: Right, so if somebody had AF in Diamond, and they had a low -- I guess it is less than 60 creatinine clearance, what was their dose?

DR. PRATT: Before the algorithm it was 250, after the algorithm it was 250 or less.

DR. RYDER: It was less if they were -- if they had a creatinine clearance less than 40, which was the next categorical change in dosing. The recommended dosing is, if your creatinine clearance is greater than 60, 500; 40 to 60, 250; 20 to 40, 125; and that is from the first dose on.

The next change, the only other adjustment that is allowed is after the first dose, in order to asses individual pharmacodynamic responsivity, QTc is looked at, after the first dose, two to three hours after the first dose, if it is greater than 500, or greater than a 15 percent change from baseline, we are conservative, whichever criteria is met, then the dose is lowered.

No other adjustments are allowed for QTc. The threshold that then comes into play is

discontinuation. And that would be if you have a 500 millisecond absolute value after that period of time you are discontinued from the trial.

And the reason for the dose adjustment after the first dose is that the reason for dose adjusting is to try to get the best efficacy but limit Torsade. And Torsade is an event that in our data set mostly happened early on.

And so the dose adjustment is after the first dose. And when you do that adjustment, that is the analysis, this all pertains to the analysis that Dr. Pratt has.

DR. PRATT: Dr. Califf, I didn't quite get to finish the extra data I was going to show, we kind of got sidetracked by who they were, so --

ACTING CHAIRMAN CALIFF: Would it be helpful?

DR. PRATT: I think it will.

ACTING CHAIRMAN CALIFF: Okay.

DR. PRATT: I believe so. Could we put backup slide 3 back up there?

This is, again, the 500 BID real life

doses. So if we could go to backup 5 now, this is one analysis that you didn't see. You see there is no mortality signal, and this is across the board for both males and females, dosed according to the algorithm, 500 BID, for men and women across all the trials.

And there is the point estimates and mortality given in a way that we recommend giving it.

ACTING CHAIRMAN CALIFF: I think Dr. Lipicky and Dr. Temple both had comments.

DR. LIPICKY: I'm not sure I followed the discussion. What are you trying to figure out?

DR. GRINES: Well, I was trying to figure out whether we had an adequate safety profile based on the recommended dose.

DR. LIPICKY: Based in what, in patients with AF?

DR. GRINES: That was what I was initially driving at, if we are approving it for atrial fibrillation --

DR. LIPICKY: Well, we purposely advised the company, and maybe we shouldn't have, and maybe

that is the issue, that all of their experience is pertinent to the safety data base.

And that all of the patients that have received Dofetilide, including those patients that have structural heart disease who do not have atrial fibrillation, is pertinent to their data base.

DR. GRINES: Right.

DR. LIPICKY: So that -- I mean, that notion can be rejected, but --

DR. GRINES: No, I think that is a good notion, I just was not entirely clear about how many patients we had with 500 BID dose.

DR. LIPICKY: In AF?

DR. GRINES: Or in the entire data set.

DR. LIPICKY: Well, that would be a good question.

DR. GRINES: Well, that would be a good question. But then there is a second part of that question, I guess, and that is, at least at the moment there is no foregone conclusion that 500 milligrams is the only dose that will be recommend.

I don't know, nobody has said that yet.

ACTING CHAIRMAN CALIFF: He said it, and I think we will get back to it.

DR. LIPICKY: Well, we don't care what he said.

(General laughter.)

ACTING CHAIRMAN CALIFF: This part of the discussion, I think, was important to almost everyone around the panel because things changed during the development course, and it wasn't clear how many patients were in which part. But I think that has been clarified now.

DR. TEMPLE: What I heard, and maybe this is going to be redundant, but as to the number of people with AF who got the 500 dose, what we've been told is that in addition to the obvious ones from the two trials in AF, there is another 150 people who should be counted that way, because if they had been meant to be given the 500 dose they would have been reduced to 250 because of their creatinine clearance.

And then there is other people who didn't have AF who got 500 in other trials.

ACTING CHAIRMAN CALIFF: So, anyway, are

there more questions?

DR. PRATT: Cindy, just one last fact that may help, and that is, that in the Diamond AF population that would have been included in this analysis, 128 of those were followed at least for one year.

ACTING CHAIRMAN CALIFF: Peter?

DR. KOWEY: Jeremy, would you or Craig like to tell us why you think this drug doesn't work for paroxysmal fibrillators? And the reason I bring this up is because again my concern, and I think Tom's concern earlier was, we are concerned about practitioners. Practitioners are not used to thinking about drugs for AF working for some AF and not all AF. And it doesn't work for PAF.

First of all, do you think that is true, what I just said? And, secondly, if it is true, then why do you think it is true?

DR. RUSKIN: Well, I don't disagree with your statement, the short answer is I don't know why it doesn't work in PAF, and certainly the lack of a clear benefit in those populations is perplexing, and

persistent atrial fibrillation who are converted. That is the information.

ACTING CHAIRMAN CALIFF: Just a point of clarification, Peter, since you asked the question. Are you saying that you regard the data that was in the submission to be definitive that the drug doesn't work, or do you think the studies were adequate and prove that the drug does not work in paroxysmal atrial fibrillation?

DR. KOWEY: Yes.

ACTING CHAIRMAN CALIFF: Would it be fair to ask the sponsor if that is their conclusion?

DR. KOWEY: I asked Jeremy, I didn't ask the sponsor, I guess we can do that.

DR. RYDER: I think that there are some potential design issues, but it is hypothetical, but the fact is that there are no data to show that Dofetilide works in PAF, and it is not a claim in the data, it should be laid out.

DR. KOWEY: My next question, Craig, you mentioned, and I don't know whether you have a slide to show us, one of the questions we are going to get

asked about is using the drug in patients with ischemia, and you mentioned it, I know that you went over it, probably because you saw the question.

Do you have a slide to show us on that, or some way of showing us the data?

DR. PRATT: Well, I have the data. What I did, first of all, could we put back safety core slide 14, please?

Peter, I guess the first thing is, when we've been on the committee, and when guidelines have been established, there has been a lot of requests in the guidelines for more patients with structural heart disease. There they are, right there, Diamond CHF and Diamond MI.

In terms of ischemia, I just call your attention to the right. I mean, there is no signal there in an early MI population. And what we did, for both populations, is we took all those patients that had, on one of their case report forms, angina, checked yes.

And, of course, that was war, that was -- let's see, 488 in Diamond MI and 325 in Diamond CHF.

They are equally distributed for baseline risk factors, and they are equally distributed between the two groups, and the relative risk of being on Dofetilide in Diamond CHF is 0.98, and the relative risk in Diamond MI is 0.84. And we would have liked to have had that kind of information in a lot of trials.

DR. KOWEY: I thought that is what you said. I wasn't disagreeing with you, I just wanted to hear you give us the numbers again, because we didn't have a slide.

DR. PRATT: Well, I went over it very quickly, and I apologize.

DR. KOWEY: That is fine. Do you know what the Torsade rate was in 345 in the sotalol arm?

DR. PRATT: There were zero cases. On 80 BID of Sotalol.

DR. KOWEY: Can you give us some idea, I would like to explore a little bit the 750 milligram dose, and the fact that it was used for a while, and then it was dropped, for obvious reasons, there was a high Torsade rate in that population.

Do you have any data on blood levels and QT data in that experience of the 750 milligram patients?

DR. PRATT: Steve, you might --

DR. RYDER: I think that the clinical pharmacology group, I would ask them to comment on this, because I believe that higher doses, even above 750 micrograms BID up to, I believe, 1,250 micrograms BID was administered in the clinical pharmacology trials.

And perhaps maybe Don Nichols would field that question. Yes, but he needs to come up and use the mike. And while he is doing it, I just remind you, in the clinical trials there were 908 normal subjects with doses up to 1,250 BID and zero Torsade.

DR. KOWEY: I wasn't concerned about the Torsade as much as I was concerned about looking at blood levels and QT data.

DR. PRATT: And now I'm sitting here as the microphone holder, waiting for somebody to come up.

MR. NICHOLS: You may be talking about

something different than I'm thinking about, but in core slide 19, clinical pharmacology core slide 19.

This is this graph of the change in sensitivity over time. But these are doses of 750 micrograms -- I'm sorry, 1 milligram twice a day. So, again, that is why that bar, that white bar going across there is where 500 twice a day puts you, and you see that those levels to the far right are, you know, around twice that, and that is why, this is twice as big a dose. These are healthy volunteers.

DR. KOWEY: That helps, thank you. I think I have one more question. The way this drug is going to be used is in a way that is not similar to the way we -- I think I said this earlier, similar use the antiarrhythmic drugs today.

Let's say, for example, a patient is assigned to a dose based on creatinine clearance, and they are dosed with that drug dose, and they don't have a QT prolongating effect, and they don't convert their arrythmia.

Is there any experience with titrating upwards on the dose? There is absolutely no experience

doing that?

DR. RYDER: That dose regimen was not explored, upward titration.

DR. KOWEY: It has never been done in the history of creation?

DR. RYDER: With Dofetilide it was not done in the clinical program.

DR. KOWEY: Because it brings up another labeling issue, because the response the physicians will have, again I'm acting like a country doctor, I don't know why I'm doing this today, but the reaction that doctors are going have is, if I gave the drug at a dose that I thought was a reasonable dose based on whatever it is that I calculated, and it doesn't work, and it doesn't prolong the QT interval, then maybe I will just use a higher dose.

And so we have to make sure we tell them not to do that, correct? Because we have no data to support doing that, right? What do you think?

DR. LIPICKY: Did you ask me, or --

DR. KOWEY: Yes, I was asking you.

DR. LIPICKY: I don't think I would say

that, what you just said. I will grant you there is no empirical information that says it works, but I think the properties of the drug have been well laid out, and that just because someone did not empirically verify that that works, I think I understand the properties of the drug.

DR. KOWEY: I'm confused. So you would tell people that it is okay?

DR. LIPICKY: I would not tell them they cannot. And if someone elected to, I would not put into writing, if thou doest this, thou are not.

(General laughter.)

DR. KOWEY: I wouldn't recommend putting thou in the package, I don't think that is ever a good idea.

DR. LIPICKY: And I don't think that would necessarily be inappropriate use of the drug, given what you know about it. I would not advise, I would not recommend it be done by saying this is an option.

ACTING CHAIRMAN CALIFF: Bob has a comment on that.

DR. KOWEY: I just want to make sure this

is being taped, so we have this for posterity.

DR. TEMPLE: But the point is, we are asking you questions like that, and it is very nice that you asked Ray, also, but if you reach the conclusion, you collectively, that the lack of empiric information about using it that way is a reason not to, you need to tell us that, and then we need to figure out -- I guess I want to say this for most of the discussion.

There is a million options here, and it is almost hard to talk about anything without thinking of them. But as you think about each of the things that concern you, consider whether that concern is so overwhelming that, you know, you have a negative view, or whether there is something that the company could try to do to solve that problem.

Well, some things are obvious, you put stuff in the label. Other things are less obvious. I just want to remind you of this. One of the concerns with the use of Tamoxiphen to reduce the risk of breast cancer is that physicians would not know how to calculate what is called the Gayle score, which is how

you calculate the risk of breast cancer.

The company is providing a little calculator. Well, I forget, they are either providing a calculator, or they have the website that has the calculator on it, so that everybody can calculate the Gayle score.

Well, you could do that with creatinine clearance, it was a surprise to me to hear that nobody knows how to do that. But there are things that one could think of that would make that possible, whether those will be material to you or not, you all have to figure out.

But there is a lot of possibilities. You can even imagine registering people at the time they get into a hospital, and not allowing people to get drug unless they've been through a hospital, in case you are worried about people slapping folks on the drug without going through the hospital phase.

There is a lot of things to think about that may or may not be relevant to you, and this is one of them. Ray thinks, what the heck, go try it. You are in a hospital, if you get Torsade they will

bail you out. Someone else might think it is not worth it, you don't know if you can bail people out under those circumstances.

So you are free, and we are asking you to think about all of those possibilities as we go on.

DR. GRABOYS: Let me just go through another possible scenario. Pete, you said, if there was breakthrough, and I think Jeremy said then you would just go up on the dose. No?

DR. RYDER: No.

DR. GRABOYS: No one said they would go up in the dose. Is there any experience that a patient reverts to atrial fibrillation and has been on 250 twice a day, and now gets 500 in an attempt to augment that?

DR. RYDER: No.

DR. GRABOYS: Do you have any data on that?

DR. RYDER: No.

ACTING CHAIRMAN CALIFF: Peter, any further questions? If we could just -- there were two things that were said that I think might deserve some

comment, because there are bunches of frameworks of reference that can be brought to bear, and I want to introduce one.

And that is, this word maintenance implies that people can break through, okay? There is another framework of reference, that is that if you have atrial fibrillation it will always come back, and that all you do with the drug is to increase the duration of time before it does.

Now, that is a different framework of reference, it doesn't say there is breakthrough, it doesn't say the drug failed, can you make it work again. It says that the time to recurrence gets longer.

And I ask you to thing about that framework of reference as you talk about things, as opposed to it breaks through because it failed. So that is thought one.

Thought two is I was willing to have the sponsor brings the PSVT trials here, and argue that they work. And I would have supported that notion. So I don't think the trials that exist prove it does

not. That is just one other person's opinion, and that was a question.

I don't think we know it does not work in PSVT. It doesn't look real promising, I admit that. But I don't think we really know it does not work. There is nice dose related stuff all through all those trials.

DR. LIPICKY: Are you talking about PSVT or PAF, or both?

ACTING CHAIRMAN CALIFF: Fine. I'm sorry, I don't know what I'm talking about.

(General laughter.)

ACTING CHAIRMAN CALIFF: It is the conglomerate data for the paroxysmal tachycardia.

DR. KOWEY: Including AF?

ACTING CHAIRMAN CALIFF: Including AF.

DR. KOWEY: I don't think I totally disagree with what you just said. But I think for the purposes of the discussion today, whatever it is that you did say, I would be happy to explain what you said later.

I think that you are right, there maybe --

there is a signal, perhaps, that there is some efficacy. But I think for the purposes of what we are going to discuss today, it ain't there.

ACTING CHAIRMAN CALIFF: I'd like to give Ralph a chance to bring up any statistical, or clinical issues that are of interest.

DR. D'AGOSTINO: In the vein of country documents, I'm a country statistician from Boston, and I have just a couple of rules that I sort of look like, sort of lay down, wiling to bend them as we go along.

But I tend to, in these settings, say do we have two studies, are they reproducible, were the analysis that were laid out in the protocol implemented, and did the results come from two confirmatory trials?

Now we don't have that here. There is the study 345, which is quite substantial, and the study 120, which is being discussed as a sort of support, or what have you.

And it means a lot to me to understand why 120 isn't saying the same, or is it saying the same,

and what is it saying.

120 doesn't have the dose response. If you look at 345, it looks like the 250 dose, and the 500 dose are almost the same. If you look at 120, the study 120, it looks like the dose 500 and 250 numerical differ. And 250 looks like 125.

So I'm not sure the dose that I'm talking about in terms of carrying away from the studies. If you say it should be 250 in both trials, well, if you say it should be 500, 500 was good in the first study, 250 looked like 500 in the first study, it doesn't in the second study. So is it a chance fluctuation, do I really think 250 is all right, 250 is like 500, or do I think the 500 is the only thing that is sort of reproduced.

And I guess what I would like to hear some answers, 120 was the smaller study, the analysis was more stringent, it had a bigger placebo effect, the population was different, it was probably a more severe population.

Can someone from the sponsor, or the sponsor's representative help me sort out what am I

supposed to carry away from the study 120?

DR. RYDER: Perhaps Dr. Andrews can address that. Glen? Dr. Loyd Fisher --

DR. FISHER: I would like to make a couple of points. To begin with, about the two studies, we had a lot of discussion about whether 120 was positive or so on. And the advice I gave the sponsor was that it was somewhat of a moot point for the following reason.

Let me first discuss 345. There is current guidelines out for what one large convincing study should be, and I have a paper that will be coming out in the DIA Journal in a month or so.

And that, at a minimum, it seems to me there have to be two elements. One is, if you weigh evidence in terms of P values, the corresponding minimum value of the two positive studies is .00125. Which study 345 makes handily.

The other reason, well, at least one other very good reason, we want two different studies to be positive is to show the results can be replicated in different settings, that there isn't -- otherwise

there may be something very idiosyncratic.

And the approach that I have advocated in this article, and that we did here was, I said, if I was going to divide the clinics up, they have two separate studies, I would divide them up in ways such that the minimum power was as large as possible, which is equivalent to saying, try to make the sample sizes in your two subsets of your sites, which you are going to mentally think of as different studies, as equal as possible.

We did that, we only did it once, we didn't fiddle around, and in fact it wasn't even run until two days ago. But, not surprisingly, given the overall level of the P value on 345, the P values in the two parts were 0043 and 0001.

So I would argue that, number one, 345 alone has strength of evidence equivalent to two studies, so I don't think we should really -- maybe I'm oversensitive to this, because of the recent history of this committee, and the arguments about P values around .05 and so on.

So I think it is somewhat of a moot point.

120, if you read the protocol, I went back and got the original protocol, actually doesn't totally specify the test. They talk about 6, 9 and 12 months, but the first paragraph says that it is a six month endpoint, which I think is kind of silly, actually, in a 12 month study. But be that as it may.

And they say they will use a log rack test, but there is at least two log rank tests you want to use in that setting, the most natural one to me would be a log rank test that takes account of the fact that this is a dose ranging study, and we at least expect a monotone response.

Apparently the P value they had in mind was the omnibus 3 degree of freedom log rank test for these four different parallel groups, which is not significant.

But if you take 6, 9 and 12 months, and you take the linear test for trend, with the log rank, and the omnibus test, out of those six tests the only one that failed, actually, was the .125.

So I commend them for their honesty, but mentally I told them, to me, if it is not a positive

study it is within Epselom, but it is a very moot point.

The second thing you brought up was how consistent are the results. I haven't actually looked at the confidence intervals, and so on, but my -- from having read through it, is that it is really not that inconsistent.

I've often made the statement, I've never seen a totally consistent clinical development program. And I think it relates to just the multiple issue. I don't see a great discrepancy between it. It looks to me like 250 works, 500 works better, but I do have to say, once I'm convinced something works, I don't take the dose so much as a hypothesis testing thing, everything has to differ at the 5 percent level. I think it is an estimation problem where you try to estimate those response.

DR. D'AGOSTINO: If you had 19,000 subjects in your study, I guess I'm sort of sympathetic to the idea of one study. If you have a few hundred subjects I start worrying that maybe the one study isn't enough. That is an issue which we can

carry on here, obviously.

This notion of the consistency, in the writing of the protocol, if I read the protocol correctly in terms of the way it was designed and what have you, there was a lot of enthusiasm to see an effect on all these different drug doses, and the study was powered in such a way that they were basically thinking that they were going to see an effect on all the doses, and they didn't see it.

So I don't know if they really knew what was going on after 345, maybe they did, but maybe they didn't. The point still comes, the point comes, I guess, that I don't think you have answered my question in how do I interpret the studies, specially 120.

What is the dose that is being recommended, what do I carry away from this, this is the dose, or how do I -- is it regiment? Listen, I'm willing to listen to a lot of different answers. Is there a sort of sequence that you go through? I'm not sure it is clear to me what it is that is being recommended.

DR. LIPICKY: Well, Steve -- it is recommended, start at 500, go below the dosing algorithm where you look at the estimated creatinine clearance with Cocockroft--Gault equation, and so on.

DR. TEMPLE: Not 250?

DR. LIPICKY: I'm sorry, there were 15 arms, all told, in those four trials. And the thing ordered every time, right? That is placebo was the lowest, the next highest, the lowest dose was next, the next highest dose was next, the next highest dose was next?

DR. D'AGOSTINO: I don't know if you can call 46 versus 51 percent --

DR. LIPICKY: You are looking for a statistically significant difference between the two points. I'm just saying that there were four chances to order 15 arms, and each time it turned out --

DR. LIPICKY: But in 120 -- no, in study 120 it was 29 for the 125, it was 28 for the 250, and for the 12 months. I mean, I don't know if we should look at numbers, if --

DR. LIPICKY: I'm looking at three months.

DR. D'AGOSTINO: So, I mean, I don't know if that is the point.

DR. LIPICKY: But what is the likelihood of that happening if in fact there isn't a dose related effect?

DR. D'AGOSTINO: What is the dose that we are carrying away, where do we start off --

DR. LIPICKY: No, different question. I don't -- well, I'm going to advocate something, and I will argue this a couple of times this afternoon.

The idea here is not to pick a dose. The idea here is to figure out whether it is, whether it works --

DR. D'AGOSTINO: That is an answer.

DR. LIPICKY: And then you have to figure out how to use it.

DR. D'AGOSTINO: That is an answer, and that would be an answer to my question, what do I carry away from this here in terms of how to interpret it. That is an answer.

DR. LIPICKY: But if you believe what I just said, and other people around the table may not,

how would that influence your thinking?

ACTING CHAIRMAN CALIFF: Well, Ralph, I thought the sponsor had been pretty clear about their interpretation, at least, of a dosing regimen, not a dose.

DR. D'AGOSTINO: But how do the studies line up with --

DR. LIPICKY: With what they are recommending?

DR. D'AGOSTINO: The 120, the study 120 actually laid that out. Is the 120 consistent with that? I'm not sure it is, is it?

ACTING CHAIRMAN CALIFF: So what you are really asking, then, I think is does -- how does 120 support the conclusion that they came to about the dosing regimen that they chose?

DR. D'AGOSTINO: Right.

DR. RYDER: As far as the creatinine clearance, I just wanted to mention about the temporal sequence. Virtually, in fact, I think the entirety of 345 was conducted after the amendment was introduced, and for 120 I can be corrected, but my memory is about

70 percent of the patients were entered after the amendment.

So it is about 30 percent of the patients before the amendment. So about 30 percent of the patients, for example, would have been receiving 500 micrograms BID before the amendment, even though their creatinine clearance was actually, say, 50.

Whereas our current recommendation, and after the amendment would be, from the get go, from day one, they would be receiving 250 in order to get their exposure in the zone that we wanted.

DR. D'AGOSTINO: Can I go to another question? In terms of the way the studies were, and the way the drug is laid out, if I understand it, there is this ability to convert, and then there is the ability to prolong the interval.

I'm not sure, again, are we saying that in the ability to convert that there is differences across the drugs, or are there not? Is there a difference between the drug and the placebo, with the 500 starting, versus the placebo, is there a difference between it?

Is the drug, in fact, producing more individuals converting, is that being said by the company? If I look at the numerical individually, the number of individuals here that are in these analysis, they seem to be the same.

So there is this bit of the -- the converting seems to have favored the drug, yet when I look at the number that in the analysis population, that all seems to have the same numbers of individuals.

Could you just explain how these tables sort of look different from each other? One is the significance with these Kaplan-Meier curves, and the other seems to have the same, approximately the same number of subjects in these final 12 month analysis, and six month analysis.

DR. RYDER: Perhaps Dr. Friedrich can review the design. The design included both pharmacological conversion, and then if you didn't, which very few people did on placebo, and about 30 percent did on Dofetilide 500 micrograms, you are electrically cardioverted, then you were back in

normal sinus rhythm if -- except for the 20 percent who did not get back into normal sinus rhythm, and then you were receiving blinded drug for the duration of the trial to see if that normal sinus rhythm was, in fact, maintained.

DR. D'AGOSTINO: Okay, good. Then as you produce individuals dropping out along the way, were those individuals not who went back to AF, but individuals who dropped out, were those individuals being considered censored individuals in the analysis, or were they being considered failures in the analysis?

DR. RYDER: Dr. Andrews, go ahead.

DR. ANDREWS: They were considered censored. But I would add a corollary to that. We actually did another analysis which actually treated them as failures, in study 345.

DR. D'AGOSTINO: So if you went to failures it still would have come out the same?

DR. ANDREWS: It still came out the same.

DR. D'AGOSTINO: And in terms of the hazard ratios that were done, did you use Kox

regression on those analysis to get the hazard ratios?

DR. ANDREWS: Yes.

DR. D'AGOSTINO: And did they carry any problem about the proportionality? I'm not questioning them so much, but did you worry that the analysis may be a bit --

DR. ANDREWS: We looked for evidence in non-proportionality, and there was some in the first couple of days.

What I would say, though, is both the log rank and the proportional hazard models basically gave the same conclusions in terms of inference.

DR. D'AGOSTINO: Just one last question. When I think of AF, I think of lots of people with stroke, for example, and lots of people with other serious ischemic type conditions.

And I know we've wandered in and out of it, but I would just like to hear the answer. What is being suggested for those individuals who are recently from stroke, and so forth, in terms of how the package is being put together?

DR. RYDER: Excuse me, Dr. D'Agostino, are

you referring to the number of people who had a stroke in the clinical program? We can report those numbers to you.

DR. D'AGOSTINO: No, in terms of what -- is anything being suggested in terms of how this drug is actually going to be used for those type of individuals?

DR. RYDER: Used in patients who had a --

DR. D'AGOSTINO: Who just came out of a stroke.

DR. RYDER: Unstable patients were precluded from admission. But if they had a history of a cerebral vascular event in the relatively distant past, then they were included.

DR. D'AGOSTINO: So historically they could be from stroke, but not recently from --

DR. RYDER: I believe that that is correct, yes.

DR. D'AGOSTINO: Great, thank you.

ACTING CHAIRMAN CALIFF: Ralph, I wanted to ask you one question, it is along the lines of interpreting the total package.

What we saw were a number of studies, I think something like 12, all in related rhythm disturbance problems, and then there are two which form the pivotal package.

And if I understood what you said, one you felt strongly met the positive trial criteria, the other at least by a binary yes or no, would not be a classical P less than .05 for a pre-specified primary endpoint.

How do we consider the other ten trials in terms of thinking about what the P value is? At first shot it doesn't seem quite right that you would ignore them.

I mean, if you did 12 trials and two were positive, to only think about the two that were positive?

DR. D'AGOSTINO: I think it is a good question, I'm not sure I know how to answer it in a sense of giving you a quantitative answer to it. I think that these are ways you put the data together and what have you.

I don't think that any of them are sort of

overwhelming that you say that they make up another study, if that is the question that you are asking.

DR. RYDER: Dr. Califf, may I clarify one point? There were four trials in what Dr. Kowey has termed persistent atrial fib. Two dose ranging trials, 311 and 320, that were both conducted prior to the creatinine clearance amendment, and included a few patients at 750 micrograms BID.

They are presented in your briefing book, and the other two trials are the ones that are under discussion. The remainder of those trials were the ones that Dr. Kowey was referring to, that were in patients with paroxysmal disorders, either PAF or only PSVT that Dr. Lipicky referred to, and one was a mixed bag, both PF and PSVT.

So 8 paroxysmal, 4 persistent, 2 early dose ranging, and then these two.

DR. D'AGOSTINO: Yes. And I just don't think you can do much with those others, but look at them.

ACTING CHAIRMAN CALIFF: Yes. I guess -- I don't want to dwell on this too much, but I think --

we commonly see this, and one person may look at this and say paroxysmal is clearly different than persistent, and another person might say, there is a lot in common between paroxysmal and persistent atrial fib.

It is perplexing that the drug would work in one and not the others, no explanation for why they should be different, and that somehow ignoring the other trials doesn't seem --

DR. D'AGOSTINO: Well, this is what I was trying to get at, even within this context, in terms of the regiments and so forth. It isn't clear, from the two trials, that even the regimen that worked in one works in the other, is it a smaller sample, is it a more sever population, is it a placebo effect that is larger?

It would have been nice to have a discussion that would have said let's take a look at the numbers and see what we can make out of what this study shows, as opposed to suggesting that one study is enough.

ACTING CHAIRMAN CALIFF: Bob?

DR. TEMPLE: Ralph, I thought Rob was raising another question that has never been raised at any of these sessions, but I want to raise it, because we slightly raised it in a document we wrote.

He is basically saying, suppose you did ten studies of a variety of things, total mixture of things. And it is in an exploratory mode, you don't necessarily expect it to work in all those, but nine of them show nothing, so you throw those away, you don't bother us with them. One of them works out.

What is the true P value? Let's say there is only one in chronic atrial fibrillation. Now, do you get to just say, okay I only have one trial, I don't have to make any adjustment, or do you have to sort of count the environment out of which these thing arose?

And I want to say, no one has addressed that point, to my knowledge, anywhere, and it is terrifying.

When I first raised that point with Dr. Woodcock, she said, yes we also have to consider all the trials done in the parallel universe, too. An

ironic statement to point out that this is a very hairy kind of problem.

But it is one of the main reasons that you want replication, because if one of them is just a fluke, you really don't expect to see the same thing in the next one, in the very same place.

So I thought that is what Rob was sort of starting to get at, and it is a very interesting question.

DR. D'AGOSTINO: Yes, that is the way I tried to answer it, as opposed to the particulars, is that what do you do with the accumulation. I think in this case here, that there isn't much information that you can get out of it, but I think in general there may be some good information.

Even though a statistician, I get very concerned when people start attaching P values to these things in a retrospective fashion, and I would like to sort of suggest that one carries away, to start with, that does it supply some information and justification for it as opposed to attach automatically a P value.

DR. TEMPLE: I have one other question for you, though. The -- I understand your reservations about the 120, because it didn't exactly line up with all the pre-specified end points. But you also seem to be saying that it suggested something different about dose.

And I must say I don't see that. They seem to order the same way, even if they are not, even if the comparisons don't show up. And, you know, the higher dose is always considerably better than the other one, or at least it looks that way.

DR. D'AGOSTINO: And that is an answer also. I mean, what I wanted to hear is what the sponsor had to say about it, because the 250, in the study 120, the 250 dose looks very much like the 125 dose, so is there something that you just don't -- I'm using the book that the FDA put together, which I --

DR. TEMPLE: That is true, but 500 looks different from both of them in both.

DR. D'AGOSTINO: Exactly, and that would have been an explanation, that we are focusing on the 500, but then what happens to the 250? I mean, is it

something that is a population that you need to use a higher dose, and then are we getting in a situation where you need something like 500 and suddenly it is creeping up to 700 in natural practice, where we are a bit concerned.

So that is the type of question I was asking.

DR. RYDER: Dr. Califf, Dr. Friedrich thinks he may have a point about --

DR. FRIEDRICH: Can I make one point that might just answer your question? Because I think there is a little bit of a confusion here.

In study 345 the primary endpoint looked at an analysis which took the maintenance population, as we call it, which are all patients that made it into sinus rhythm, okay?

So if we look at slide 13, that is a maintenance population. And if you compare this to study 120, where the maintenance population was the secondary endpoint, I would submit to you that you see very similar things.

So can we have efficacy core slide 13,

please? At the one year.

So, in other words, here you see the dose response relationship that was mentioned by Dr. Temple. When you go up one dose level you see more efficacy starting with 125, 250, and 500.

Now, can I have slide 20, please? And then here is the same analysis, starting again with all those patients that made it into sinus rhythm. And, again, you see less of a difference between 125, and 250, but you still see, you know, up to 500.

DR. D'AGOSTINO: I don't want to beat this over and over again. In study 120 the 250 dose is very close to the 125; in study 345 the 250 dose is very close to the 500, and that is the point I was trying to make, or making, and what you said doesn't contradict that.

DR. LINDENFELD: Just one point. In the two studies wasn't there a difference when there was a dose reduction in how they were given? I think 345 was -- the dose reduction was given only once a day, and in 120 the dose was reduced, but given twice a day.

And that may have a little bit of bearing on efficacy, or the difference in the doses.

DR. FRIEDRICH: You are quite correct that you are stating that in 345 some patients received, some patients that were dose adjusted received a once a day dose regiment. That is correct.

DR. LINDENFELD: Like I said, this is what has to come up again if we decide we want to -- how we are going to dose it, if the dose is reduced, that is going to be an important question.

DR. D'AGOSTINO: That is what I'm trying to get out of the discussion.

DR. FRIEDRICH: We felt justified to do that because the AUCs between regiment of 250 BID and 500 QD were very similar. And, in fact, when you look at the outcome of those patients dosed with 500 QT in study 345, also those in 120, dose 250 BID, you see a similar hazard ratio.

If you are interested I will look for the slide.

DR. RYDER: These are patients with the creatinine clearance below 60. He is talking about

lower creatinine clearances.

DR. FRIEDRICH: Backup slide 99, yes.

DR. RYDER: If I could make one comment while those slides are coming up, I just got data from Glen. If you look at 120 and 345, the confidence intervals overlap between the two studies for every dose for maintenance.

So it is consistent with statistical variability. That doesn't show it is there, but --

DR. D'AGOSTINO: But it is only the 500 that beats out the placebo, and the 120 -- so you may have just said a statement that everything is equal, even 500 is equal to the placebo, because 500 is equal to 250, 250 is equal to 125, 125 is equal to the placebo.

So I'm looking for a simpler answer, I guess.

ACTING CHAIRMAN CALIFF: Dr. Atkinson, you had a point, then I want to go around to everyone else, and if we could try to avoid discussing things we've already discussed.

DR. ATKINSON: Thank you, Rob. I would

like to try to bring two discussions that we've been having together, and maybe we could have core efficacy slide number 24, please.

We've been discussing the fact that it is not surprising, if you lower the dose, according to the dosing algorithm, you can reduce the incidence of Torsade.

But we've been talking about efficacy, we've been talking about fixed doses. And I think it is important for us to consider, since we are being asked by the sponsor here not to approve a fixed dose, but a dosing algorithm to think a little bit about what does the dosing algorithm do to efficacy.

And this slide troubles me a little bit because it seems to me that, first of all, there is a very small N involved. But it looks to me, on the bottom here, that when you reduce the dose according to your algorithm, that the confidence interval for efficacy and maintenance therapy now overlaps the null point.

I wonder if the sponsor would like to comment on that?

DR. FRIEDRICH: You are correct that the confidence interval overlaps, and it is probably an effect of the small numbers that you see here. But on average efficacy is preserved in these patients.

DR. ATKINSON: But these are your two pivotal studies, is that right? And you are asking us to approve not a fixed dose of say 500, but a dosing algorithm where a dose is adjusted according to creatinine clearance?

DR. RYDER: And this is a segment, this is segmenting the entire randomized group. Thirteen more patients are actually included, and Till doesn't have them on the slide here because our statisticians wouldn't allow us to put them on the slide, because we could not have -- did not have a comparable placebo group that had dose adjustment for QTc prolongation.

And that was where he said nine out of those thirteen patients had maintenance of sinus rhythm at twelve months.

So I guess that is a point estimate of like .75, or something. But we weren't allowed to do that. I would just point out that those 13 plus these

41 is 54 plus the 106, that is the entire group that was randomized, and this is sort of segmenting it down, and what you see are the data in the confidence limits.

DR. ATKINSON: My concern here is one that Bob Temple referred to earlier, and that is that we may not be able to separate efficacy from toxicity here. And also in the spirit of one of Dr. Temple's admonitions to us to think a little bit out of the box, if you could show core slide 35?

It shows what happens when patients are started on therapy, and I believe this is without a loading dose that we are looking at the institution of various maintenance dose programs.

The -- this is sort of an inverse Kaplan-Meier type curve showing response of patients with time. And if you look at the top curve, when it does appear, you will see that most patients are converting within about 36 hours, which is not unreasonable, if you can sort of visualize the blood levels increasing over time to reach a steady state, and let's say 90 percent at steady state, and 3.3 half-life, so that is

-- if it is a ten hour half life, this response curve is roughly mirroring what the blood level probably is doing.

The point is, there are some patients who are converting before 36 hours, and they are converting before they get to steady state levels at 500 milligrams BID, or micrograms BID.

The question arises then, can the therapeutic index of this drug in clinical practice be increased by maintaining these patients at lower doses, lower effective blood levels?

Are these patients who are going to be more responsive to your drug than others? In other words, I think in -- as we think about dose ranging, and developing drugs we are tending to move away more and more from a maximum tolerated dose strategy to a maximally effective dose.

What I'm talking about here is perhaps going one step beyond your algorithm and individualizing dosage according to patient response during this -- while therapy is being started.

Do you have any data that suggests that if

a patient converts to the lower blood level, that they can be maintained effectively at a lower blood level as well?

DR. RYDER: That experiment was not done, the adjustment was based on their pharmacodynamic response as assessed by QTc, and downward adjusted if they had a prolongation that was excessive.

DR. ATKINSON: I understand it wasn't done. What I'm trying to suggest is a way that you might think of increasing the therapeutic index.

DR. RYDER: Dr. Friedrich, did you have a comment?

DR. FRIEDRICH: Yes, can I make one point on the previous slide 24, if you could bring that up again, please?

I think I made the point, during my talk, and I apologize if it didn't really come through; but I think you cannot exclude here the possibility that in the group reduced for creatinine clearance you have different patient characteristics. These probably are much sicker patients, the probably not just have impaired renal function, but they probably also have

more structural heart disease, concomitant diseases.

So the comparison is not as strict, I think, looking to the statisticians here.

DR. ATKINSON: So you are proposing that impaired renal function is an independent factor than, for lack of efficacy of your drug?

ACTING CHAIRMAN CALIFF: Well, or that it goes with a constellation of other clinical findings.

DR. PRATT: I think in general we all appreciate the fact that patients with most severe structural heart disease keeping them in sinus rhythm with atrial fibrillation is more difficult than someone with none.

So that was not the only factor that was making those two point estimates different.

DR. ATKINSON: I understand, thank you.

ACTING CHAIRMAN CALIFF: Okay, Dr. Lindenfeld?

DR. LINDENFELD: Just a few questions. Can you reassure me that the risk of stroke is the same in the atrial fib populations between placebo and drug? Just a simple yes or no is enough.

DR. PRATT: Yes, I have the numbers, in general SVA trials the risk of stroke was about one percent in both populations, the risk of stroke plus TIA and embolism in Diamond was somewhere between 5 and 6 percent, both placebo and Dofetilide randomized patients.

DR. LINDENFELD: And can you tell me, throughout the course, at least of the atrial fibrillation studies, an EKG was done about every month. How many patients were withdrawn from Dofetilide because of a prolonged QT interval during that period of time?

DR. RYDER: Dr. Friedrich has that information.

DR. FRIEDRICH: Yes, there were 12 patients. Let me get this slide up for you. It is the lower line there, CQT, QTc prolongation beyond 500 or 550 milliseconds, 12 patients.

DR. LINDENFELD: Then how often are you going to recommend that EKGs be done in the first year?

DR. FRIEDRICH: Say again?

DR. LINDENFELD: How often will you recommend EKGs be done in the first year?

DR. FRIEDRICH: They were done in the clinical trials whenever a visit occurred.

DR. LINDENFELD: Because they were done in this trial every month?

DR. FRIEDRICH: Yes.

DR. LINDENFELD: And is that true of Diamond too, were they done every month?

DR. FRIEDRICH: Excuse me, did you say one month?

DR. RYDER: Every three months.

DR. FRIEDRICH: They were done every three months, I'm sorry.

DR. LINDENFELD: Okay, all right.

DR. TEMPLE: Dr. Lindenfeld, didn't you ask him to say how often they were going to recommend doing it and labeling?

DR. LINDENFELD: Right.

DR. TEMPLE: Did you hear --

DR. LINDENFELD: No, I didn't hear the answer yet.

DR. RYDER: We would be driven, I mean, the labeling discussions really haven't started or have just been -- the dialogue has just started, and information from the clinical trials is really what will drive the labeling, and as was reported we can say that --

DR. TEMPLE: I guess the question might have been a hint.

DR. RYDER: Every three months.

DR. LIPICKY: I thought we had to approve it before we talked about labeling.

DR. LINDENFELD: And what was the average ventricular response in the atrial fibrillation groups? Just the average rate, at the beginning of the protocol.

DR. RYDER: Baseline heart rates?

DR. LINDENFELD: Baseline heart rates. And as a follow up to that, maybe the same data is -- how are the rate controlling drugs handled in that run in period, were they generally discontinued, or were they continued?

DR. FRIEDRICH: Slide 18 shows the

distribution of the heart rate at baseline. And since all patients started the trial in atrial fibrillation, this is in atrial fibrillation.

DR. LINDENFELD: And did we see analysis of the risk of prolonged QT with the heart rate, did I miss that? Just with the baseline heart rate?

DR. FRIEDRICH: Yes, this was --

DR. LINDENFELD: Okay, I'm sorry, you showed that.

And did you say how the drugs, the rate controlled drugs were handled, was there any specified protocol?

DR. FRIEDRICH: No, there was no specified protocol that could be --

DR. LINDENFELD: So that was left up to the physician?

DR. FRIEDRICH: -- local practice, yes.

DR. LINDENFELD: And just my last question, in the Sotalol arm was the Sotalol dose decreased in the same way that the Dofetilide dose was decreased for QT

DR. FRIEDRICH: Yes, it was a double dummy

technique, so it was a blinded study supplied to all patients.

DR. GRABOYS: Was the mean heart rate, was that -- did that include individuals who were entered and they were on drugs, right? So you had -- what percentage were on Dig, for example? I mean, that has reference to ultimately discussion of quality of life, and symptoms, because if the patients are coming in with heart rates of 90 or 95, essentially no -- that is at rest, their rate control is poor, and they are going to be quite symptomatic, then.

DR. FRIEDRICH: Can I go to backup slide 18, please? I meant to say core slide 18, I'm sorry.

DR. LIPICKY: Are these resting heart rates, or just any old heart rate?

DR. FRIEDRICH: That is resting. Here is the breakdown of concomitant medications, 80 percent on Digoxin.

DR. RYDER: And study 345 was similar?

DR. FRIEDRICH: Yes, a little bit less.

ACTING CHAIRMAN CALIFF: Tom, don't you think those rates are pretty representative of what

you see in a population of typical patients? I mean, we would all like to think that we keep better control than that, but it looks like what we see.

DR. GRABOYS: Well, if those are the rates, and they were on those drugs, it meant that there was no rate control at rest, and if there is no rate control at rest, obviously not going to have any rate control when they are walking around, and they are going to be very symptomatic.

I mean, my point is that -- is that atrial fibrillation can be viewed as a rhythm of choice, you kind of declare victory when you are going back and forth on all these different drugs, in order to do that, then you have to be committed to significant rate control, which means the resting ECGs should have a ventricular response to AF of 50 to 60.

That way you can assure yourself, when they get up and walk around, they are not going to be symptomatic.

ACTING CHAIRMAN CALIFF: But you would also agree that that strategy has never been tested?

DR. GRABOYS: Good point.

ACTING CHAIRMAN CALIFF: It is your preferred strategy, but it has never been tested in a clinical trial?

DR. GRABOYS: We are willing to accept all comers.

DR. TEMPLE: What sort of dose of Dig were they on, for one thing, and would you, in your clinical estimation, you ordinarily need to achieve reasonable rate control? I mean, Dig for heart failure has come down, and we all hope that mortality is coming down with it.

What is the dose you need here for rate control?

ACTING CHAIRMAN CALIFF: I think that is a point of great confusion. I would be delighted to hear a clear answer from one of our electrophysiologic colleagues.

DR. KOWEY: I don't think this works at any dose, very well. And people with normal AV nodes, I think the only time we see Dig work in patients with AF is in patients that have conduction system disease.

DR. GRABOYS: I mean, that raises a whole

other issue, which we haven't even talked about, is the age issue. I have no idea whether you are looking at 85 year olds who are AF, or 80 year olds in terms of their problems, or their issues.

If you are 80 years old, and we are trying to rate control, Dig can be very helpful, because they have intrinsic increased phagiatonia and they may have some conduction abnormality to help with rate control.

I agree with you, Peter, that 65 year old who comes in on the traditional doses of Dig, is not going to have great rate control, unless you use it in concert with a calcium channel drug you are using, in concert with a beta blocker.

DR. RYDER: Dr. Graboys, would you like to see the age distribution of the patients?

DR. GRABOYS: Sure.

ACTING CHAIRMAN CALIFF: I think you have shown that a couple of times already. And they were an old population.

DR. FRIEDRICH: In 345 the breakdown of the population age.

DR. TEMPLE: So what sort of doses would

people be getting for the lack of effect that Peter thinks is there, or the effect that people think is there?

DR. RYDER: Do we have information on the dose of Dig? I'm not sure we have that right now, but we can ask some of the technical people to try to search for it.

DR. LIPICKY: I don't know the single trial that has looked at that.

ACTING CHAIRMAN CALIFF: We are all in a great state of confusion right now because the Dig trial, as you know, seemed to indicate that patients on a lower dose of Dig had a better survival.

And, of course, that is not a population with atrial fibrillation, but it makes one worry about the higher doses that used to be advocated, where we said, don't worry about the Dig level, just give a dose until you control the rate.

So I don't think that there is going to be much useful discussion about what the right dose of Dig is, because there is no --

DR. TEMPLE: I wasn't asking what the --

ACTING CHAIRMAN CALIFF: -- it is just opinions.

DR. TEMPLE: -- I just wanted to know what the actual dose usually is, and would then worry appropriately depending on how high it is.

ACTING CHAIRMAN CALIFF: Tom Bigger is probably -- you've looked at this as much as anybody. What are people using now?

DR. BIGGER: Using much -- they tend to add a beta blocker instead of pushing the DIG.

ACTING CHAIRMAN CALIFF: Okay --

DR. LINDENFELD: Can I?

ACTING CHAIRMAN CALIFF: Yes.

DR. LINDENFELD: Just one final question, I just wanted to hear a little speculation. We saw the risks with many type III drugs for Torsade, prolonged QT interval, structural heart disease, female gender, and yet none of those were significant with Dofetilide. And yet it is a very clear type III drug.

Could I just hear why? I mean, speculation?

DR. RYDER: Speculation why the mortality is --

DR. LINDENFELD: Why we don't see those in your analysis as a risk for Torsade with Dofetilide? And that is true with all the other type III drugs.

DR. PRATT: Just to reiterate the data base that we presented today, like all IKR blockers, there is definitely a risk of being female and taking Dofetilide for the risk of Torsade de points ventricular tachycardia.

With this specific treatment algorithm an inpatient initiation and adjustment of dose, there is no mortality signal. And I think that is the difference.

ACTING CHAIRMAN CALIFF: Dr. Piña?

DR. PIÑA: I want to follow up on Joan's point about the EKG frequency. Since some of these patients seem to have had very little symptoms to start with, they could have reverted back to atrial fibrillation before the three months. And if you haven't done the EKG, you may not know it.

I mean, a lot of my patients don't even

realize when they go back into atrial fib. So maybe the three month frequency isn't that great in people who recur, they usually recur pretty quickly. And that was one of my observations.

I have a question, are you going to have an assay for blood levels of this drug made available?

DR. RYDER: Dr. Pratt, do you want to address the utility, or Don Nichols? I mean, perhaps I can take it.

The short answer is that we believe that by assessing QTc you are looking at one step better, you are looking at pharmacodynamic responsivity, and a very nice correlation between QTc and plasma level has been shown.

And so we are going one step better. We are assessing not just the individual plasma level, but the response of that person, that individual to a certain plasma level.

And if they are one of the people who respond with a higher QTc, we are suggesting that they down-titrate after the first dose, or if it persists, at the level of 500 milliseconds, that the be

discontinued, that they be dropped from the Dofetilide.

DR. PIÑA: And I have just one final observation, the comparison between CHF stat and the Diamond CHF trial, I don't believe that the mortality is the same. I think that the mortality in the Diamond CHF at six months is higher than the CHF stat trial.

So I'm not sure that comparison is valid.

DR. RUSKIN: Yes, it is true that the mortality rate is somewhat higher in Diamond CHF than in CHF stat. I think the key point is that there was absolutely no difference between treatment groups in the two trials.

But you are right, there is a higher absolute mortality rate in the Diamond CHF than in the Amiodarone trial.

DR. PIÑA: And most of your population was really class 3, you had a few class 4's but it was primarily class 3, and that to me looks like a little high mortality for six months in class 3. I don't know what Dr. Konstam thinks of that, the six month mortality in Diamond CHF.

ACTING CHAIRMAN CALIFF: I might comment on that, because we are interacting with the Diamond investigators now in other trials, and it is a unique system in Denmark, where they actually enroll sick patients in trials as a matter of policy, and at least their argument, in the number of trials they've done is that in the U.S. we tend to exclude anyone who would be at risk of dying, people that we are worried about.

They consistently see a higher mortality and maintenance because they actually enroll most patients. So it is not unique to this particular comparison, but in other trials that they do.

Now, we could talk a long time about whether we believe that is a correct argument, but that is at least what they've said.

Tom, do you have issues?

DR. BIGGER: I just have one issue. I wondered how you were going to approach it? And, again, this may just come up in the negotiations. But starting on this premise, that the fundamental action, electrophysiologic action of Dofetilide that relates

to its efficacy, is also related to the increase in QT, and the Torsade de points risk.

And there is not, there is overlap in the concentrations that produce efficacy and prolong the QT, that drug interactions may be critically important here.

And a number of drugs that even your own spokesman said thought would bear some further study, have yet to be done, which I guess translates into very conservative labeling, or further studies, or both, to make doctors comfortable in prescribing this.

Because I think doctors hearing what we are hearing, are likely to dose lower than what you recommend because they are nervous, although people over here seem to think they are going to be overdosing folks.

And I just wonder, what is your approach going to be to this drug interaction problem in terms of labeling, or further studies, or how are you going to approach that?

DR. RYDER: I think it was summarized by Dr. Pratt, and I completely agree with what he said.

As far as labeling goes, I think the information that we have should be presented as we gather new information.

And he mentioned a number of clinical trials, clinical pharmacology trials that he has recommended to us, and he is our expert consultant in this area, and we are going to be discussing with him, and with the Agency, and be working from that place forward.

As more information comes in, I would think that the labeling would evolve.

DR. KOWEY: I just want to follow up on that, because I'm still stuck on this Dig question. And I know, Craig, when you presented the data, and when you were making your presentation, as we had requested you to do, you focused on the mortality, but you didn't talk about the Torsade.

And I agree with you that we all want to know about mortality, but I'm also worried about Torsade. And this questions that Tom just asked, the reason it made me think about it is because it is going to come down to a labeling question.

What are we going to tell doctors about using this drug with Digoxin? Do you think that that finding of more Torsade with Digoxin is real, or not?

DR. PRATT: Well, why don't we go back to the data? It is a good place to go, I guess. Let's start with backup 20.

And this, of course, is all in that drug interaction document, Peter, and you are well aware of it. So it had already been discussed, and so this is the information unadjusted and adjusted.

Of course, people on Dig are different than people not on Dig. And this is a five thousand and fifty some patient data base of which about 2,400 are on Dig, so it is pretty robust, so there is a lot of deaths. So 1,115 deaths.

So the risk ratio there of adjusted is 2. And there -- as you know, statistical adjustment is not exactly the same as taking into consideration everything that is different about those patients.

And then if we go to the next slide, those are the point estimates of mortality, and the confidence intervals around that point estimate for

Dig, given that there are 2,300 patients is fairly narrow.

Now, what are the limitations of the data base? Well, there is only, thank goodness, 43 cases of Torsade. There is 1,016 deaths. Statisticians would have to tell you and I, Peter, how much we can really make out of that when we go to section this up and slice it, and dice it in 15 ways.

So that is the information. I certainly think that right now there is no compelling data to say that you can't use Dig to control rate in atrial fibrillation.

However, it is not my drug of choice, anyway.

DR. RYDER: Dr. Califf, I just want to point out, and it is in your briefing document, I'm sure that you've reviewed it. But the information comes from the combined Diamond plus SVA data set.

And I just think it is germane to say that there were 43 Torsade in the total 2857 patients, one and a half percent if you considered everybody.

If you subsetted it down to the 30

patients who had Torsade on Dig, that is 30 out of 355, 2.21 percent. The flip side of that I would have to do some quick math, but it would probably be in the order of, say, 0.8, or something like that, 0.9 percent.

So I still think that it is pertinent to know that the frequency of patients taking Dig was quite high, throughout the Diamond trials. That is the bulk of the information that we are providing the committee in terms of the safety of Dofetilide, and specially its mortality signal that Dr. Pratt is referring to.

DR. PRATT: Peter, just one last point. I mean, there are three deaths in patients attributable to Torsade. Once you get to be an outpatient the only signal we can look for Torsade is arrhythmic death, syncope, total mortality. We've looked at all those in every possible way.

ACTING CHAIRMAN CALIFF: Marvin?

DR. KONSTAM: Craig, let me -- I have a couple of questions, but this sort of leads into one of them, so let me ask it now.

You know, we have -- you have 12 deaths in the superventricular arrythmia data set on Dofetilide. And can we -- can you tell us anything about those deaths?

And I guess the question there, in follow-up to the point that you just made, is how are we going to be assured that those are not related to Torsade?

DR. PRATT: Well, of course you are not going to be sure, because outpatient deaths, our classification system kind of stinks, as you know. And we have written some papers about that.

So that is a tough thing. You can look at signals, we looked at arrhythmic death in the SVA, and it is something like 0.4 versus 0.5 percent.

Actually Jeremy and I looked at the individual deaths for the presence or absence of structural heart disease. All but two of them, we think, are in patients with structural heart disease.

You can look at the syncope, syncope is almost identical in peoples both in the SVA and in Diamond.

So when we look at all the sort of imperfect options that we have, they all come out a wash. I've already showed you the arrhythmic deaths survival curves, Kaplan-Meier for Diamond and I've already given you the rates of arrhythmic death in the SVA population. Those are the markers that we have.

DR. KONSTAM: I guess the specific question that I was interested in, from anybody in the sponsor is, what can you tell us, specifically, about those 12 deaths, in terms of mode of death, or anything that helps us out in terms of what might be happening there?

DR. PRATT: You want to call -- whose backup is this? Safety, this is additional safety backup, probably isn't even available, is it? Just read it, I think you should read it, I can't read that.

DR. RUSKIN: Dr. Pratt is being supplied the information.

DR. PRATT: I was given a one font copy.

DR. RYDER: It is a simple listing of the deaths, I believe.

DR. PRATT: I would almost just be happy if you would take this, what specifically would you like to know?

DR. KONSTAM: I don't know, just what do we know about them, what --

ACTING CHAIRMAN CALIFF: Marvin, do you ever find mode of death analysis to be useful for anything?

DR. KONSTAM: Well, I tell you -- let me just say, in general terms, I -- you know, I think most of -- you know, we have an enormous data set, I think, relative to other existing approved antiarrhythmic agents.

And it is, in fact, going to be the source of some degree of reassurance about --

DR. PRATT: I just want to see you for a change.

DR. KONSTAM: Yes, that is good. About safety. And you've made that point a few times, that maybe we shouldn't worry too much about Torsade, because don't have a mortality signal.

But I think the assurance about that is

coming predominantly from the Diamond trials. And the frequency of mortality, and the mode of mortality, and the drivers of mortality in those data sets, that is heart failure and post-MI, is going to be very different, all going to be very different from the superventricular arrythmia population at large.

So I guess I'm still trying to look for any help I can within the superventricular arrythmia group.

DR. PRATT: Let me just go through. There are three presumed placebo arrhythmic deaths, and there are -- let me see now, I have to do this fast. I think there are six Dofetilide associated presumed arrhythmic deaths, and there is almost a two to one randomization.

And that is how you get with that numerator denominator to 0.4 versus 0.3 percent. Let me also -- let me just tell you, the one other population I guess we would all agree is relevant is Diamond AF, in which the number of arrhythmic deaths on placebo is two higher than on Dofetilide.

So I mean, every data base we have --

DR. KONSTAM: I hear you, and I guess we are not going to be able to draw any kind of conclusions from that. I guess I just reflect that I don't easily go from saying, we do have Torsade, but we don't have any mortality signal associated with Torsade, because that is really being driven from Diamond.

And I still -- we still don't know about these 12 that died, and whether some of them didn't die of Torsade. And I guess that is just -- I just reflect on it.

DR. PRATT: And I think it is a very valid point, and I know I don't know that either. But just let me give you a little bit of background, having been on the Sword trial.

I was trying to figure out what was really different about Sword and Diamond, and I think this three day initiation as an inpatient, and not just removing patients from the drug that have had Torsade, but removing patients from the drug that have an unusual QT response.

I think that really makes the difference.

I think you remove hundreds of patients that otherwise would be at risk for this as an outpatient. And I think that is why we don't see a mortality signal.

DR. BIGGER: Okay. Now, I just want to ask a couple of things about the Diamond population, particularly the AF Diamond population.

And, again, this is in light of saying, this is the population that we are really going to try to draw some comfort from with regard to overall mortality signal.

So then I'm still struggling with the fact that the AF population within the Diamond trials, which is of course going to be the indication here, AF, was managed differently, somewhat differently by somewhat different algorithm than we are thinking is going to be the treatment algorithm, namely that they started on a lower dose, regardless of -- even with the normal creatinine clearance.

So I guess I will start, first question I have about that is, why did you do that, why did you decide to, you know, to start all of the Diamond AF patients on a lower Dofetilide dose?

DR. RYDER: Dr. Marshant?

DR. MARSHANT: This is something that was recommended, or in fact, insisted upon by the Diamond steering committee at the initiation of the study, and their concern was, as explained earlier, was that in these patients who were particularly sick with very severe structural heart disease that the risk of proarrythmia may be that much higher.

DR. KONSTAM: No, but it is the group with structural heart disease who have AF that you started on the lower dose?

DR. MARSHANT: There was concern within the steering committee that short long short sequence that would be typically seen in atrial fibrillation patients may predispose to Torsade.

DR. KONSTAM: So I guess the question, then, that follows from that is how do we know you weren't right? I mean, how do I know that -- I mean, that was your reasoning going in, that this AF population was going to be more subject to Torsade, and presumably mortality, than the overall Diamond population.

And so you manage them differently, and I guess I'm wondering, maybe you were exactly right. Maybe the mortality signal was low, because you managed them differently?

DR. MARSHANT: What I explained was a concern that existed before the study started. Five months into the study we introduced the dosing algorithm by renal function.

And by that point the steering committee had an increased comfort level. And so when they introduced the dosing algorithm they didn't introduce a further dose adjustment for patients with creatinine clearance between 40 to 60, which is why all renally impaired patients in the Diamond AF study equivalent to having been dosed at the 500 and dose adjusted on renal function.

DR. RYDER: So the bottom line is that now we have two thirds of the Diamond AF population receiving exactly the dose that we would recommend?

DR. KONSTAM: But nobody in -- I'm sorry to interrupt, but nobody, and correct me if I'm wrong, nobody in Diamond in AF was started on the 500 BID

dose?

DR. RYDER: That is correct.

DR. KONSTAM: So that leaves me with a problem, because that is the dose that we are going to be recommending for AF.

DR. RYDER: No, no.

DR. KONSTAM: It isn't?

DR. RYDER: You will be recommending that for patients whose creatinine clearance was greater than 60.

DR. KONSTAM: Right.

DR. RYDER: Fortunately --

DR. KONSTAM: But we don't have any patients like that in Diamond, we don't have any patients with creatinine clearance greater than 60 who are in AF, in Diamond, who were started on 500 BID.

DR. TEMPLE: And you would have --

DR. RYDER: That is correct.

DR. TEMPLE: -- had 85, that is how many you would have had.

DR. KONSTAM: We would have, but we didn't -- but we don't know how many of those 85 would have

died.

DR. TEMPLE: That is right, that is what you are missing, the 85 people who would have gotten the 500 --

DR. KONSTAM: Is that 85 from the treatment group, or 85 from the whole 500?

DR. MARSHANT: From the whole 506.

DR. KONSTAM: 85 from the whole 500. But I'm still left with that problem.

DR. MARSHANT: I'm sorry that has come up. It is 85 from the Dofetilide treated patient.

DR. KONSTAM: Dofetilide treatment group, so it is 85 out of about 250?

DR. TEMPLE: It is about one third. So you do not have that data, that is true.

DR. KONSTAM: The only other question I had, I mean, this is just a general question. We have some concerns, and you've addressed them, really, fairly meticulously, as far as I can see, with a strategy, and then you've implemented that strategy, we have a terrific data set.

But we've heard concerns from the panel

about how are we going to really implement the strategy. And I guess, to me, this is going to impact on my thinking about approvability, because it is going to be contingent on saying that there is going to be some strategy here that is going to, you know, approach what you are able to achieve in the clinical trial data set with regard to dosing strategy, and with regard to having people in the hospital for five doses, or two or three days.

So I guess I would like to hear something from the sponsor about what your thoughts are, what would you propose that you would do, to make sure that this is the way patients are treated?

DR. RYDER: The dialogue on this has really just started, but it is our complete -- we have a complete commitment that the way Dofetilide was used in the clinical trials is the way that it should be used. You have to use it in the right patient and in the right way.

A lot of education, and perhaps some new things, Dr. Temple mentioned a few, we haven't had the chance to even discuss these in any depth, whatsoever.

I would want to point out, though, that one of the things that is, I think, important for the Committee to consider is that the bulk of the Diamond data come from a very large segment of the Danish hospital base, and that as Dr. Pratt described, there was no central QTc reading done by a centralized reading center.

This was QTc reading done on the wards by the investigators, by the sub-investigators, and patients were dispensed bottles of medication. And these patients were elderly.

So in that way, although it was a clinical trial, it was not radically different, in my opinion, from some aspects of --

DR. KONSTAM: Well, I appreciate what you are saying, but I mean, I don't know how clinical trials are conducted in Denmark, but I still would say it is radically different from just having the entire population of clinicians in the United States prescribe the drug.

So, I mean, like I said, I would like to ask just Bob and Ray, because I mean, I think

logically the question of approvability is first, and then the question, okay, then what do we do?

But I guess in my own mind some sense that we are going to have a strategy of succeeding is going to impact on maybe people's views about approvability.

DR. TEMPLE: There is a number of possibilities. You could, since this program has obviously not been developed and presented to you, you could say you are not ready to reach a final conclusion until you see what it is, and that you think it is necessary. That is one possibility.

You could conclude that you will leave it to the company and us to work out, but give some general guidance.

I mean, there are all those possibilities, and I have to acknowledge, we are heading toward new ground. The only two examples that are worthwhile, I would say, the way Clozapine was marketed.

You could not get your next dose unless you show the results of a blood test. Well, one can imagine that you would get some sort of bar code when you have your three days in hospital, and you are a

bona fide guaranteed acceptable QT, and that would be the only way you could get medicine.

How to do that is not known to me, but that doesn't mean it can't get done. And there are a number of possibilities of that. I mean, if you believe QTs cannot be read by most people properly, they could work out a way of reading people's QTs, as well as -- or they might, they don't have -- they might not be willing to do that, I don't know.

But if you all thought those things were central, communicate that, and figure out what is essential and what is not. But there is a lot of possibilities, and we have reasonable authority, you should know this, under our accelerated approval rule, which is usually thought of as allowing approval based on the results of a reasonable surrogate for effectiveness, there is also a provision that if a drug cannot be marketed safely, without particular limitations, those limitations can be imposed.

They were used to approve Thalidomide for certain exotic conditions where you definitely didn't want it spreading widely through the community.

So in that case physicians are registered, there are a lot of possibilities, only imagination limits those. And to the extent you think those are important, you need to tell us. Because if they are not important, they are very burdensome.

ACTING CHAIRMAN CALIFF: Ray, briefly.

DR. LIPICKY: Well, really two comments. The first is going way back to the question about Dig, and there is an anecdote that I would like to relay to everybody that -- because I can't show you the data.

When Anafrodil was approved, there were Torsade reported, associated with its use. The vast majority of the Torsade that were reported with Anafrodil, were people with heart failure, who were on Dig.

We were told by the community at that time, not you guys, but another community, that that is commonly known, that Dig is a bad actor. We said, okay, we will find out if that is true or not, we will go to our adverse drug reaction reporting system, and pull every Torsade that ever has been reported, irrespective of why it was, and just look and see what

the incidence of Dig was, in that population.

It was something on the order of 60 percent of the cases. We haven't done anything, we are not advising doing anything, but there is some other evidence that suggests that what was seen here is true. That is all I'm saying. and so that is a little anecdote.

The only other very short thing is, there is another conclusion you could come to from the conclusion that Bob presented, okay? Or suggestions.

You could conclude that clearly this drug does something to alter the recurrence of atrial fibrillation when you are an outpatient, that it clearly does something to the QT interval. That both of those things are dose related; that the safety margin is very narrow, and that a doctor might start at some very low dose, and the patient will say, geez, my atrial fibrillation came back, I don't like that, it is too fast, jack me up a little.

And then, well, still a little too fast, I would like it to be about 8 months, jack me up a little. So I don't see that as -- if you believe that

in fact the agent works, that its working is related to the dose and/or plasma concentration, and that the QT interval, in fact, is also related to dose and/or plasma concentration.

So the latitudes here are pretty enormous. But that would require doing something no one has ever done, and that is say I don't require an arm of a fixed dose trial that in fact beats placebo.

DR. PRATT: Could I make just one comment? Because I think it is pretty related to this Dig issue.

ACTING CHAIRMAN CALIFF: Quickly.

DR. PRATT: Would you allow one slide? Backup 23, same study, the drug interaction study, 5,000 patients. This is the ECG QTc change with the present combination of Dig plus Dofetilide and Dig without Dofetilide. I don't see a signal there. I just thought you would like to know, in 2,300 patients.

ACTING CHAIRMAN CALIFF: Now I have to make a comment. No, I won't, but I will when we get to that. Let's move to Dr. Atkinson. Do you have any

further questions?

DR. ATKINSON: Well, yes, there is a question, and that is, any time when you see a drug effect that over time loses its efficacy, if you will, and here we are talking about a 40 to 50 percent relapse rate after a year, there are a number of reasons for that.

One is that the drug is not working, the other is that the patient is not taking it. I wonder if you had, in your trials, any way to estimate what the role of non-compliance might have been in the recurrence rate?

DR. RYDER: Bradley, do you have some information on compliance? Dr. Marshant.

DR. MARSHANT: I don't have information on compliance, but I can tell you that the QTc difference between Dofetilide and placebo was maintained throughout the studies, so that is as good as evidence as we can get of compliance.

DR. ATKINSON: When the patients relapse did you check their QTc to see that they were still prolonged?

DR. MARSHANT: When the patients relapsed they were --

DR. ATKINSON: From Dofetilide, before you stopped the drug, presumably, did you measure the QTc to see if it was still prolonged?

DR. MARSHANT: We don't have that data, sir.

DR. ATKINSON: I mean, what you are proposing is that you don't need to measure blood levels because you have the QTc as a surrogate for the level, if you will. What I'm suggesting to you is that if you are going to use the QTc as a surrogate, you've got to help the physicians, because if the patient relapses they have one of two choices to make.

They can say, look, this is a drug failure, and I'm going to switch to Amiodarone, or they can say the dose was too low, or maybe the dose is appropriate and the patient wasn't taking the dose, and that isn't a very sophisticated way of using blood levels, but that is one of the ways that we use them.

So if you propose that QTc is going to obviate the use of plasma level monitoring, I would like to

see some evidence that has been useful to you in looking at things like compliance.

DR. RYDER: Dr. Ruskin?

ACTING CHAIRMAN CALIFF: If it is a direct response to the question.

DR. RUSKIN: I think it is. I think the data that you are asking for don't exist, but I think that relapses reflect the nature of this disease process.

And, in fact, with every treatment option that we have available, we see relapse rates of around 50 percent in a year, and even with Amiodarone, which has an infinite half life, we see recurrence rates in the range of 30 to 40 percent in a year.

So I think we are looking at a reflection of the biology here, of the problem, rather than an issue specifically related to Dofetilide.

I want to take five seconds, also, to draw an analogy. I agree with everything that is said about the concerns regarding the in-patient initiation, and the difficulties of the measurements that have to be made, but this is not an absolutely

unique situation.

We use Sotalol every day, and Sotalol requires adjustments for renal function, and it has to be dosed according to QT interval changes. So this is not an entirely new phenomenon, it is not a perfect analogy, but it is not an absolutely unique situation.

ACTING CHAIRMAN CALIFF: Just a point for others developing drugs for this indication. I take it from the discussion that we would recommend that those who relapse should be looked at, and that follow-up shouldn't stop at the point of relapse the first time?

Does anyone on the panel disagree with that? I mean, I think that is a very important point that has arisen from these data and the discussions, is that we really wish we knew what happened to the people who had a recurrence.

Dr. Graboys, do you have further questions?

(No response.)

ACTING CHAIRMAN CALIFF: Okay. I think what we ought to do is then move into the questions,

and it seemed -- Bob?

DR. TEMPLE: It is sort of related to the questions that will come.

Who do you think this drug is for; everybody who is fibrillating, everybody who is immobilized by its symptoms, everybody who hates his life, who, what subset.

DR. RYDER: Are you asking the sponsor?

DR. TEMPLE: Yes.

DR. RYDER: The type of patient who I would envision being treated is the type of patient who was enrolled in the clinical trials, and I think Dr. Ruskin summarized that in his benefit risk.

DR. TEMPLE: Wow, 50 percent of them weren't even symptomatic, right? You want to do that?

DR. RUSKIN: No, I guess I would state it a little differently, and that is that I would see the use of this drug as no different from any other rhythm control agent in atrial fibrillation.

And, again, I'm speaking personally now, and the indications for me would be highly symptomatic atrial fibrillation, where the risk of the therapy is

outweighed by the benefit. And that is a very difficult decision to make sometimes, but we all have patients like that, we try to reach those decisions using clinical judgement, and interaction with the patient.

But the straight answer is symptomatic patients, not everybody with atrial fibrillation, by any means.

DR. TEMPLE: Just to pin that down, that is not exactly the population entered into this?

DR. RUSKIN: That's correct.

DR. TEMPLE: Nor need it have been, but it is somewhat different from the people studied.

DR. KONSTAM: -- ask Jeremy what -- could you just expand on that slightly? So, I mean, somebody whose symptom is palpitation, but is driving you crazy and himself crazy because he has palpitation, is that, what would you do?

DR. RUSKIN: Marv, I think it is more a question of the level of functional impairment, and I think there are lots of people on the panel who could answer this question as well as I can, who see these

patients.

The issue for me is, really, the degree to which the level of symptoms interfere with functioning, and quality of life. And that is largely an answer that one gets from the patient.

I think that for me the symptoms that are most troublesome, that I hear about in this population, relate to diminished effort tolerance, fatigue, dyspnea with minimal activity, in which there is a strikingly noticeable difference between atrial fibrillation and sinus rhythm.

DR. KONSTAM: Jeremy, would you add to that contraindications to anticoagulation, add to the group?

DR. RUSKIN: Well, I think certainly most clinicians would be influenced by that, that is our attempt to maintain sinus rhythm would be much more aggressive in patients who cannot take Warfarin, but we don't have evidence, definitive evidence, that suppression of atrial fibrillation with antiarrhythmic drug therapy prevents stroke.

It is a perfectly logical hypothesis, but

as you know we don't have an answer to that question.

ACTING CHAIRMAN CALIFF: I think we ought to move into having the panel address the questions, unless there is a non-philosophical question, but a data related question for the company, or the experts.

DR. GRINES: Rob, I have an electrophysiologic question, and I wonder how certain electrophysiologic experts are that QT prolongation is predictive of Torsade? Because even in this trial, even though the ECGs are monitored very closely, there still was a higher incidence of Torsade compared to placebo, even after hospital discharge.

And then secondly I think there are examples, in fact I think they've showed one where Digoxin did not have a longer QT, and yet there is a two-fold increase in Torsade, and I believe Amiodarone is similar, you can't necessarily use the QT interval to predict Torsade.

So I'm concerned about how we monitor these patients, and whether in fact, we should draw blood levels.

DR. KOWEY: As a sort of general answer to

that, and I will take a crack at it, I think that there clearly is a generic predisposition of Torsade in the population, and it is probably a genetic abnormality for which someone is hetero, rather than homogenous.

And I don't think that there is any way, a priori, to know who those people are. And there is always going to be a risk of Torsade without much QT prolongation in those individuals. I think that is the explanation why some people take a couple of doses of quinidine and Torsade, for that much of a change in their QT interval.

But I don't really see that as being a problem that is unique to this compound. It is an IKR blocker, I think we understand it, I think we understand its electrophysiology. I don't think it really -- I agree with something Jeremy said a little bit ago, which is actually a good comment, which is, it is not that far off from things that we already do with other drugs.

So I don't think it is really fair to hold this drug to that kind of a higher standard when we

know, for a fact, that drugs that prolong the QT interval are going to have some mortality disadvantage, and they are going to have some mortality disadvantage.

Craig, I mean, I know I see the data, I believe the data, you did a wonderful job with it, but some people are going to die on this drug, and there is really not much we are going to be able to do about that.

But that doesn't make it not approvable. So I think that is where the discussion sort of has to go.

DR. GRINES: Well, I don't know whether we are going to talk about this issue in the questions, but I think that several members of the panel are concerned about just approving drugs for surrogate endpoints when we don't have the mortality information.

And, clearly, we know that antiarrhythmics have caused a higher mortality in numerous studies. And as you stated yourself, just because we were ignorant two years ago doesn't mean we have to

continue to be ignorant.

DR. KOWEY: I don't disagree with you, I think this is the crux of the discussion that the panel is going to have in the next hour, can you see your way past a risk which is, as best as can be defined, defined.

I mean, I think the data base is very robust, and we have a lot of very good data, but you still have to take a leap in order to approve the drug for clinical use.

And the question is, can you or can't you? And you have to answer your conscience, I guess. It is a tough call.

DR. GRABOYS: That is part of the problem. We are looking for a hook to hang some help to define vulnerability to death, and when we used to call antiarrhythmics as poisons with desirable side effects, which the traditional -- the reality is, 15 years ago we looked at 1A agents and couldn't find any relationship between QT prolongation and risk of Torsade, or even prime RVF in that case, and levels were no help.

Levels were helpful if the patient had a recurrence, and you took a level and you didn't find it, that was helpful. But otherwise it was not helpful in predicting. And that is part of the concern, I think, that we all have in terms of the approving of this drug.

DR. GRINES: As a follow-up to Bob's question, as to whom would you give this drug to, if you look at the Diamond population in the heart failure world, there would be probably two reasons that you would want to get somebody out of afib, one would be to improve their output, and the second would be hoping that if there is a rate related cardiomyopathy, that if you can restore sinus rhythm and control rate, that some of the ventricular dysfunction will improve, which we've seen.

However, in that case, would you perhaps not chose Amiodarone since some people think that there is actually a mortality protection, and it is currently being studied.

DR. BIGGER: Well, I'm just going to respond to the point that Cindy is bringing up. I

think actually in the sponsor's data, and gathered by their investigators, they started to adjust for creatinine clearance, and the QT interval response to the drug, they had a substantial drop in the rate of Torsade.

And I think that is -- it is not perfect, but it is relatively direct evidence that this algorithm does work to some extent. It is better than not adjusting, for sure.

ACTING CHAIRMAN CALIFF: I think this is going to be the key. Well, you are right, it is not directly addressed in the questions. I guess we ought to have this discussion now.

DR. GRINES: Well, I just have some concern because if you compare this to a thrombolytic, which has a rate of intracranial bleeding that is very close to the rate of Torsade after hospital discharge, we would not approve it on a sample size like this.

And so I don't understand what the difference is, and I guess I'm not convinced that the data base is as robust as -- I don't know, it just doesn't seem like we have enough patients to answer

some of the important questions.

ACTING CHAIRMAN CALIFF: Well, maybe I could give a little different perspective, because I think it is the number of -- and there is a subselection here, in my opinion, that is a difficult issue.

But it is really the number of deaths and not the number of patients that is the critical thing to look at in terms of sample size.

And we have a data base with eleven hundred and something deaths. And the subselection issue, which I grant you is a very difficult one, most of the deaths are not in the primary atrial fibrillation population, so there is a difficult issue there.

The 1,100 deaths is not far removed from what you would see in a large thrombolytic trial where the mortality rate is substantially lower, admittedly again, over a shorter period of time.

And I think your analogy, though,is a good one, and I was thinking the same thing with regard to cardiac surgery, for example, or percutaneous

intervention, where the issue is not do you occasionally create harm, because that happens with all those treatments.

The issue is, on balance, does the harm that you create outweigh the potential benefit? And I think that is what we have to struggle with. It does concern me to focus just on the risk of Torsade, because we send people to surgery every day, we -- you know, even beta blockers, which we use very commonly, we know reduce mortality, do occasionally create substantial harm.

So that is what -- I know that is what we are struggling with.

Bob?

DR. TEMPLE: I think you are slightly talking past each other in one way. Dr. Grines is basically saying there aren't that many people with AF that have been treated.

You are obviously counting the results of the other study, which is huge, and has a large number of deaths, rather than any thrombolytic trial that I know about, by the way.

So there is a discontinuity there. Are both equally relevant to this, or are they not? And I think you haven't met on that question yet.

ACTING CHAIRMAN CALIFF: One way of approaching this would be to have a question 1D, which would allow us to discuss, more formally, the tradeoff.

I think the question 1 is really oriented towards the benefits in the prevention of the recurrence of atrial fibrillation. If we felt that the evidence was not there for question one, then we could essentially stop at that point.

But if the answer to 1A, B, and C, is positive, then we have to come back to a discussion of how does that weigh against the risk.

So what I would like to do is to move right into question 1, and come back to the -- how do we balance, if the answer to that is positive, against the risk that we've seen.

So question one: Is Dofetilide superior to Placebo in terminating -- and there is a tantalizing converting in parentheses -- episodes of

atrial fibrillation. If so how strong is the evidence?

Peter, if you could start?

DR. KOWEY: I think the answer to that question is yes, and I think there is enough data, my opinion is there is enough data from studies 345 and 120, in a placebo control fashion to answer the question positively.

So I would say yes to that.

ACTING CHAIRMAN CALIFF: Cindy?

DR. GRINES: Well, my answer would also be yes in the basis of two trials showing approximately a 30 percent rate of conversion, but I have to question its clinical relevance because, clearly, with electrical cardioversion you have a higher rate, and it is faster, and potentially less expensive.

ACTING CHAIRMAN CALIFF: Tom, if we could start with you and come back around?

DR. GRABOYS: I'm in concert with Cindy and Peter. Yes.

DR. KONSTAM: Marvin?

DR. KONSTAM: I will say yes. I guess I

will point out that the obvious -- that there is not, we don't have a study that was specifically designed with this as the primary endpoint. So we don't have that.

So we have to sort of say, okay, based on what we have. But I think the data in the trials that we have are pretty strong, so I will say yes.

ACTING CHAIRMAN CALIFF: Tom?

DR. BIGGER: Yes.

ACTING CHAIRMAN CALIFF: Ileana?

DR. PIÑA: Yes.

DR. D'AGOSTINO: I agree, but I think we do have strong data, I think it is secondary, but it is quite consistent and quite striking. I mean, here is the case where the foreseeable rate is extremely low, and by the time you get to the higher regiment, or at least one that starts off at a higher dose you have a fairly substantial conversion rate.

So I definitely say yes.

ACTING CHAIRMAN CALIFF: Joan?

DR. LINDENFELD: Yes.

DR. KOWEY: Can I just ask one

clarification? Do we have a breakdown for fib and flutter in that percentage? It is 29 percent in -- or 30 percent, as Cindy said. Was it substantially higher for flutter?

DR. RYDER: We do have that segregation, and I guess the numbers are going to be retrieved, but it is higher for flutter.

ACTING CHAIRMAN CALIFF: I would vote yes, too, on 1A.

1B I guess I would like to ask, in the sense of -- the question is, to what extent does the evidence consist of data from dosing regimens no longer recommended by the sponsor?

Maybe there should be a graded response here, and I know Marvin brought this up. Either a lot and it is concerning, a lot and it is not concerning, or not much. Those would be the three options.

DR. KONSTAM: I'm not sure I raised the concern about with regard to efficacy.

ACTING CHAIRMAN CALIFF: Okay, Peter, maybe you can --

DR. KOWEY: I don't think it is a problem.

I don't think there is much of it, and 345 was a study done completely after the creatinine shifted, or the creatinine clearance adjustment was made.

And 120 was substantially within that time frame. So I don't have a problem with the data.

ACTING CHAIRMAN CALIFF: Bob?

DR. TEMPLE: Do I remember correctly, the conversion rates at the two lower doses were trivial, so it really is only the higher dose that has anything going for it at all, here, right?

DR. RYDER: That is correct. The numbers for the 250 and 125 were low. And we do have the numbers, Dr. Califf, for flutter and fib.

DR. MARSHANT: Yes. For the pool across 120 and 345, for fibrillation there were 46 out of 179 patients on the 500 mig dose converting, which is 26 percent, compared to one percent placebo rate. And for flutter it was 15 out of 27, which is a 56 percent conversion rate.

DR. KOWEY: So the numbers are lower, but proportionately higher?

DR. MARSHANT: Compared to a placebo rate

of three percent.

DR. KOWEY: So the number I heard was about 28 percent for fib, and about 56 percent of flutter, which is pretty much in the frame of what we've seen with other class III drugs, so it is sort of in the same ballpark, proportionately.

ACTING CHAIRMAN CALIFF: Okay. Does anyone in the panel disagree with Peter? Then we will move along.

Is conversion from AF to sinus rhythm of self-evident benefit, if not are there data to show that symptoms are reduced, or that irreversible harm was averted?

DR. KOWEY: I'm going to put -- I want to make sure that the panel understands that when I answer this question I'm doing it with a clinician's hat on, and not a regulatory hat, because I can tell you that categorically, that most physicians want to have their patients restored to normal sinus rhythm.

And the reality is that they are going to do it. They are going to do it specially in patients who have the kinds of symptoms that Jeremy outlined

earlier.

So that, although I think the data in this application are not compelling with regard to symptoms, I think the data are going in the right direction. The directionality isn't bad.

It is not as compelling as I would have liked it to be, there certainly wasn't a primary endpoint anywhere in the trial.

And it is a benefit to many of the patients who are in these trials. So I would give this a weak yes. But I would give it a yes, without a whole lot of enthusiasm, but I do give it a yes.

DR. GRABOYS: I'm really underwhelmed in this regard. First of all, I think there is a huge placebo effect with atrial fibrillation. In other words, patients come in, they are in AF, they hear the word fibrillation, they think they are going to have a cardiac arrest, they are sure they are going to have a stroke. A well meaning doc points it out, you have atrial fibrillation, they never had a symptom before, now they have symptoms all the time.

And when I was looking at the quality of

life question, there, again I was underwhelmed by that, because I think as a physician we can deal with these patients, very often, and decompress them psychologically.

So I'm under, underwhelmed. Yes.

ACTING CHAIRMAN CALIFF: Cindy?

DR. GRINES: I just want to clarify that they are talking, and question 1C is just about the acute conversion.

ACTING CHAIRMAN CALIFF: Yes.

DR. GRINES: And actually there is zero data that I saw that acute conversion alters symptoms. The only data that were provided were one month quality of life, to my recollection.

ACTING CHAIRMAN CALIFF: But the first question there is, is acute conversion of self-evident benefit.

DR. GRINES: No, I don't think we have data to support that, and I don't think the sponsor provided any information about the acute conversion.

ACTING CHAIRMAN CALIFF: Bob?

DR. TEMPLE: Well, I'm looking at -- that

is a slightly weird question, because nobody is going to use --

ACTING CHAIRMAN CALIFF: We've gotten used to those.

DR. D'AGOSTINO: Yes. Nobody is going to use it to convert acutely, the point is to convert this way, as opposed to with cardioversion, and then keep people on the drug. So the real question is whether long-term suppression is a self-evident --

DR. LIPICKY: But that is not what this question was about.

DR. TEMPLE: What is it asking?

DR. LIPICKY: -- terminating AF.

ACTING CHAIRMAN CALIFF: That is question 2, that is the next question.

DR. TEMPLE: Well, but is the question --

DR. LIPICKY: So if someone is in AF --

DR. TEMPLE: Right.

DR. LIPICKY: Is it self-evident they shouldn't be? That is exactly what the question was meant to ask.

DR. TEMPLE: That still seems a funny

question, because the people contemplating this are planning to convert one way or another, and then maintain the patient, otherwise what is the point?

So maybe --

DR. LIPICKY: Well, but that was what was being asked. I know everyone is going to cardiovert. Why? Is it self-evident that you should be in sinus rhythm?

DR. TEMPLE: To me that question comes up when you ask about maintenance.

DR. LIPICKY: If it is self-evident, if it is not self-evident you should be in sinus rhythm, why does everyone cardiovert?

DR. TEMPLE: That is the maintenance question.

DR. LIPICKY: And that is what this question was asking.

DR. TEMPLE: It is still a dumb question.

DR. LIPICKY: Okay.

DR. GRINES: Well, I am not convinced that everybody cardioverts. I mean, maybe the electrophysiology people see a different patient

population. But in my clinic there is lots of people in afib who nobody has ever tried to cardiovert.

And you know I guess I'm not convinced that, for example, if you ask the question, is chemical cardioversion better than electrical, I don't think that we have any information on that.

ACTING CHAIRMAN CALIFF: So what I would like to do is just specifically answer the question. It may be very quick, it may be no and no for everybody else in the panel. I heard Peter give a lukewarm yes, it is self-evident benefit.

Marvin?

DR. KONSTAM: I am going to answer yes to the first part of that question, after taking the liberty to modify a little bit.

You know, I think the thing is that you can't -- first of all, I think it is sort of what Bob was saying, you can't talk reasonably about maintaining sinus rhythm until you cardiovert.

I think you can get into -- clearly, as the sponsor pointed out here, if there is an advantage, which is debatable, it is that a third of

the patients are spared the shock.

I mean, I guess that is really the thing. And one could debate whether that is a good thing or not, but that is the thing. You know, I read the question more a question of is it a good thing to be in sinus rhythm independent of whether or not you can demonstrate symptom improvement.

And I am skeptical that the sponsor's clearly demonstrated symptom improvement, but I'm not too worried about that, because I think it is self-evident that there is a sizable population that will benefit from being in sinus rhythm. I think being in sinus rhythm is a good thing.

So that is a modification. I will say yes.

ACTING CHAIRMAN CALIFF: One other interpretation of this, at least that I'm taking, which is that if you are going to be developing evidence for evidence based medicine, or trying to develop a new therapy, would it be enough to simply show that you caused a higher rate of conversion, or would you need to show that you improved symptoms?

DR. KONSTAM: Can I just say -- I mean, I think that the higher rate of conversion would be meaningless if you didn't also demonstrate maintenance by some method. So let's just say that.

But I think with regard to the question that you are asking, I think the problem with insisting on demonstrating symptom improvement is that we don't know how to show it, all right?

We really do know whether somebody is in sinus rhythm or atrial fibrillation. And given that I'm willing to take liberties with saying, and it is really based on some of the things that Jeremy said, that there are sizable populations of patients that we know, as clinicians, are going to be better off in sinus rhythm than atrial fibrillation.

ACTING CHAIRMAN CALIFF: Tom?

DR. BIGGER: They didn't have a lot of evidence for drawing on personal experience. There are a lot of people who decompensate and have a --

ACTING CHAIRMAN CALIFF: You are going to have to keep pressing your button, it turns off automatically, like on the slide projectors.

DR. BIGGER: -- get better when they are converted, and they get better reasonably quickly. So there must be some in here, it is just that it could have been much better documented, for sure.

DR. PIÑA: I don't think that my goal to convert people to sinus rhythm necessarily has anything to do with symptoms, but it has to do with the far reaching effects of being in atrial fibrillation, which I think we are leaning more toward that is not a good thing.

So I would have to say yes for the first part, and I'm not convinced about any symptoms in this, at all, so I would have to say no for the second part.

DR. D'AGOSTINO: I'll say no based on the day-to-day presented.

DR. LINDENFELD: I'll say no to both. I think it is likely that people benefit, but I just haven't seen evidence that makes me sure that is so.

ACTING CHAIRMAN CALIFF: And I would also say no to both, but I also believe it would be very easy to demonstrate, if you just ask people how do you

feel right before hand, and how do you feel right afterwards, that you could pretty easily show a symptom benefit.

DR. LIPICKY: But that is what they did here, and they didn't -- and you say you are not convinced they found it?

ACTING CHAIRMAN CALIFF: No, no. They didn't do it for acute conversion. That would be a question you would ask five minutes before and ten minutes after, and there would be a big difference.

Now we get to the maintenance, which is, I think, the issue you are raising. I'm presuming, based on the discussion we've had so far, that for 2A everyone agrees that the evidence is strong, because we've been through that with regard to acute conversion.

And for 2B, is there anyone who feels differently than they did for the question above?

(No response.)

ACTING CHAIRMAN CALIFF: So we really come to 2C, is deferral of relapse into atrial fibrillation of self-evident benefit? And if not, if you answer

yes to that then you are saying that there are two trials here that show a clinical benefit.

We have yet to discuss the other side of the equation, which would be next. If you answer no to is it a self-evident benefit then are there data to show that symptoms were reduced, or that irreversible harm was averted?

Peter?

DR. KOWEY: As I -- the first one I answered more towards the first part, and less to the second part. This one I will do the opposite and say that I'm less convinced that over the long term, specially since there is a risk over the long term of toxicity, and for the reasons that Tom brought up earlier, talking about people getting diuretics, or getting diarrhea, becoming hypokalemic, taking other drugs, specially other drugs.

We are exposing patients to a longer period of time in -- with a risk of an adverse effect. So it is not as self-evident that it is a benefit, because of the potential -- I think because of the potential risk. That is my opinion.

However, it isn't the question exactly, Marv, but it is really clinically important, and I think it is the way I'm going to answer it, so you can answer it the way you want to.

But the second part of it I feel a little more strongly about. I think that they do have some data in here that suggests that patients did feel better, and did fare a little bit better, and felt a little bit better, and could do a little bit more.

So that I think the data for -- it is less self-evident, but the data support the claim a little bit better for this part of the question than for the other part.

DR. GRINES: Was that a yes or a no?

DR. KOWEY: It was a very lukewarm yes, mostly for the second part of the question.

DR. GRINES: Okay. You know this one is a little more difficult. I agree in large part with what Peter said, but I have numerous concerns. One of them is that this wasn't the primary endpoint of any trial.

The second thing is if you look at some of

the FG reviewers comments, these weren't pre-specified endpoints. You know, there is some question on how to interpret that, none of the P values were adjusted for multiple times of measurements.

And, you know, I guess I don't know why we are only shown the data one month, when in fact the endpoint to these trials were six months or twelve months.

And the question comes up, is there no benefit, no symptomatic improvement at that time? Because even at one month there is only a few things that appear to be significant.

So I'm not entirely convinced that it has been shown, based on the treatment received, that there is a huge improvement in symptoms.

The second thing I think is very dangerous to draw assumptions that just because they are in atrial fibrillation they are going to be better of without it. We have numerous examples of trying to improve ejection fractions, trying to suppress PVCs where we harmed patients.

And I don't think we can just leap to

those conclusions. So I guess my answer would be no.

ACTING CHAIRMAN CALIFF: Tom?

DR. GRABOYS: No, to both.

ACTING CHAIRMAN CALIFF: Bob, you had a comment?

DR. TEMPLE: I just want to be sure people address this. I didn't think that some of the people who thought that there were obvious benefits from being in normal sinus rhythm thought that because of anything they saw in the data base here.

And this data base didn't even enter symptomatic people, so it is very suboptimal for trying to show that. I just want to be sure that people address the question, for example, Jeremy said he thought it was just obvious everybody knew that there were some people who did badly.

Now, if nobody agrees with that, we need to know it. But that is more the basis for concluding that it is worthwhile to keep people in sinus rhythm, I would argue, than anything that is in here.

And so we need to know whether you think that is a credible argument, or not.

DR. GRINES: Well, I guess I'm confused as to what is an acceptable endpoint, because I've sat on this committee for a few years now, and have been told that surrogate endpoints don't count, you have to have a clinical benefit that people agree on, and not only has this trial not shown a clinical benefit, we are being asked to just give our thoughts on whether we think this is an okay surrogate with no data to support it.

DR. TEMPLE: Surrogate endpoints can be used in drug approval, and are. Drugs for life threatening ventricular arrhythmias, for example, have historically been approved on endpoints that nobody would consider definitive. Maybe one of these days now that we have defibrillators that will change, but it certainly didn't change in the past.

There is some judgement in this. If, for example, you all believe with your experience that it was obvious that there were some people who feel much better when they are in sinus rhythm, you might not believe that, that is okay, too.

But if you believe that, that could make

the ability to stay in sinus rhythm longer a credible endpoint. It is a judgement, and you are certainly free, under the Food Drug and Cosmetic Act to make that kind of judgement.

DR. GRINES: Well, I guess I didn't interpret the question that way. So if the question is truly do some people feel better in sinus rhythm, then I would have to say yes.

ACTING CHAIRMAN CALIFF: Well, the first question is, is it self-evident, independent of any data you've seen regarding this particular drug, that going into sinus rhythm is beneficial.

DR. GRINES: The answer to that is no.

ACTING CHAIRMAN CALIFF: Okay, so I think you've answered it.

DR. GRINES: Yes.

ACTING CHAIRMAN CALIFF: Marvin?

DR. KONSTAM: I see this as a somewhat theoretical question, and I guess it depends on how you construct it. And it seems like there are two issues to me about it.

One is, you know, I guess is the

conversion to AF a reasonable efficacy surrogate. And I guess then the question is, certainly in the end of the day, in terms of deciding on fibrillity, for example, you are going to look at cost and benefit, and I see this, really, as a benefit question, exclusively.

So I'm going to not think at all about adverse effects that the drug is causing. And so I will say, in those -- really that is the way I'm addressing this question.

I guess the next question that has to be asked is, what are -- are you saying uniformly in all patients, or are you saying, are you pretty confident that there is a population of patients that barring adverse things going on, are better off in sinus rhythm.

And I think the answer to that is yes. And so taking this purely as an efficacy question, and saying that it doesn't necessarily apply to the entire population of patients with AF, but certain subsets of population, I think the answer to the first part is yes.

ACTING CHAIRMAN CALIFF: Tom?

DR. BIGGER: Before I heard all this I had an answer,a nd nothing I heard changed my mind, so I'm just going to put it forward.

I wrote down in some, even many patients the answer is yes, in my opinion, for the first part of the question. I thought there was some data in this data set to support that symptoms were reduced, but I didn't think it was very -- you know, it was powerful.

ACTING CHAIRMAN CALIFF: Ileana?

DR. PIÑA: I am going to be consistent and say yes for the first part, and again, I'm not overwhelmed with the reduction of symptoms, so I would have to say no for the second part.

ACTING CHAIRMAN CALIFF: Ralph?

DR. D'AGOSTINO: Let me go back, just briefly, to 2A, because I think we all said it was strong data, strong evidence. But I think that they do have the two studies, we are not sneaking by on a single study.

I think that the way they put together

this, I can study the 120 was a mistake, and I think the way -- a perfectly correct position to say that they should have analyzed it like the 345, and that gives them the two positives. We aren't changing our rules.

As far as the 2C, I think the -- I think it is self-evident, and based on this data I think it is no. But, I mean, for example, at Framingham we spent a lot of time worrying about AF and looking, going in and out of AF, and I think that the longer you can keep them out, the better it is not going to be. It is not in this data base, but I definitely do think that there is a self-evident aspect to it.

ACTING CHAIRMAN CALIFF: Joan?

DR. LINDENFELD: I think the first answer would be yes, but I'm not at all confident that I know how many patients that is, if it is a very small number, and I suspect that it is a small number, where there is a very clear benefit. And the second part is no.

ACTING CHAIRMAN CALIFF: Dr. Ryder, you can go ahead and sit down if you are more comfortable

sitting down, because we are not going to ask you any more questions, I don't think.

DR. LIPICKY: The time between recurrence of AF was detected here because people became symptomatic, and then they were documented to have AF. Now, not all of the patients in the trials, that end point did not mean that for all of the patients in the trials.

Some of the patients were found to have AF on a routine visit. But part of the signal that one saw, in fact, was because before the interval of time, the patients weren't having any symptoms.

So, you know, for the paroxysmal atrial tachycardias we take pushing the button to send an ECG when you have symptoms as being a symptom driven endpoint.

So I want to be sure that you know what the end points were when you say that I'm not so sure that symptoms were effected here, and that we are simply dealing with a surrogate.

I just want to be sure you know what you are saying, because I've heard the word surrogate many

times, and although this has a surrogate quality, it isn't all surrogate.

ACTING CHAIRMAN CALIFF: Right. So I think my vote would be yes, and no. I'm sorry, no and no. But let me explain.

I think we all agree that, there has been unanimous agreement by the panel that there is strong evidence that this drug prevents recurrence of an ECG finding.

And what you are pointing out, Ray, is that the ECG finding is detected sometimes because it shows up in a routine clinic visit, and sometimes because the patient feels bad and comes in to get checked out.

And I think that on the C part of the questions, I think there is disagreement and confusion that, at least in my estimation, reflects the true status of the clinical world, which is that some people feel strongly that every patient should be put in sinus rhythm, and some feel that it is a waste of time to try to do it.

And I think that these particular studies

were not very helpful in sorting that out because that was not how they were designed.

And I think that accurately reflects the point of view of the panel. Bob?

DR. TEMPLE: Marv, in answering, said I think, obviously a lot of people it doesn't make any difference, but there is a subset of people in whom it does.

Do the people who said no here explicitly disagree with that, or do they think it is not well defined, or what is the nature of this? There seems to be a -- we've heard two different things. I just want to be sure the issue is joined.

DR. GRINES: Well, I disagreed because I didn't see any data looking at a subset of patients that had symptoms that were strong enough that they had perfunct benefit from being cardioverted.

And the second thing is, you know, I'm just not convinced that treating an ECG abnormality, in and of itself, is of clinical benefit to the patient, it may be of some harm, based on some other antiarrhythmic trials.

DR. TEMPLE: Well, that a sure certainty. If someone is asymptomatic, and you put them on a drug that might produce an abnormal rhythm that is dangerous, those people would be harmed.

But, still, when Marv says that, there is some people -- and Tom says, there is some people who plainly are discomforted by this.

Do you think that is not true, you are worried that the drug can't be restricted to those people, what is the nature of it?

DR. GRINES: I don't think that we --

DR. TEMPLE: We heard two opposite things.

DR. GRINES: I just don't think that the studies that were designed showed me that data. That if you take a symptomatic population they fare better, or if that symptomatic population, maybe they have more side effects from the drug.

I mean, basically it was relatively asymptomatic population that was tested. And a lot of the data that people have quoted along the table, like the Framingham study, either personal experience, it might be related to the substrate of the patient. I

mean, older patients, hypertensives, LVH, etcetera, they have atrial fibrillation, and they are going to do more poorly because of the substrate, perhaps.

And it is not that the rhythm, per se, is giving them a higher mortality, or more symptomatic problems. They have an underlying problem to start with.

DR. TEMPLE: I don't mean mortality but -- okay, I think I heard you.

ACTING CHAIRMAN CALIFF: Okay. What I think might work would be to do question 3 and question 4, and then come back to the -- actually never asked in here, how do we weigh the two, and I think we should do that after question 4.

Does Dofetilide cause significant side effects other than QT prolongation and Torsade. Peter?

DR. KOWEY: No, I don't think we have seen anything else that is really terribly important.

ACTING CHAIRMAN CALIFF: Cindy?

DR. GRINES: I agree.

ACTING CHAIRMAN CALIFF: Does anyone

disagree?

(No response.)

ACTING CHAIRMAN CALIFF: Okay, so we are unanimous. The only side effect or safety issue is the proarrythmic risk, and the questions is asked, are the proarrythmic hazards of Dofetilide affected by the presence of other factors, namely structural heart disease, active ischemia, and LV dysfunction.

It seems like it might be better just to go down the line and ask people for their interpretation of the analyses that we've seen, because there are other factors that were analyzed in addition to these three. Peter?

DR. KOWEY: I want to just say I think that it was a very good job of analyzing the data base. The problem is, as has been pointed out repetitively all through the day, that when you are dealing with a relatively small number of events, of true cases of proarrythmia it is very difficult to define factors which may be the most important in predicting which patients are going to have those things happen to them.

And it is all, obviously, defined in terms of probability. But I'm reasonably satisfied, and it is consistent with what we have seen with other drugs that, yes, in fact these things, left ventricular dysfunction and structural heart disease are important.

The active ischemia part is very difficult, because the only data we really have are data that are probably not adequate to the task. And no one has really ever studied this. I mean, nobody runs around giving patients with active ischemia antiarrhythmic drugs.

The only experience I ever saw with that was intravenous Amuterine, and it wasn't really, it wasn't ever sorted out that way, but we did get patients with active ischemia iviamerine and we do it now.

But I don't think we can answer B, honestly. I think it is a non-answerable question. But I think we can say, for A and C, that there is reasonably good data that, yes, the hazards are increased by those factors, and other factors that

have been defined, that we don't have to go through.

ACTING CHAIRMAN CALIFF: Cindy?

DR. GRINES: I agree.

ACTING CHAIRMAN CALIFF: Tom?

DR. GRABOYS: I don't know how you can not agree. Structural heart disease and LV dysfunction, I think the sponsor, also, was referring to active ischemia as post-MI, but I think that when we are talking about proarrythmia which is actually the umbrella which Torsade comes under, we are talking about all different forms of proarrythmia, then I think that this drug could have provoked proarrythmia in a setting of structural heart disease, post-MI, and LV dysfunction.

ACTING CHAIRMAN CALIFF: Marv?

DR. KONSTAM: Yes, you know, I agree. I just want to say, more strongly, we don't have any information about active ischemia. I think the point about the Diamond MI trial doesn't really help me all that much.

ACTING CHAIRMAN CALIFF: Tom?

DR. BIGGER: I agree. The power is very

low to get any kind of definitive answer, or estimate any fixed size, or anything like that. But it is pretty suggestive that structural heart disease and LV dysfunction were important.

ACTING CHAIRMAN CALIFF: Ileana?

DR. PIÑA: I agree.

ACTING CHAIRMAN CALIFF: I agree.

DR. LINDENFELD: I do too.

ACTING CHAIRMAN CALIFF: So I think the summary is that the panel was impressed with the analyses that were done given the data that was available, that factors were identified, gender was another one, and multiple possible drug interactions as being factors.

If the vote was to approve, that there would have to be considerable work to figure out how to get those into the label, and into the training.

DR. LIPICKY: Just to be sure I understand the answer to the question, could you give me one piece of data that says that structural heart disease increases the incidence of Torsade in this data base?

DR. GRINES: The only data I know is from

the Diamond study, where they actually looked at the CHF, and did a --

DR. LIPICKY: And the presence of CHF increased the incidence of Torsade?

DR. GRINES: Right.

DR. LIPICKY: That is what you said?

DR. GRINES: Right. And that is all. There is nothing about -- a few of the studies looked at the ideology of atrial fibrillation, and some of them had valve disease, left atrial enlargement, but I didn't see any analysis based on the echocardiographic findings.

ACTING CHAIRMAN CALIFF: I interpreted what most panel members are saying is that they would prefer to emphasize the factors that came out in the analysis that was done as being the key factors to be considered.

DR. LIPICKY: Well, for most antiarrhythmics the instructions for use say don't give to anybody with structural heart disease. Is that what you want to end up saying here?

ACTING CHAIRMAN CALIFF: But I think that

is a different issue, because that involves a total assessment of the risk benefit.

DR. LIPICKY: What you have said, right now, is that you have identified in this data base, the fact that the adversity of Dofetilide increases in people who have structural heart disease compared to people who do not.

DR. GRINES: That is true.

DR. LIPICKY: That you don't know whether people with ischemia are adversely affected because there isn't enough data. And that people with heart failure are certainly at greater risk of Torsade.

And you concluded all of this from the 43 events that you saw?

ACTING CHAIRMAN CALIFF: Which is the best data base that we have access to, or that we've seen.

DR. LIPICKY: But it is from that 43 patients that you drew those conclusions?

ACTING CHAIRMAN CALIFF: That is all we have. But I think denoting increased risk, and specifying who should be treated are two different things.

For example, we know patients at highest risk of complications from bypass surgery are the very ones who probably should be treated. So it has to be an assessment of risk and benefit.

Which gets us to, I think, we have to add a new question five, which is really the key question. I think the panel has unanimously agreed that the drug is effective in preventing relapse of atrial fibrillation, and also in converting.

There is differences of opinion over the importance of that relative to symptoms, and there is unanimous agreement that proarrythmia is the only concern.

And now we have to, I think, weigh those two issues and say whether we think, on balance, this is a drug that should be -- should be approved. Is that question 8? Okay.

I think if the answer is no, then the rest of these questions become relatively unimportant. If the answer is yes, then I think they become very important.

DR. LIPICKY: Well, I guess it depends on

your logic, right? It seems to me if you cannot decide what dose should be used, you can't answer the question. That certainly has to influence your answer to question 8.

If you can figure out what dose to use that has to influence your answer to question 8. So it isn't clear to me that although, granted, you could go to question 8 right away, and then not answer any of these other questions, it sort of is like, well I'm sure it works, therefore it should be approved, but I don't know what dose to give it in. That is not a good recommendation.

And similarly 6, if the notion is, we know there are bunches of things available out there, and they have no risk at all, and this has a risk, I don't see how you can answer 8 until you make the decision about what else is available in the area for treatment.

So you can -- I wouldn't object if you go to 8 right away. I'm just pointing out there is some reason for going this route, as opposed to jumping.

DR. KOWEY: I for one would like to hear

the Committee talk about these questions before we get to 8. I think there is an order to this, and I kind of appreciated the order. And I think if we go to 8 right now it is going to preempt a lot of good discussion we need to have.

So I would vote that we continue.

ACTING CHAIRMAN CALIFF: Is everyone else in agreement with that? I almost feel like the impeachment hearings. I guess we will call the witnesses if that is what people want to do.

(General laughter.)

ACTING CHAIRMAN CALIFF: So question 5. Peter, you wanted to talk about this?

DR. KOWEY: It is okay. It is not going to be comfortable, but I think we should do it. The answer to this is I think yes. I think there are other considerations -- the question has to do starting the drug during a three day hospitalization with dose adjustment to take account of renal function and observed changes in the electrocardiogram.

Are there considerations of patient's weight, sex, and phenotype? Phenotype I don't

understand. But yes for patient weight, sex, drug/drug interaction, organ dysfunction, which should affect dosing. Yes, the answer is there certainly are major ones.

DR. GRINES: Yes, I agree. I think the low body weights, female gender, moderate liver dysfunction, all these drug interaction appear to be of some concern.

ACTING CHAIRMAN CALIFF: Bob?

DR. TEMPLE: Yes.

DR. GRABOYS: Yes, and I just want to add my continued discomfort about the heart failure in post-MI populations, where the approach used by the sponsor in Diamond was different from in the rest of their population. And I'm still stuck with that.

So I guess I would add that as another point, is that in patients with atrial fibrillation who are post-MI, or with heart failure, I think we have to consider, and I don't know what to do about it, but consider a slightly different dosing approach, based on the data that we have.

ACTING CHAIRMAN CALIFF: Tom?

DR. BIGGER: Yes. I think there are issues here that have to be labeled, and that is about it.

DR. PIÑA: Yes, but I really don't know what kind of recommendations that we should give on dosing, because as Marvin said, all we have is the dosing that were used in this regimen, and I'm not sure how to say to a clinician you need to adjust downward because of gender, or because of -- I know about renal dysfunction because that is an easy -- and I know about looking at the QT, but I don't know what advice to give, but I think yes, that it needs to be addressed.

DR. D'AGOSTINO: Yes.

DR. LINDENFELD: I think yes for some things. Drug/drug interactions, I think weight is taken into account in the creatinine clearance calculation. And the sex concerns me because that wasn't done in these protocols, and if we do it, and we adjust downward for women, are we going to have any effect at all?

So this is a confusing set. But I think

for some of the clear drug interactions yes.

ACTING CHAIRMAN CALIFF: I would say yes, also. Incredibly complicated, and as we will get to, maybe requiring much longer discussion in a different venue. Bob?

DR. TEMPLE: As various people pointed out, no adjustments were, in fact, made in the Diamond trial for any of these factors, and at least as far as drugs go, everybody was on lots of them. How does that affect you?

I think Joan's question is perfectly right. How would you know you had any effect if you have the dose in women, how would you know anything? So, if we discovered some major interaction that doubled everybody's blood level, okay, we could figure out how to deal with that.

But short of a major new discovery what is one supposed to do? Or maybe what you are saying is that when you discover something that has a major impact on area under the curve, make appropriate adjustments.

ACTING CHAIRMAN CALIFF: My interpretation

of what people are saying is that so much data was presented today, there were some relatively specific things, like Verapamil, and then there were some general drug classes where more work needs to be done. They are the nephric patients who have not been studied.

DR. TEMPLE: Well, they don't recommend -- I think they don't recommend the use for anybody below 20 creatinine clearance, right?

ACTING CHAIRMAN CALIFF: But we also know that people will develop, in the course of treatment, will develop deterioration of renal function that needs to be dealt with.

DR. TEMPLE: So that implies to me that you think there ought to be something about continuous monitoring of renal function.

DR. LIPICKY: Well, are you talking about the acute phase that is the conversion phase, or are you talking about the maintenance phase, or are you talking about the in-hospital preparation for the maintenance phase, or I--

ACTING CHAIRMAN CALIFF: All the above.

I think there have to be recommendations.

DR. LIPICKY: Well, don't you think -- I mean, I'm just, it seems to me that those are very different situations in the acute treatment phase, you know, Dr. Atkinson suggested that it could be that a lot of people convert at lower blood levels than it looks like on the slide, and you could certainly do some titration if you are convinced that the stuff works, even in the absence of an empirical data base that says that that is true for the preparation to go out-patient, right? You have to get on some stable dose that gives you a QT that is tolerable.

So you could shoot for a low dose and wait for a recurrence. And I mean, recurrence of AF is no big deal, you just get converted again, right? And if that isn't the right thing, then you up the dose, again, in the hospital.

And then maybe you would finally get the, so I'm not sure I know what of those three different potential ways you can solve all of these problems, for each of the three phases, and I don't think you should lump them?

DR. KONSTAM: I think the problem that I have with the last approach that you are mentioning is that we don't have any data about it. And we don't have any efficacy data --

DR. LIPICKY: Sure you do. What do you mean you don't have any data?

DR. KONSTAM: Well, to tell us what would happen, and how, and what rate of success --

DR. LIPICKY: You don't know what would happen if you went from a low dose to a high dose? How can you say that? You certainly have the data that tell you that at a dose of somewhere around the lowest dose something might happen, but it isn't spectacular.

And in between there and the highest dose there is a relatively big change. You know that. Can you seriously doubt that that would happen if you did that in practice?

DR. TEMPLE: You sort of do have data, you know what the recurrence rate was on, say, 250. So if somebody thought it was a good idea to say your initial crack at this ought to be limited to 250,

because you think that would be safer, you know that the recurrence, you know, the time of recurrence will be thus and such, better than placebo, not as good as 500.

And there is no particular reason to think that if you then went on to 500 they would be any different from patients entering on 500. So you sort of know, even though it wasn't done that way.

DR. LIPICKY: There is no more reason here to hit people with the biggest gun than there is when you start an anti-hypertensive drug. Now, some people would say you should, you know? But you certainly can start with the small dose and up it.

I guess I look around the panel I don't hear anybody basically disagreeing with you that this is any different than hypertensive trials where you start at a dose and may work your way down.

DR. KONSTAM: I think you are convincing me, so -- but the only difference is that the efficacy here is not truly by variate. It is really, we are talking about efficacy in terms of the endpoints that we see, in terms of statistical likelihood of staying

in sinus rhythm.

DR. LIPICKY: No, you only had three arms, so you can only get three bars, and that looks like it is not continuous. But the QT versus plasma concentration looks continuous, right? And it doesn't -- I mean, we are not talking bivariate, trivariate, or anything else.

All you have to do is assume that there is a continuous relationship between plasma concentration in any of these things. If you really think it is some big mystery, like somehow or another you will fall into that box, and if you don't fall into that box nothing happens, then you have to think of it in some discontinuous way.

But I see no reason to do that here.

ACTING CHAIRMAN CALIFF: I don't see anybody really disagreeing with that.

DR. LINDENFELD: Well, let me just ask. If you start people with a normal creatinine clearance on a lower dose, you are not going to expect to get the same efficacy that --

DR. LIPICKY: You would apply the same

rules. You know, if you were going to start, if you thought 125 micrograms was the one that was a reasonable starting dose, you would 125 microgram that person according to the same rules, and then you go up to the 250 according to the same rules. And then you would go up to 500 according to the same rules.

ACTING CHAIRMAN CALIFF: You are saying we have definable relationships, and you might get to the same point by several different approaches. And I think we are saying, based on the data we've seen, we can't say which approach is best.

DR. LIPICKY: The only decision you have to make, I think -- I'm not supposed to talk you into anything, right? I mean, that was the wrong thing to say, Marvin. Is that the stuff works, and that there is a way in which it can be administered that is consistent with how you understand it works.

And then you have to evaluate, as best as you can, the risk benefit. And the only critical thing is whether you think 125 is better than placebo, okay, because that fixes one end of the extreme that you are working with.

DR. KONSTAM: I see this as applicable to the chronic maintenance phase. I don't think it is at all applicable in the acute phase, because I don't see dosing up over a week.

DR. LIPICKY: -- in a hospital, and there are 47 incidences of documented Torsade, three deaths, 8,000 patients, 47 documented Torsades, and three deaths.

I mean, what are the odds of somebody dying of Torsade? I thought Torsade was lethal, right? You got Torsade you were dead. No, they had 47 and only three died. That surprises me. Isn't that what the data is?

DR. KONSTAM: They have 47 known Torsade.

DR. LIPICKY: Torsade, and three deaths.

ACTING CHAIRMAN CALIFF: Well, let's move on to B and C, which I think can be lumped together. B is, if people do it perfectly, as in the trial, do you think that patient experience will mirror what happened in the trials, and C is in the real world do you think things will be different?

DR. KOWEY: It appears, in the clinical

trials that if you think of the first, of the hospitalization period being three days, although it doesn't have to be three days, that three quarters of the events were in the first -- in that hospitalization period.

So a quarter of the events should occur out of a hospital. However, I think the only way to get any kind of an estimate of what kind of mayhem could be created with this drug is to look and see what happens when the drug is overdosed.

And -- because that is the fear we have, is that people will use an inappropriate dose, in an inappropriate patient. And when you do that, chances of Torsade go up about five fold according to what happened in the 740 milligram, or microgram experience.

So if you guys want some kind of an idea of, is the world going to come to an end? Well, I think that is a lot of Torsade. And I think that is five-fold differences is pretty dramatic.

So I think there is opportunity here for a lot of havoc if people don't pay attention to the

way they should dose the drug. If that is what the intention of the C question is, that is what I think would happen.

DR. TEMPLE: It is to get at all of those. If they don't use hospitalization, if they don't get rid of people whose QT gets too long and, of course as you said, if they use a bigger dose, you could probably think of more things, too.

DR. GRINES: I think it is difficult to answer B, but question 5C, you know, there is no way that the clinician is going to monitor the patients as closely as what the trial did.

DR. TEMPLE: Do you mean in-hospital or after?

DR. GRINES: Both, absolutely both. They are not going to measure ten to fifteen beats to average the QT, they are not going to give frequent ECGs. You know, I don't know anybody who sees a patient back as frequently as any of these trials request.

And, furthermore, you see a lot of patients who revert back to atrial fibrillation whose

doctors keep them on Quinidine for 15 years. You know, they don't even both to ever discontinue the drug.

So I think it is likely that in the real world there is going to be a much higher side effect profile. So the answer to 5C would be, increased incidence. 5B, if everything was done perfectly I suppose it would be a pretty low incidence, similar to the trials.

DR. LIPICKY: Do either you or Peter, since you were answering this, think that this is likely to wreak more havoc than Quinidine does?

DR. KOWEY: No, I wouldn't say that.

DR. GRINES: No.

DR. LIPICKY: Okay, so that is fine.

DR. KOWEY: I think that is coming up.

DR. BIGGER: I took some encouragement from the setting in which the Diamond studies were done, where a large fraction of the population was treated, and is mentioned, a lot of it was FP/IM and not cardiology. And the results, adverse effects, were pretty low.

DR. GRINES: Yes, but they monitored them very closely, and 50 percent of them decreased or stopped the drug. So I don't think in the real world that is going to happen.

DR. GRABOYS: I think it is going to depend on what the substrate is, and it is going to depend on what the clinical profile of the patient is. I think Peter used the word mayhem, and I think that is an appropriate word, and that is going to describe what is going to happen if this sloppy dosing, which I think there is every indication there probably will be, and particularly if there is a vulnerable substrate, if you get a cardiomyopathic, or you get a patient, most of these patients in AF, with structural heart disease in a polypharmacy, anyway.

DR. KONSTAM: You know I don't think we know what the incidence of at a hospital lethal arrythmia is going to be. I think that the we don't know as much about it as I think we think at first blush.

I think if you look at the Diamond trials you are dealing with one year mortalities in the 20

percent range, and that is against the defined Torsade incidents during observation, or to a degree of confidence we know that the Torsade incidence in the .8 percent range.

And I don't even know what the time frame is that that represents, exactly. So we don't really know to what extent Torsade or lethal Torsade is hiding within the Diamond population.

So, you know, in terms of what is the percent, you really have to look at, for example, the supraventricular arrythmia data set, you know, again where you have 12 deaths out of 1,300 patients, about half as many in the placebo, so maybe it is .5 percent lethal arrhythmias occurring, maybe it is, maybe it isn't, because the number of events is pretty small.

So we don't really know. I mean, it is -- we know it is finite, I would not believe that it is zero, it is probably -- no reason to believe it is any worse than Quinidine, my guess is it is better than Quinidine.

But the good news is, here, we know tremendously more about it, and what we might, and an

approach to dealing with it that we don't' have with other antiarrhythmics that we have.

So I don't know if that answers B or C at all, but that is my feeling about the whole subject.

ACTING CHAIRMAN CALIFF: Tom?

DR. BIGGER: -- real world setting in which they did this, they didn't encounter a lot of problems. I think actually doctors, when they read this label, the way I envision it is going to look, are going to go low on the doses, anyway.

ACTING CHAIRMAN CALIFF: Ileana?

DR. PIÑA: I agree with Tom. I think that if used properly the out of hospital malignant arrhythmias may be small. What would happen in prescribing is less careful, I really don't know, but I suspect that there would be more proarrythmic events if people get careless with higher doses.

DR. D'AGOSTINO: I think the 5B, the 5C, could potentially be quite high, and this is what I was concerned about in terms of the second study is, were they going to go higher and higher to get the effect.

I think the way we are talking about start off with a low dose and build up, if it is done like that, and held, again 5B will be low, and 5C has potential of problems, but there is nothing more that we can say then I think that we could possibly have serious problems.

ACTING CHAIRMAN CALIFF: Joan?

DR. LINDENFELD: I agree, I think B will be low, although I don't think it will be as low as in this study, because I think there is a difference, from regular clinical practice in having a coordinator making sure that these things are done in each visit.

I think C will be higher. The one thing that concerns me here is that we don't see with Quinidine, is the problem with renal failure, the patient with severe heart failure who comes in with a doubling of their BUN and creatinine, which will affect this drug a lot more than Quinidine.

ACTING CHAIRMAN CALIFF: Well, I would say to B that I would guess more like -- there will be more like the clinical trials, since the trials tended to be more real world than other clinical trial

packages that we have seen, which I think is a very important part of the development program. I agree with Tom.

And C could be a disaster if not handled very well. Just the incredible use of Quinidine that we saw this morning probably is a tremendous disaster, I would say.

So it is a concern. And I guess the message we are giving is that if this was allowed out, it would need to have a very careful program of some kind.

We move on to 6, which is really oriented, Peter, as you see, to the question of how do we weigh this against other agents which are currently in use.

DR. LIPICKY: Since time is flying, I will just -- this could have been a very interesting discussion, but your answer to these questions could be as simple as, how the hell do we know, they didn't do anything head to head.

It could be a very interesting set of discussions that would rely on a bunch of stuff. So use your head how you are going to --

DR. KOWEY: It is a good thing to use. Actually, I was going to answer all three at once, because I think they are all part of the same -- rather than trying to do each one separately, because I do think your -- I think you are probably right, although there is a little bit more you can add.

If you look at the Sotalol comparator in the 345 trial, it looked like the drug was -- Sotalol was in the middle of the pack in terms of those Kaplan-Meier curves that we saw.

But that is not really a dose of Sotalol that we use in real life for atrial fibrillation. I mean, we usually use higher doses than that, and that is probably why they didn't see any Torsade in the Sotalol arm.

So the answer to the question, I would like to be able to see comparator data, I thought I was, when I first started reading 345 and got a little excited and thought we would actually see some data. But I don't think they include anything from that.

I do think that looking at its non-proarrythmic side effect profile that, clearly,

without a comparator trial, I don't need one, thank you.

But it clearly is better tolerated than most 1A drugs, and probably better tolerated than Amiodarone over the long term, because we just simply didn't see any, or very much in the way, we already admitted that, side effects.

So I think C is probably -- it is superior. A and B I think I agree with you Ray, I'm not really getting the feeling that we can answer that question adequately.

ACTING CHAIRMAN CALIFF: Cindy?

DR. GRINES: I think I agree, in general. I just wanted to ask the sponsor, I think it was in the FDA review they talked about small trial compared to Quinidine, and they commented on more discontinuation due to some test results in the drug arm compared to Quinidine. And the number that I wrote down here is 23 versus 12 percent.

But I don't know which trial, specifically it was.

DR. RYDER: I believe that was a small PAF

study comparing Dofetilide. Do you recall the dose? 250 micrograms to Quinidine, and the dose of Quinidine I don't recall.

DR. GRINES: But what were the test results that resulted in 23 percent of patients having the drug discontinued?

DR. RYDER: We will have to check that.

DR. GRINES: Okay.

ACTING CHAIRMAN CALIFF: Tom?

DR. GRABOYS: I can't answer A, probably not to B, and yes on C.

ACTING CHAIRMAN CALIFF: Marvin?

DR. KONSTAM: I agree that I can't answer A. I think with regard to B, I can't really answer it, except to say I do think that we have an approach to dosing of this drug that I believe is going to -- if adhere to rigorously, will be less proarrythmic than what we have out there.

So I think given -- in that context I think it has the potential for being less proarrythmic.

And I think that as others have said, that

non-proarrythmic side effects are considerably less than the other drugs that we have available.

ACTING CHAIRMAN CALIFF: Tom?

DR. BIGGER: I took this on by just thinking about the literature, and I think for 6A that it doesn't seem to be markedly more effective or less than available therapy, that is pretty clear to me that it was true.

I don't think it is markedly more proarrythmic than drugs we have available to us, and it has some other toxicity seems to be lower, aside from the proarrythmic type.

And I didn't think the proarrythmic side effects were more prominent than available therapy. That is not giving a great recommendation, however.

ACTING CHAIRMAN CALIFF: Ileana?

DR. PIÑA: I personally can't answer 6A or B definitively. I agree that the side effect profile here is, at least in my experience, much more acceptable than what we have right now with the drugs we have.

DR. D'AGOSTINO: No to A and B and C I

don't know.

DR. LINDENFELD: I think A and B are about the same, and C is better tolerated. I think A and B is about the same as what we have now, probably.

DR. TEMPLE: Rob, can I ask something? Every large trial I know about involving Quinidine showed that it was worse than -- that it was highly proarrythmic, lethal, and all that.

Here you have the Diamond trials and they show nothing like that, nobody is impressed by that?

DR. GRINES: Yes. I would like to comment on that. You know, a lot of these Quinidine trials were done back in the era when nobody recognized proarrythmic effect, and they weren't monitoring QT intervals.

I think this is very different, these patients were very highly selected, they had the drugs discontinued, or decreased for the, you know, numerous reasons.

DR. TEMPLE: Absolutely. I meant when used as it was used, all those other drugs, nobody knows how to use them, or at least not that anybody

can say.

DR. GRINES: Right.

DR. GRINES: Well, I would hope now that if I had a patient with Quinidine and they had a long QT interval I would do something, or if they had a proarrythmic event I would stop it.

DR. TEMPLE: It is not that that couldn't be, but the only attempts to pool available data with Quinidine have shown disastrous outcomes.

ACTING CHAIRMAN CALIFF: Well, my answer was going to be related to that, which is markedly more effective. I wish we had a head to head trial, I can't say, does it appear to be more proarrythmic? It looks markedly less proarrythmic than Quinidine the way it was used.

But I think we are caught between not knowing whether this is intrinsically badness of Quinidine, or just absence of knowledge about Quinidine.

So if the question was, is a less proarrythmic than Quinidine used in the absence of current knowledge, the answer is clearly yes, in my

opinion. Could the Quinidine problem be corrected? We just don't know, because it hasn't been looked at, but we would like to know.

And I think everyone has answered C, that looks like less side effects.

So we come to 7 and 8. We could go step wise, Ray, or could we answer 7 and 8 together?

DR. LIPICKY: Sure. You can answer them together.

ACTING CHAIRMAN CALIFF: Because I think we've agreed on the efficacy side for both 7 and 8, that the evidence is there.

Now we come down to the balance. Should it be approved for use in all patients, or for use only in some subset of patients? If so, should it abe approved.

DR. LIPICKY: 7 and 8 are, do you want to approve conversion, and 8 is do you want to approve prolonging the time to recurrence. And you can put both of them together and get a simple yes or no answer, if you wish. Is the whole package approvable or --

DR. TEMPLE: But if you didn't want to approve maintenance you would never approve conversion.

DR. LIPICKY: No, no, no. Ibutilide was approved for conversion and it had no maintenance regimen at all. It doesn't have to be.

ACTING CHAIRMAN CALIFF: Let's try them both, and if it doesn't work we will go back.

DR. KOWEY: I would vote yes for both.

ACTING CHAIRMAN CALIFF: Cindy?

DR. GRINES: I think I'm going to vote no.

ACTING CHAIRMAN CALIFF: Do you want to elaborate, since --

DR. GRINES: Well, I agree that it is efficacious, but I'm just concerned that we don't -- I mean, if you read into 8A, and some of the qualifying statements I would make if I did recommend approval, I can't even qualify it, because I haven't seen the breakdown of these highly symptomatic, or various subsets of patients.

And so rather than, you know, dig myself in a hole I would have to say no.

ACTING CHAIRMAN CALIFF: Tom?

DR. GRABOYS: No.

ACTING CHAIRMAN CALIFF: Marvin?

DR. KONSTAM: I am going to vote yes. You know, but we are being asked -- we are voting on both at the same time because I think we are also being asked, in all patients, or with subset of patients. And I wouldn't approve it on all patients in --

ACTING CHAIRMAN CALIFF: No, that is the next question.

DR. KOWEY: Let me just make sure that I stipulate that as well. The question is, is it approvable? But we haven't talked about what populations, or what labeling, or anything like that yet?

DR. TEMPLE: Yes means under some conditions for some population, no means under no conditions for any population, right?

DR. KONSTAM: Yes.

ACTING CHAIRMAN CALIFF: Tom?

DR. BIGGER: Yes, I would think it is approvable.

DR. PIÑA: Yes.

DR. D'AGOSTINO: Yes.

DR. LINDENFELD: Yes.

ACTING CHAIRMAN CALIFF: I would also vote yes on that question. So we now come to the issue of, should it be approved for use in all patients, or for use only in some subset. And for those who voted no, it is not that you are out of the vote here, I think.

I think we are all still interested in your opinion on this.

DR. KOWEY: This is, obviously, the most important part of this discussion, from my point of view, because it now gets into the question of how this drug is -- this is the beginning of the discussion about labeling.

My own opinion about this is that I don't -- even though the FDA reviewers have felt fairly strongly about this, and have actually put forward, I think, a fairly cogent argument that it only should be in patients with class 2/3 neocard association class, for example, I don't agree with that.

I think the data really do extend across

most functional groups, or all the functional groups that were examined. I think it would be inconsistent, at this point, to limit it, especially if one looks at risk benefit.

And we have already said that we think there is more risk in those patients that have LV disfunction. So I would, as I -- I guess that is a long winded I would vote that it should be approved, potentially, for patients with and without structural heart disease, pending further discussion about other labeling issues.

DR. KONSTAM: Goodbye, Dr. Califf. I've been asked to take over the chair.

Can I just ask Bob and Ray, the people who voted no should -- you want their opinion about what subsets they would approve it? I'm not sure what the logic about it --

DR. LIPICKY: Sure. It really -- they voted no because they were worried about something, and they were probably worried about something for some particular reason, and that would contribute to this.

DR. KONSTAM: Right, but I assume that if they voted no they are saying there is no subset of patients in which they would approve it?

DR. LIPICKY: Well, that is --

DR. KONSTAM: Is that not true?

DR. GRINES: Well, I guess --

DR. LIPICKY: Under any condition. There was no subset under any condition. There may be some subset under some condition.

DR. KONSTAM: Do they have to go back and change their other vote to yes? If we could get them to do that?

DR. LIPICKY: Well, that is how it happens sometimes.

DR. KONSTAM: Cindy is there some population that you are thinking about --

DR. GRINES: Well, I guess so, we've tossed around a lot the symptomatic patient, and I agree that there are patients who are very symptomatic, low cardiac outputs, and need the atrial kick, etcetera, that could potentially benefit from a symptomatic standpoint.

And I guess the reason I voted no was due to my concern about proarrythmic effect, and also the fact that we weren't able to see the data on that population.

And so it is very difficult for me to even suggest a population without having any data to support that.

DR. KONSTAM: So there isn't any population that you think is close?

DR. GRINES: No, I think theoretically, theoretically there are a number of patients who may benefit. I just don't think that the data that has been provided allow me to vote in that direction.

DR. KONSTAM: Bob?

DR. GRABOYS: I just don't trust the physician population out there. I think that is my concern. And that the large fraction of folks with atrial fibrillation, AF is a benign problem, meaning you put a patient on anticoagulants, you do -- you effect rate control, it is a benign situation.

But I can see that benign situation all of a sudden turning into a malignant situation because of

a drug that has significant potential for proarrythmia or Torsade.

DR. KONSTAM: Bob, did you have a comment?

DR. TEMPLE: Yes, I just wanted to say, there can be a number of reasons that you might want to limit a population, and at least in some cases we haven't always thought you needed data.

For example, if on safety grounds you want to reserve a drug only for people who were intolerant of another drug, we've not insisted that you literally prove that there are people who are intolerant of the other drug and then study them, because it was perceived as somewhat obvious that as long as there are people who are intolerant of another drug they are probably not intolerant to this one, too.

You could argue those points, but one could do it. So if someone thought here that these risks are acceptable only in people who are significantly disabled by their disease, you could recommend that to us, even though you don't actually have a population of people who were disabled by their disease on the grounds that it is obvious if they are

disabled by being in fibrillation, then they have more to gain from that.

So you could do that even though we don't actually literally have that population. It would be not so easy to find that population, unless they are a large fraction of it. But we could listen to that recommendation, even though you don't actually have data, if on safety grounds you thought that was a reasonable limitation. Now, you might not think that, but you could.

DR. KONSTAM: Tom?

DR. BIGGER: Well, I'm looking at this large data base which is more than we usually see, and I would be willing to approve it for symptomatic patients who are, in the judgement of the physician, the benefits outweigh the risks.

DR. KONSTAM: Ileana?

DR. PIÑA: I would agree with that. I think symptomatic patients, where the benefits of conversion to normal sinus rhythm is desired, and I would also look at the Diamond data. I mean, it is a very large body of data of patients with ventricular

dysfunction. And I think that is very powerful data.

DR. KONSTAM: Ralph?

DR. D'AGOSTINO: I think it should be approved for all patients. Obviously you have concerns about how you would treat individual subsets, and so forth, but I think the approval should be for all patients, which are chronic AF.

DR. KONSTAM: Joan?

DR. LINDENFELD: I like the statement symptomatic patients, I think that -- at least then hopefully we are subjecting patients who have a greater potential benefit to the risk of the drug.

DR. KONSTAM: I'm going to come down fairly close to what Tom Bigger said. I would not approve it in all patients. I would approve it for patients who were significantly symptomatic, and/or limited by atrial fibrillation, and exactly the words that he used, in whom the physician's judgement is that the risk benefit ratio warrants its use, even considering the risk of Torsade.

Bob?

DR. TEMPLE: Those are somewhat different

answers that people have given. I don't know if you want to try to get together and resolve them, or just leave us with that.

But everyone agreed -- almost everyone agreed it should be for people who are symptomatic. But symptomatic could mean an occasional palpitation, symptomatic could also mean, I think about it all the time, my life is poisoned.

Any other comments from -- or we can hear a range of views, and we've heard that. I just wonder if anybody who said symptomatic wants to respond to the more stringent symptomatic description than Marv just gave.

DR. KOWEY: I would like not to do that. I would actively like not to do that, because I think we are going over physician judgement, and really something Tom said a little bit earlier about how devastating this disease can be to people who may not necessarily have provable hemodynamic compromise, for example, but whose lives really are sometimes ruined by this arrythmia.

And it really is necessary not just to

counsel them, but also to get them out of it.

DR. KONSTAM: But, Peter, why is that different from what Bob just said?

DR. KOWEY: No, he said significant symptoms and I don't want to get into a discussion. I personally don't want to get into a discussion of what is significance. I don't think that is something that we should do.

I think we should just tell the physicians, if the patient is symptomatic, and in your judgment that patient will benefit from being in sinus rhythm, and the benefit outweighs the risk, then that is when the patient should get the drug.

That is what I think.

DR. TEMPLE: Tom, is that what you meant?

DR. KONSTAM: I'm not sure we disagree. I mean, Peter, what you just said is there are some patients -- I think you said something like there are some patients who are going to be devastated by having atrial fibrillation. And something like that.

And why is that different from saying, I mean --

DR. KOWEY: Because I've been at other meetings like this where we've gotten into discussions of trying to define what we mean by significant symptoms. And it really becomes a trap, in some extent, that you can't -- it is really very hard to do that.

DR. LIPICKY: You would get into which symptom is significant, how you can tell that it is significant, and what kind of documentation --

DR. TEMPLE: You don't have to. You don't have to. There is more than one way to do this. But say symptomatic is one thing, to say symptomatic in a way that really severely affects the patient's existence is another. I mean, there is a range of things one could say.

DR. LIPICKY: Yes, but what is the difference between those words? That is what Peter was saying.

DR. TEMPLE: Symptomatic mean I'm aware of my fibrillation because I have an occasional palpitation.

DR. LIPICKY: Yes. And the others?

DR. TEMPLE: Severely symptomatic is I think about it all the time, I can't exercise worth a damn.

DR. LIPICKY: But that doesn't differentiate it for me, okay? I mean, the same patient you described I think would be, unless there was some operative definition of what severe meant.

DR. TEMPLE: I'm just trying to find out what message the committee would like us to --

DR. LIPICKY: Peter said he didn't want to do that.

DR. TEMPLE: There have been several different things, they are not identical.

DR. LIPICKY: Well, I haven't heard another suggestion yet.

DR. GRINES: Lifestyle limiting.

DR. KONSTAM: What about the concept that Tom said of wording with regard in whom is the physician's judgement that the risk, that the benefit outweighs the risk, or the risk of Torsade.

DR. TEMPLE: We have certainly used language like that, that is another version of how to

do that.

DR. KONSTAM: The problem with that is we don't know exactly what the risk of Torsade is. Maybe we do.

DR. BIGGER: Well, they are going to put it in.

DR. TEMPLE: Just to further check on the reasoning. My assumption is that the people who are comfortable with this are comfortable, at least partly, because the Diamond data is reassuring.

Is that part of everybody's -- the Diamond study data is moderately reassuring on these questions, and that is why people who are comfortable with this are comfortable with this.

DR. BIGGER: Yes, that is true, but if you -- let's just stop and think, you know, there is a bunch of risks listed up there, and there is all this stuff about the drug interactions, and unknowns in this region, and Torsade is a major issue here, so I will be thinking like, is the benefit of giving it for afib, that way the risk of Torsade, because that is the only risk we really --

DR. TEMPLE: I understood that. For example, Peter, who didn't want to be too precise, and you don't want to be too precise about what the risks should be, I'm asking whether that is because you take some assurance from the Diamond data that the risk isn't awful?

I'm just trying to check the reasoning. Okay.

DR. KONSTAM: Okay. Maybe we can go on to 8B. What sort of program, if any, should be instituted to determine what fraction of patients receiving Dofetilide in accordance with the recommended dose finding scheme should form mechanisms perhaps similar in spirit to the no blood/no drug scheme used with clozapine be implemented to reduce the likelihood of non-recommended prescribing and dispensing practice.

Peter?

DR. KOWEY: I like the idea of having some mechanism to ensure this. I think Bob already said that there are lots of different ways to do that. I kind of trust you guys -- yes, I mean, it really is

breaking new ground, and I honestly can't say that I understand how easy or how difficult it would be to implement those things.

I don't know, I think what you want to hear from us, should you? The answer is yes, I think you should. And the thing that really makes me very concerned about this is the creatinine clearance.

I think that issue, more than anything else, stands out in my mind as a stumbling block to adequate use of this drug, because it is such a key element.

It is foreign to doctors, doctors don't know how to do it, they don't do it, they don't think about it, they always look at the creatinine and they make assumptions about the creatinine clearance serum.

And you guys are saying something that isn't completely and utterly different. And I think the other thing that is different is the way the dosing is going to go on in the initial phases. This requires a very intense educational effort, which I'm sure that this company is going to undertake.

I just want to make sure that everybody

understands how important that is, that it be done at a very high level, and very thoroughly. I'm very concerned about it.

DR. LIPICKY: But, Peter, so that I understand what your recommendation is, or why it is, should we also do that for Quinidine?

DR. KOWEY: If I had my druthers? Yes. I think we should educate doctors about how to use Quinidine.

DR. LIPICKY: Right. But I guess I want to be sure I -- you know, we do require studies like were performed, okay? But it almost seems like you are better not doing those studies, because then you don't have these horrendous requirements imposed upon you.

And I would like some reaction to that.

DR. KOWEY: I don't think that is entirely fair. I think that when I give a talk to a medical audience about atrial fibrillation, or when I do in the future, and this subject comes up of how to dose Dofetilide, it certainly is not going to be without some mention of how you dose Quinidine or

procainamide, or disopyramide.

I think something Tom said earlier about don't underestimate how naive doctors are to drug dosing, you can't underestimate their naivete. And for that reason -- I'm not holding these guys to the fire any more than I am anybody else, they just happen to be sitting here today.

DR. LIPICKY: Right. But I guess I'm just trying to differentiate between what the impetus is. There is clearly more information here with respect to what you ought to do.

And the question is, why does lack of information make one not want to monitor other drugs too?

DR. KOWEY: I didn't say that, I didn't say that I didn't want to monitor other -- of course I want to monitor other drugs. But these guys are coming up with a specific way of doing it that is novel to physicians. Physicians don't use creatinine clearances, is the point that I was making.

And so for that reason, talking about this particular drug, and this particular way of dosing,

they have to make sure that that is done in a way that physicians will understand.

DR. LIPICKY: Because their data convinces you that that is what should be done?

DR. KOWEY: Oh, they convinced me, yes.

DR. LIPICKY: Yes. Because you saw what happens if they don't do that?

DR. KOWEY: Yes.

DR. LIPICKY: And that was in the one 750 milligram --

DR. KOWEY: I think Craig Brater showed me enough data to make people believe that if you don't dose the drug properly, and you don't pay attention to the creatinine, you don't know what the creatinine clearance is, or you overestimate the creatinine clearance, that you will drive the QT interval to ranges where you clearly will have a higher Torsade risk.

So I don't have any problem believing that, that is easy.

DR. LIPICKY: Okay, fine, thank you.

DR. KONSTAM: You know, Ray, I think this

is interesting --

DR. LIPICKY: I believe him.

DR. KONSTAM: I just was going to say -- I think is the issue here that -- or maybe this is a corollary to what you are saying is that some people around the table may believe that we are sort of in better shape here than we are with Quinidine because we have a lot more data here, and we actually have an approach. And that might be a good thing, and might, even under those conditions some of us, I think, believe that is less proarrythmic than Quinidine.

And given that I guess it is worth considering what impact whatever we say in answer to this question is going to have on the relative use of this agent, versus the use of Quinidine, which we may think is less safe.

So I guess that is sort of the issue.

DR. TEMPLE: Yes, I mean, there is a sort of warrant here, that if you use it the way we tell you, things will work out pretty well, we have all this data.

But if nothing is done to make sure people

can actually do that, then the warrant is misleading.

DR. KONSTAM: Cindy?

DR. GRINES: Yes, I'm all for having creatinine clearance mandatory, but also the follow-up ECG, I think, will have to be considered, and this three day hospitalization. 75 percent of the Torsade apparently occurred in-hospital, and somebody said, you know, maybe you can discharge them earlier than three days, but we don't know that, we haven't seen actually when the Torsade is occurring in hospitals.

So -- I mean, those are the three big things that I think will be important.

DR. KONSTAM: Tom?

DR. GRABOYS: Nothing to add.

DR. KONSTAM: Tom Bigger?

(No response.)

DR. KONSTAM: Ileana?

DR. PIÑA: I am as concerned about physicians not doing creatinine clearance calculations as I am about improper measurement of QTs, specially when you have a patient with afib where the R/R interval is varying all over the place, and they may

not know which R/R interval to pick, to measure the QT, and I heard the sponsor, who had given the, I think, mandate or suggestion in the protocol that there be, you know, X number of R intervals measured, and then an average taken.

So I don't know how tight you can get in the recommendations to put something about the QT. But I think it can't be ignored.

And I think it may at least remind physicians that they need to do it, and if they don't know how to do it, maybe they will go find out how to do it, and do it right.

DR. KONSTAM: Joan?

DR. LINDENFELD: I think there needs to be some reminder, some stimulus, I'm just not sure what it is. It will be easy in the hospital, you can just put in a policy that you have to order Dofetilide with a creatinine clearance, and check the QT three hours later, in-hospital will be easy.

I think the harder thing will be out-patient, I don't know what it is.

DR. KONSTAM: I guess I just want to add,

to say that every -- to the degree with which we've developed a comfort level around the safety issues here, we've done so in the context of dosing and monitoring, as has been done in the clinical trials, and therefore I think it is forging new ground.

But I think we have to forge that ground, and I think we have to say that if we don't do it that way, we have no idea what the risk is going to be, and we should make every effort to do that, and I'm not sure that we have really answered exactly how we are recommending to do it.

I think there were a couple of different, the point about -- and I would add to what has been said, maybe somebody did say, that we should do something specifically to assist in the calculation of the creatinine clearance. And I don't know exactly what that is going to be.

We heard about nomagrams, but something other than just an educational program. And I would like to see some kind of a surveillance of how effective whatever program that has come up with is.

I guess I would add, in spirit, that I

would like to try to do that without persuading people that Quinidine is more safe than Dofetilide. So I'm not sure exactly how to do that, too.

DR. LIPICKY: I guess I would just like to get a feeling for whose responsibility you think that is. That is, is it FDA's responsibility to be sure that doctors use every drug that is approved, correctly; and should they have some kind of an inspection system that goes through the hospitals and looks at prescriptions, and stuff like that; and then sues them or something, if they are not doing it right?

Whose responsibility is this, where does the state society fall into this, where do medical schools fall into this, where do the attending physicians fall into this?

It is not clear to me that you have made a -- although I don't disagree with anything that has been said, it is not clear to me why it suddenly is FDA's responsibility to ensure that doctors use the drugs properly.

And I know one shouldn't sort of say here

is a car, drive carefully, you know? That is not being responsible.

On the other hand it isn't clear to me that outside of some really -- whose responsibility this is. And you have just laid it at FDA's feet. I don't know if you did that inadvertently, or purposely.

DR. LINDENFELD: Ray, I personally feel that it is a physician responsibility to make choices, and to take the responsibility of the consequences of those choices. However, in hospitals, and in medical schools, there are overseeing committees of the proper use of drugs.

JCAH, Joint Commission, comes down very hard on pharmacy and therapeutics committees that don't have drug usage and evaluation committees, so this is --

DR. LIPICKY: I understand, but in your response to this question you just laid it at FDA's feet, and we are going to try to do something. Bob?

DR. TEMPLE: Not entirely FDA's. I think they've asked us to make sure the company puts in

place labeling and facilitating efforts that might make it happen, whether we should be sending letters to people is another question.

For what it is worth, a lot of people are raising questions just like this. You know, there have been publications citing 100,000 adverse drug reaction deaths per year, and there is at least some implication that this is our fault.

We don't entirely believe that, we think it is, you know, everybody else's fault. But the question could arise, can labeling maneuvers, patient labeling, and other things, make that better?

And we are actively thinking about this. For what it is worth, when we hear about a mixup, because people don't realize how many milligrams there are in a vial, and they inject the whole vial instead of some smaller amount, we feel obliged to make sure the labeling is changed right away. The company does it, of course.

So that those mixups won't happen, even though you could say if people were paying reasonably adequate attention, those mixups wouldn't have

occurred.

So we and the people we regulate have at least some role in that, I would say, and there is a lot of public discussion about how much of that role everybody has, and how much we should be doing.

DR. KONSTAM: Tom?

DR. GRABOYS: We come as a body to advise, and there is a whole host of kind of sociologic, and ethical, and moral issues here that obviously come out.

The fact is that I think the sponsor has to put the fear of God into the user of the drugs, the physician, that all these terrible things could happen, and therefore it is the physician's responsibility, but it is clearly the sponsor's responsibility, and the FDA's responsibility to enact this.

DR. KONSTAM: You know, I would like to answer it a different way. I think if you are really serious about influencing serious about influencing physician behavior, and if you feel like it is the FDA's role to influence physician behavior then,

really, I don't know how you would do it without having some way of judging the effectiveness of what you've done to influence that behavior, otherwise you have no idea what the impact is.

DR. LIPICKY: But if I said I don't think that is FDA's role, then what?

DR. KONSTAM: Should we ask that as a formal question of the panel?

DR. LIPICKY: You might. You really want me to influence what you do in your practice of medicine, is that what you are saying?

DR. TEMPLE: Ray, the trouble is we do it all the time.

DR. LIPICKY: I understand that. But this is -- we do it by making things available. They are asking, at the moment, for us to do things that are directive, thou must not, or thou shalt --

DR. TEMPLE: In the form of labeling that says that, and in the form of urging the sponsor to provide some way of calculating creatinine clearance, fairly conventional methods, if a little more aggressively --

DR. LIPICKY: Well, if it is limited to that, that is okay. But that, you know, how do we know that that influences anything?

DR. TEMPLE: Perhaps asking the sponsor to visit some hospitals and see how it is going. Those are all within the range of things that have been done.

DR. LIPICKY: Where do medical schools fit into this whole business of sort of making sure that physicians know what they are doing. Why does it all fall on drug companies?

DR. KONSTAM: I just want to say that I'm beginning to sense a certain degree of lethargy by the panel, so -- you guys are -- so the question -- I mean, we will take it as far as -- have we helped you enough on this, or not?

DR. LIPICKY: Yes, you have, indeed.

DR. KONSTAM: 8C, what recommendation if any should be made in labeling as to anticoagulation during sinus rhythm in patients who have been converted from chronic atrial fibrillation and are being maintained on Dofetilide?

Peter?

DR. KOWEY: None.

DR. KONSTAM: Cindy?

DR. GRINES: I believe that they maintain anticoagulants in the atrial fibrillation trials. Is that correct? And so I --

DR. KOWEY: In the firm the design is that the investigators are not really told to discontinue anticoagulants. So it is not mandated, necessarily, but they are not told to stop.

Let me just amplify it. I was probably being a little flip in just saying none. But this is another area where we don't have enough signs to answer this -- there is no signs to answer this question, there has never been a study to answer this question.

And so it really isn't fair to answer this question for Dofetilide when we don't know about any other antiarrhythmic drug. So it is just -- it really would be a quagmire to get into this. I think it is just leave it alone.

DR. GRINES: Yes, bargaining unit don't we

have guidelines on conversion of atrial fibrillation and anticoagulation? I mean, we could merely quote the guidelines, or quote the fact that in these trials we --

DR. LIPICKY: We don't write textbooks that have clinical gospel in them.

DR. GRINES: Well, we have a lot of doctors who don't know these things.

DR. LIPICKY: I understand. That is your problem, not ours.

DR. TEMPLE: Well, Ray, we could certainly be describing what was done in this population, and if it is of concern say that it is not known that it is safe to stop anticoagulants. I mean, there are some things one could do to describe your lack of knowledge.

DR. LIPICKY: It is also not known that it is safe to continue them. So we should say it is just unknown, not that some one part is unknown.

DR. TEMPLE: Well, anticoagulants are known to prevent serious consequences in atrial fibrillation.

DR. LIPICKY: Only if you get your I&R measured at weekly intervals in your local I&R shop. And if you don't do that, you are in real trouble.

DR. KONSTAM: Can I just -- I mean, this strikes me, the question seems not quite in place. I mean, you know, if the question is should the FDA -- should the panel recommend a set of guidelines on anticoagulation in atrial fibrillation, wouldn't we want to spend a day discussing that, and put some data into it?

DR. LIPICKY: Or longer. The full expectation was, Peter's answer is none.

DR. GRINES: Well, I don't know, I think if we are going to make a recommendation about --

DR. LIPICKY: Okay, but we thought we would give you some --

DR. GRINES: -- QT intervals, why not make one about anticoagulation? That is the standard, to anticoagulate when you are cardioverting somebody, and continue that anticoagulation after --

DR. LIPICKY: But you have no information to give any recommendation on the basis of. There is

nothing in these trials.

DR. GRINES: Not in these trials, but in atrial fibrillation trials.

DR. LIPICKY: That is the only trials we have to write Dofetilide's label with. We are not going to, I don't think, or maybe we will, I should ask Bob, we are not going to talk about how you can avert stroke with anticoagulants in Dofetilide's label.

DR. TEMPLE: No, you don't have to do that. The only point that seems pertinent here is that it might be worth telling people we don't know. If your patients were already on anticoagulants, we have no information about whether --

DR. LIPICKY: As to whether to continue them or not.

DR. TEMPLE: -- while you are using this stuff it is okay to stop them, we just don't know.

DR. LIPICKY: Or whether you should continue them or not.

DR. TEMPLE: We don't know --

DR. LIPICKY: We don't know either one of

those.

DR. TEMPLE: Right, right. But it would be worth telling people that, I think.

DR. KONSTAM: Can I ask the panel? Peter said no, I think Cindy said no.

DR. GRINES: Wait, I didn't say no.

DR. KONSTAM: You didn't say no?

DR. GRINES: No, I think you need to --

DR. KONSTAM: You didn't say no?

DR. GRINES: No, I think you need to --

DR. KONSTAM: You said yes?

DR. GRINES: I think that if everyone of these trials they anticoagulated them before -- for 14 days beforehand, plus they continued anticoagulants. For us not to even mention that, I don't think is right.

DR. KONSTAM: Okay. Tom?

DR. GRABOYS: No. I don't think we have to deal with it.

DR. KONSTAM: Tom?

DR. BIGGER: None, but it is a conundrum, really, but I would trust Bob and Ray to come up with

the right words for it.

DR. KONSTAM: Ileana?

DR. PIÑA: I wouldn't make any specific recommendations, but I do think, as Bob said, you can say in the study anticoagulation was continued, period. In other words, exactly describe what was done here, and that is it, and leave it at that.

DR. LINDENFELD: I agree with what Ileana just said.

DR. KOWEY: Is it in anybody else's labeling, Ray? No.

DR. LIPICKY: Well, I don't know that any of the trials -- you know, there is only one other drug, and I don't know that the Quinidine --

DR. KOWEY: -- and Flecainide?

DR. LIPICKY: No, it --

DR. KOWEY: It is for PAF. But I'm saying, is there any data about anticoagulation in any drug like that?

DR. LIPICKY: No. Well, it wouldn't be in the PAF stuff, and Quinidine is the only --

DR. PIÑA: I don't think the first PAF

trial was out when Flecainide was approved. Flecainide was approved before the first PAF trial data would have came out.

DR. KONSTAM: I am going to answer no, but I'm going to do it with discomfort, because I think that there might well be something to say about this, and I'm not prepared to say it.

And I think that if you like -- if we want to address this seriously, I mean, I would propose that we do it with some data in front of us, and have some discussion about it.

9, if Dofetilide is approved, what if any post-marketing commitments, interaction studies, studies in special populations, head to head comparison trials should be sought from the sponsor.

Peter?

DR. KOWEY: The FDA, by the way, did a very nice job of summarizing things in the background package that we received. And one of the things that Shaw Chen said in his review was that it would be nice to have, it would be nice to tell the sponsor to go out and do a head to head comparison with Quinidine.

Somebody has to do that, but it is a daunting task, and I don't think that we should make that a condition for approval, and I don't think we should necessarily mandate a post-market. I think somebody should do that study someday.

But the studies t I think are more important, and can be done, and should be done post-marketing are interaction studies. I'm still very uncomfortable with what we know and what we don't know about patients who -- specially patients with renal impairment who receive poly-pharmacy.

And I think there is a whole -- I don't think we have time to really get into all the individual trials they could carry out, but I think that there are clearly some that probably need to be done.

DR. LIPICKY: By drug interaction do you mean pharmacokinetics?

DR. KOWEY: Pharmacokinetics.

DR. LIPICKY: Not pharmacodynamics?

DR. KOWEY: Not pharmacodynamics, pharmacokinetics interaction studies.

DR. KONSTAM: Cindy?

DR. GRINES: I agree.

DR. KONSTAM: Tom?

DR. KONSTAM: Yes, I agree. And until they are done, I think this part of the label should be pretty conservative. And that would, you know, motivate the studies that probably will make things more encouraging when you see some results.

But I think that is an area where there were concerns all day, and I think the kind of things that they agreed they ought to do, and we talked about, are in the minutes already.

DR. KONSTAM: Ileana?

DR. PIÑA: Yes, I think the drug/drug interactions and pharmacokinetics are very, very critical, because in the real world, particularly the patients with impaired renal function are going to be on a lot of other drugs.

I would personally love to see a head to head comparison with Amiodarone and heart failure patients, because that is a very commonly used drug today in heart failure for afib, and for other

reasons.

And you have this nice Diamond data, and I think that would be a great study.

DR. BIGGER: It would be nice to have in your label, someday, that we are better than Amiodarone, that would be a nice thing to have in there.

DR. KONSTAM: Joan?

DR. LINDENFELD: I agree we need to know some more drug data, specifically we've discussed Toltizim, I think that we have to know, and we may need to know that even before the drug is out, that is such a common drug.

But you can decide that. But I think the one that hasn't been mentioned, fluoxetine and paroxetine, they are commonly used anti-depressants that do have some 3A4 interaction. Since they are so commonly used I think we should know that.

DR. KONSTAM: Yes, I want to agree. I think the additional information about drug/drug interactions I think is mandatory in all of the ways in which potential drug interactions have been

identified, decytochrome 3A4 and issues of renal effects, and absorption.

And I think I would like to see more data with regard to all of those possibilities. And I also want to agree with Ileana's point about heart failure.

You know, I was just thinking that actually the medical reviewer suggested that we consider approving the drug in heart failure, as the population to approve it in. And at first that was a little tempting to me, but then I was thinking we actually don't know the efficacy of this drug in heart failure, and particularly since, again, the dosing regimen that was used in the Diamond heart failure study was different from in the populations where efficacy was documented.

So I think -- and that is a population in which we have the most to gain in terms of clinical effects, perhaps.

So I would like to see that. Bob?

DR. TEMPLE: You actually do have a little data from the Diamond component. Those people with AF were in heart failure. And they responded to a lower

dose. The other thing I will say is that we will certainly urge further examination of the population kinetic data base, especially to look for two factors at once, and they are plainly capable of doing that.

That will, I'm sure, give us some of the answers we are looking for.

DR. KONSTAM: Bob, correct me if I'm wrong. I don't think we know, somebody I'm sure will correct me, I don't think we know the efficacy with regard to effect on atrial fibrillation in the Diamond heart failure trial.

What we know is that there was a reduction in hospitalizations?

DR. TEMPLE: They do have data, it is like 47 percent at six months.

DR. RYDER: Dr. Konstam, we have data on two populations, one is the population who had atrial fib, the 50 patients, and then a certain proportion of them who are receiving Dofetilide or placebo went into normal sinus rhythm, and then we have the maintenance data in that population.

Shaw Chen refers to that, and the other

component is, there are a few patients, but still it is different between Dofetilide and placebo of the other part of the Diamond studies who did not have atrial fib but developed atrial fib during Diamond, and there are fewer in the Dofetilide group than in placebo, but Shaw Chen refers to this, and FDA, as you said, does examine this data.

DR. KONSTAM: Okay, I think we did it. Thank you.

(Whereupon, at 5:23 p.m. the above-entitled matter was concluded.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: 87TH MEETING

Before: CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

Date: JANUARY 28, 1999

Place: BETHESDA, MARYLAND

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.

Donna Willis

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