here --

DR. THADANI: No, no. On the board, yes. But we were discussing 05.

DR. KOWEY: I understand what you're saying. Yes, that's correct.

DR. THADANI: And I'm still a bit leery because symptomatic with a heart rate flowing, you're driving the episodes lower. If the patient doesn't have palpitation, he doesn't complain.

DR. KOWEY: Well, let me just put up --

DR. THADANI: But, if you have the data, we'd really like to see the data. That's what I'm saying.

DR. KOWEY: This is not a -- I would take issue with the fact that this is a problem only with the drug that has beta blocker problems. This is a problem in all clinical trials of all antiarrhythmic drugs and that is that patients, when they have recurrences, many times don't have symptoms. And you can look at Holter monitors and people on drugs for atrial fibrillation and be astounded.

DR. KONSTAM: Yes, that's true, Peter.

But here we have a mechanism that specifically will reduce heart rate.

DR. KOWEY: Sure enough. But the protection for the patient, as Tom's concern is a stroke. I'm going to point out for example, on AFRM, the NIH trial, that nobody's telling anybody to take anybody off an anticoagulant drug, even when they think that their rhythm controlled with an antiarrhythmic drug because of this fear of an asymptomatic recurrence no matter what drug you use.

DR. LINDENFELD: Well, the concern isn't just stroke. The concern is what we're showing to be statistically significant here is the time to onset of atrial fibrillation. And so, if this impacts the time to onset.

DR. KOWEY: You sort of can't have your cake and eat it, too, because in one aspect of this, is that the agency is very concerned about showing that there's some clinical benefit to reducing atrial fibrillation episodes. Well, the benefit that's most demonstrable in these studies is the reduction of symptoms. So, there has to be -- there has to be an

analysis of symptom in order to derive its clinical benefit.

So, you have --

DR. LINDENFELD: I don't think any --

DR. KOWEY: We agree that not -- having atrial fibrillation that's subclinical is not a good thing. But on the other hand, the goal of the trial is to prove that there was some clinical benefit to the patient which is reducing symptoms.

DR. LINDENFELD: I think the goal was to show a difference in atrial fibrillation.

DR. KOWEY: No --

DR. LINDENFELD: That's the primary endpoint.

DR. MARROTT: Mr. Chairman, I do have the answer to the question.

CHAIRMAN PACKER: That would be very helpful.

DR. MARROTT: We do have a Kaplan Meier curve addressing that issue which I -- we don't have a slide.

CHAIRMAN PACKER: We'll have our primary

reviewer look at this.

What we are looking at is time to first symptomatic or asymptomatic. This is any recurrence of atrial fibrillation and flutter. This is in Study 05. This is, I think, the issue which is at hand which is what asymptomatic recurrences look like. We'll just remind everyone that presumably the asymptomatic recurrences were picked up on the trans-telephonic monitoring done every two weeks.

Is this correct?

DR. MARROTT: Yes.

CHAIRMAN PACKER: And the -- this is 05. 05. 04, you already have seen.

DR. BIGGER: The only problem is that a symptomatic recurrence does not exclude the fact that the patient may have had an asymptomatic.

CHAIRMAN PACKER: This is time to either. This is time to either.

DR. BIGGER: But short of continuous monitoring, you're not going to know that.

CHAIRMAN PACKER: Well, but, it's every two weeks. I mean, you could make it every one week.

You could make it every four days. You can make it every -- You can put a Holter on for the rest of the life time of the patient --

DR. BIGGER: I know. We're getting back in terms of what are the clinical indications going to be potentially using a drug that has potential toxicity. And what is the -- what's going to be the clinical indications for use of the drug.

CHAIRMAN PACKER: It's a totally separate issue. Let's focus on the issue.

The issue is, the question that was raised was, if you included asymptomatic arrhythmias, what would the data look like.

DR. FENICHEL: That's always going to be biased, Milton, by even in the case where they are monitoring every two weeks if there is, in addition, sort of supplemental monitoring at the times that symptoms are perceived. So, it is, of course, going to be biased in the direction of a drug which is either bradycardic, or amnestic, or analgesic, or has some other censorium confounding properties that keeps people from bringing these symptomatic events forward.

This is the problem with any symptomatic claim that on the one hand when we approve antianginal, we want to say, okay, people are having fewer symptoms. Usually under a fixed stress, a treadmill or something like that. And then the reason that we don't approve ketamine and morphine, and lots of other -- benzodiazepines, lots of drugs that might confuse people and leads them to either override or ignore, or fail to perceive their anginal symptoms is say, no, no, no, it has to also be ischemic.

Now, here it seems to me a pure symptomatic claim is, and you'll be asked the question as to this, but it is certainly a possible claim saying this makes people feel better. We say, well, we could give people morphine. We could get people high on benzodiazepines all the time, they would probably would have fewer symptoms.

All right. You're got to then show this is an electrically active drug. That it indeed in some way can be shown to cause a reduction in electrical problems. But you don't have to show that in every patient. This is a symptomatic claim.

Now, what I guess Tom has pointed out is there are other possible claims. And if the change in the frequency of -- if the change in the frequency of atrial fib really didn't -- if there really were no change in atrial fib, that the only thing that happened were symptomatic changes, maybe the rate's a little bit lower or some other reason people don't perceive it, the presumably the risk of stroke has not really changed and you haven't effected that. Well, that's right. You haven't effected that. This is very much claim dependent.

CHAIRMAN PACKER: Yes, Bob, I agree with you. I think that the only reason, and I -- and trying to read the committee's intentions here, that we want to see the asymptomatic arrhythmias to understand whether the reduction in symptoms is related to a suppression of arrhythmias or maybe some other property of the drug. It's more of a internal set of mechanisms.

DR. KONSTAM: No, I would say it stronger than that, Milton. Because I think it will, to me, cut in the end directly to the issue of approvability.

I think for a couple of reasons. Mostly because when we get into the safety profile of this agent, there are going to be major issues raised. And I think we're going to want to know that its safety profile is acceptable given the specific mechanism that it achieves. If it's achieving its reduction in the recurrence of symptomatic atrial fibrillation because it's a beta blocker, then that will be important.

And on the other side of the coin is the issue that Tom raised. I think one could argue, well, all that matters is the symptomatic recurrence. But if that is interpreted by the clinician as meaning that the patient is not in atrial fibrillation, then that may influence the issue of anticoagulation.

So, I think this goes beyond an understanding. I think it will directly influence the approvability.

CHAIRMAN PACKER: Just so that everyone knows what we're talking about here because this slide isn't available and we are referring to it so it's important to know what we are referring to, the sponsor has presented to the committee, and we'll

circulate this up and down so everyone can see it, a slide that includes asymptomatic as well as symptomatic episodes. Time to first event in Study 05.

And I think that JoAnn can differ from the interpretation but I think what we're looking at is an overall splay of the curve, first time to event curve, which is fundamentally pretty similar to what we've seen for symptomatic events, with p values that, if anything, are probably a little bit smaller than the p values for the symptomatic events.

Would you agree with that? Okay.

And we will copy this and send it up and down, or we can just pass this up and down. Why don't we just pass it up and down.

DR. KONSTAM: So, I think, then, though it would be worthwhile spending a couple of minutes dissecting this out in terms of methodology. And I guess, and I think Bob spoke to this, is that it's even in the presence of the monitoring, it's an endpoint that's influenced by whether or not the patient has symptoms. And is there a way of sorting

that out, and maybe there is and maybe there isn't.

DR. PIÑA: Could I ask a question.

CHAIRMAN PACKER: Yes.

DR. PIÑA: Peter, you said in 05 that the patients who were -- who had impaired creatinine clearance for the most part weren't excluded. And patients with structural heart disease needed to be hospitalized to get into the study. Now, the patients that were hospitalized to get into the study, were they not on continuous monitoring? Where they not on telemetry?

DR. KOWEY: They were.

DR. PIÑA: So, is that data included here? I haven't seen these graphs yet, but you would have obvious --

DR. KOWEY: Yes. They would have been captured in the Kaplan Meier.

DR. PIÑA: So, this would include this monitoring here. It would have been before steady state but --

DR. KOWEY: But it would have been only in the early portion of the curve. But we're showing --

Milton, is that slide since randomization or, since I didn't see it, or presumed steady state? Do you recall?

CHAIRMAN PACKER: I don't have it in front of me.

DR. KOWEY: If it was since randomization, they would have been on a monitor. If it was presumed steady state, they may not have been on a monitor.

CHAIRMAN PACKER: Before we leave this, let me just emphasize that, and this is, I think, a correct observation. If you compare the slide which is behind us, which is the -- well, this is 04. If you look at the data in 05, on only symptomatic recurrences, and compare it to the graph with symptomatic or asymptomatic recurrences, and you just look at the exempt rate over time, it would appear to me that more than 90 percent of the events were symptomatic. Is that correct?

So, the number of asymptomatic events here is exceedingly small. Is that what one would expect or is that surprising? Tom.

If you look at the data and compare it to

page 26 of the briefing document, and you look at the percentage, the actual events, the shape of the curve, and how far -- how many patients are free of an event at any given point in time, it would appear as if the vast majority, more than 90 percent of the events in the curve which includes symptomatic and asymptomatic actually are symptomatic because they're already included in the graph on page 26. In other words, the curves don't come down. There isn't a greater failure rate because there's a lot of asymptomatic episodes being included. Is that something you would expect or not expect? In other words, the vast majority of recurrences here are symptomatic?

DR. THADANI: I think because it's a paroxysmal A fib, you're not surprised really. If you look at -- one way to look at it, look at the slide, see how many of these patients paroxysmal if they were symptomatic. Then you can find the incidence of some kind of symptoms were only 40 percent, 60 percent are going to be asymptomatic and not -- maybe (a), they are not in a fib when you're screening them every two weeks. You may not pick it up.

DR. KOWEY: Udho, the reason why it may not be just novel to the paroxysmal is the same data are demonstrable for the chronic. If you look at -- this is slide 30. Can I have slide 24, please.

This is the symptomatic since randomization in 04. And this is the same point Milton was just making which is that, if you look at the numbers here, patients in each of the curves. And then, if I could have slide 30. The numbers are nearly identical. So, this is for a chronic AFD. These are patients who had had a longer duration of AF. So, I don't think it's just because it was a sort snapshot of their arrhythmia that you weren't capturing.

I think patients who have chronic AF and have recurrences usually don't go in and out of AF. They go in AF. They stay in Af.

DR. KONSTAM: Well, let me ask whether that -- I'm not sure whether that reassures me or worries me. I mean, I guess, does somebody have some comment about -- I think Tom said something. The frequency with which recurrence of a fib is in fact

symptomatic. I think you in fact spoke a moment ago to the fact that most, or that a big proportion of patients with recurrence with a fib in fact is not symptomatic.

DR. KOWEY: But I'm encouraged --

DR. KONSTAM: And if that's the say -- Well, I'm saying if that's the case, I guess it raises concerns about the effectiveness of the monitoring process here.

DR. CALIFF: Ed has written a bunch of papers about this. It would seem like it would be worth hearing from somebody who has actually studied it rather than having opinion.

DR. PRITCHETT: The study that Rob's referring to is the study that Rick Page did in my laboratory in which we took patients who had symptomatic atrial fibrillation and were trained to use a trans-telephonic monitor. And discontinued all the antiarrhythmic therapy and put them on a Holter monitor once a week for five weeks. So that we had an estimate of the rate at which they had asymptomatic atrial fibrillation as well as an estimate of the rate

at which they had symptomatic atrial fibrillation documented by the trans-telephonic monitor.

And we defined asymptomatic event as any episode of atrial fibrillation lasting 30 seconds or more on the Holter monitor and the symptomatic event which one documented by trans-telephonic monitoring.

In the population of patients that were studied there for over that month period, we estimated that for every symptomatic episode that was documented, there were 12 asymptomatic episodes documented. So, there's a lot that. I think if you look at data coming out of pacemakers, which are collecting information on the occurrence of atrial fibrillation in patients, there appears to be a lot of asymptomatic atrial fibrillation.

But as Peter has pointed out, the claim here is for symptomatic atrial fibrillation. It's not for stroke and it's not for asymptomatic atrial fibrillation. It's for symptomatic atrial fibrillation.

DR. KONSTAM: Well, I guess in an attempt to reassure me, you've worried me more. What you're

saying, Ed, is that most -- Well, everybody heard what you said. That's not what we see in the data here as represented. What's represented in the data here, as Milton and others have pointed out, is that there are -- were not very many asymptomatic episodes picked up.

DR. PRITCHETT: Well, of course, that relates to the technique you use as a surveillance methodology.

DR. KONSTAM: So, that's right. And then, the next -- the point that follows is, maybe there was a problem with the surveillance technique here. And the reason I think that that is important, I mean, I guess this will come for discussion later on, but I, for one, have problems with saying that the indication is going to be for symptoms, symptomatic a fib, because I'm going to be stuck if I really believe that the big part of that results from rate control. I'm going to have a big problem with that.

So, I'm not really reassured by this.

DR. KOWEY: I'm having a difficult time -- I mean, I managed a very, very large number of people with AF. And if I can get a patient who has very

frequent symptoms on a drug that reduces their symptoms in a significant way, I'm not necessarily looking that gift horse in the mouth.

Now, with a proviso, Marv, that I do protect those patients against stroke risk if I have any inkling that they are having asymptomatic recurrences. So, clinical practice is that you try to make people feel better.

DR. KONSTAM: Right. I agree with that, Peter. The problem for me is going to become, is this better than a beta blocker? That's the problem that I'm going to be -- Milton is shaking his head but this is obviously not a problem for him.

But for me, it's going to be a problem because of the side effects of that profile. So, I'm going to have problem in the end of the day approving the drug for prevention of symptomatic recurrent a fib if I wind up thinking that the vast majority of that effect is a beta blocker effect.

DR. PRITCHETT: Milt, this is all germane to the further discussions. I think you have to bear with us. But, Peter, I think would agree that

essentially the indications, the three issues with atrial fibrillation are one, stroke, and two is ventricular response. And three is symptoms. And if we can ameliorate symptoms with drugs that are less potentially toxic, and we're looking at risk benefits of these drugs, then obviously common sense would dictate we go with the least noxious drug that can effect a reduction in symptoms, if you're covering the patient for rate control and covering the patient for stroke.

CHAIRMAN PACKER: Let me see if I got this. The job of the advisory committee is to evaluate data and to determine if there's evidence that establishes risk to benefit is in the patient's favor. We generally do not, although we are specifically invited to today by the question, to perform hypothetically or practically a comparison of the choice under discussion today to the other choices that might be available. There are exceptions to that rule.

DR. KONSTAM: No, I agree completely. The goal is going to be assess risk to benefit ratio and

if -- so, are we going to wind up having to do a thought experiment at the end as to whether it's better than available therapy that is less toxic. I mean, that's going to come into play.

CHAIRMAN PACKER: Let me do this. There are undoubtedly -- I think we have discussed this issue thoroughly. And we will undoubtedly discuss this issue more later on. Let me see if there are other issues related to Study 05. We're still on 05.

DR. THADANI: Yes. There are a couple more issues.

CHAIRMAN PACKER: JoAnn is first.

DR. LINDENFELD: Just one other issue. I think that the time to symptomatic atrial fibrillation, we all want our patients to have less symptoms. But the fact that someone notices a few palpitations, that would, I think, have precipitated a call here because it doesn't necessarily mean they were bothered by those symptoms or bothered significantly by those symptoms. In other words, that's a subtle difference but -- a few palpitations.

So, if I can go on to another, just as a

corollary to this. I wonder what the compliance rate with the trans-telephonic monitoring was and what the quality of those were? One, what was the compliance rate? How many were actually successfully done? What was the quality? Where they interpretable? And then, the third part of that is, I'd like to know if the QT interval was evaluated on the trans-telephonic monitoring and if changes were made based on that? Changes in dosing. Or drop outs were effected.

DR. MARROTT: I think the answer to you first question is no, we cannot give you that information.

DR. LINDENFELD: But then, the results of the study are -- we don't know how many of those trans-telephonic monitors were actually done successfully?

DR. MARROTT: No, I just realized that was your --

DR. LINDENFELD: So then, we can't really interpret --

DR. MARROTT: -- question. Could you please repeat your first question?

DR. LINDENFELD: Yes, I'm sorry. How many of the trans-telephonic monitorings that were to be done every two weeks were successfully completed? What percentage?

DR. MARROTT: Well, we can give you that information but we cannot give you that information just now. We'll have to go --

DR. LINDENFELD: I think we sort of have to have it.

DR. MARROTT: And to provide you that information. But we do have the results of the advanced telephonic monitoring recording as to what were the symptoms and then what was the resulting ECG on that occasion. So, we do have that information.

DR. LINDENFELD: I think we'll need to know to that.

DR. MARROTT: It will be contained in the report of the study. But we do not have that detail just now.

DR. LINDENFELD: At least I would need to know that to be able to assess this time to ECG recurrence is to know how many were successfully done.

There would be a big -- if it were 95, that would great. But if it were 60 percent --

DR. KOWEY: It is not a low percentage, JoAnn. We can get it for you but it was the over 90 percent of them were successfully transmitted.

DR. LINDENFELD: Were successfully transmitted with an interpretable result? More than 90 percent?

DR. KOWEY: Yes. It was virtually in the 90s but I don't have the numbers. We can get that.

DR. LINDENFELD: And then the other part of that question is, did you evaluate -- I couldn't tell in the protocol, was QT interval evaluated on these monitors and were changes made, drop outs or changes in dosage made, on that? The reason I ask this is because the patients were monitored every two weeks. It's important to know if a significant number of changes were made based on two week monitoring.

DR. MARROTT: The QT was certainly monitored in patients in whom the PDM was recorded on an outpatient basis during the earlier part of the initiation of treatment.

DR. KOWEY: The answer is yes. Yes, JoAnn, the QT was monitored by trans-telephonic and if patients made the cut off for the QT in the study, they were dropped.

DR. LINDENFELD: Can you tell us what-- The reason this concerns me is because these patients were monitored every two weeks and obviously safety is an important issue. So, I think I need to know to sort of think about how often patients should have electrocardiographic check. I need to know how many patient's doses were changed or were dropped out just solely because of trans-telephonic monitoring.

DR. KOWEY: Can I have back up slide 329, please.

This is the number of patients with QT intervals greater than 520 milliseconds in all of the studies, including 05, who are then discontinued.

DR. LINDENFELD: So, then, less than one percent of patients were withdrawn based on trans-telephonic monitoring, is that --

DR. KOWEY: That's placebo.

DR. LINDENFELD: And how many of those

were after the first, the initial, monitoring period? What I'm trying to just get at is how often do these patients need to be monitored and how many are withdrawn?

DR. KOWEY: I don't have -- we don't have data as to when they were withdrawn from the trial. By trans-telephonic, we don't have those data.

CHAIRMAN PACKER: Hold on one second.

JoAnn, do you have any more questions about 05?

DR. LINDENFELD: No, I have -- let me just ask one other question.

DR. KOWEY: JoAnn, I don't have it specifically for 05. Do you want to see it for the entire data set?

DR. LINDENFELD: That would be great.

DR. KOWEY: Can I have back up slide, please, 289. 289.

This is -- if you look at QT greater than 520 milliseconds, JoAnn, this is for the controlled studies 05, 004, 014, and 9A. This is when the patients were dropped.

DR. LINDENFELD: Good.

Now, this is just -- this I think includes 05. But it's just sort of a general question. Assuming that the recommendations will be for treatment in patients with creatinine clearances greater than 40, that was I think what the final -- is that correct? These studies didn't include patients with creatinine clearance less than 40?

DR. KOWEY: No, there were no patients in the studies less than 40.

DR. LINDENFELD: So, I just would sort of -- I've had one comment. That would mean that your average 75 year old ladies who weighed 70 kilograms with a creatinine of 1.4 would be excluded?

DR. KOWEY: Damn right. I wouldn't put that patient on sotalol now or if the drug was approved for the indication. I think that's a high risk patient.

DR. LINDENFELD: And I can't give you an exact number but as we discuss safety, my guess would be that that probably is about 30 percent of the patients with atrial fibrillation in the United

States. Somewhere near there.

DR. KOWEY: Not in my practice. That may be true in some parts of the country but I can tell you that that's not --

DR. KONSTAM: But you don't see patients in nursing homes.

DR. KOWEY: No, I don't do -- well, no, actually, there are actually two nursing homes that are attached to our hospital. So, I do see patients in nursing homes.

DR. LINDENFELD: I think we know that 70 percent of patients are over the age of 65 with atrial fib in the United States.

DR. KOWEY: I don't disagree with you at all, JoAnn. There is clearly a subset of patients who are not candidates for this drug and never will be. And it turns out that a little old lady with a creatinine of 1.4 is probably one of them. But what that percentage is of somebody's practice really depends on where you're practicing and who you're seeing.

DR. LINDENFELD: And I don't --

DR. KOWEY: It is a significant percentage of patients. I wouldn't argue about that.

DR. LINDENFELD: I think there will be -- those concerns will be written in. But I do think that many people would not consider that without looking at a carefully, necessarily, a contraindication to these drugs. I think a lot of people would look at it the 75 year old woman with a creatinine of 1.4 is a reasonably health person.

DR. KOWEY: I've had people who have put patients on sotalol who are anephric. That doesn't mean that that's right. That's a clinical mistake. I think we're not up here arguing about what good clinical practice is. The question is, is there a definable population of patients who can receive the drug? And as we'll see when we get to the safety discussion, there is.

CHAIRMAN PACKER: Let me suggest that this is really a safety issue and we'll come back to it. And maybe we'll have an opportunity to see more safety data. So, let's hold -- I just want to hear efficacy issues related to 05.

And, Cindy, you had one?

DR. GRINES: Actually, I just wanted to maybe ask any of the panel who want to comment on this, but I was kind of struck by the high rate of asymptomatic atrial fibrillation but the definition in the study quoted earlier by the Duke University. And I guess the question is, if the definition is only 30 seconds of atrial fibrillation and the patient is asymptomatic, is that of any clinical relevance?

At our very last meeting, we talked about, it was one of our panel questions. And we questioned the panel whether keeping patients out of atrial fib was clinically self-evident. And it was my recollection that virtually everybody on this panel answered yes, it was clinically self-evident. We did not have to demonstrate a reduction in symptoms.

So, that being taken into consideration, I guess I wonder what has changed at this particular meeting and why the opinions are so different?

CHAIRMAN PACKER: That's a good question. I'm not certain how to get everyone's view on this. I think maybe if with your permission, Cindy, what I'd

like to do is bring this up specifically when we talk about the first question in the panel. Because I think you bring up a very important issue.

And the only reason I'd like to postpone it is that we're still on the first efficacy study.

DR. GRINES: Well, I guess the second question I have relates to these two studies. And there's been a lot of discussion about this, whether they're symptomatic or asymptomatic and whether every two weeks of monitoring was monitoring frequently enough. And if one looks at -- I guess it was slide 25 and slide 44, at least in our paper copies, it details the median time to recurrence and the percentage of relapse-free patients. And they're pretty striking differences between placebo and the proposed dosing group. And I guess question is it pertinent to discuss and spend so much time discussing whether we're missing any relapses when the time to recurrence is so different? And could it be missed if we're monitoring every two weeks?

I mean, if we look at Study 004, the median time to recurrence of placebo was 84 days

versus greater than 150 days for sotalol. And for Study 05, the median time to recurrence was 25 days in placebo and 226 days on the 120 milligrams of sotalol.

DR. LINDENFELD: But part of the problem, I think, with that is that, on 05 at least, at the end of two months, only 40 percent of patients were left in any of the groups.

In other words, if you look at .05 and you take the drop outs and the recurrences of atrial fib in each group, it's almost all 40 percent of the patients who are left at two months.

DR. GRINES: But that shows the majority of them dropped out because of recurrences, though, isn't that correct? I mean, the SAD is --

DR. LINDENFELD: No, that's true in the placebo group but it's not true -- most of them -- many of them were drop outs in the other groups. So, part of the whole question here becomes, I think we all would like to see a drug that prolonged time to atrial fibrillation by six months or eight months. If the time in the average patient is a couple of weeks, maybe it's not -- But that data is based on only 40

percent of the patients remaining by two months.

DR. KOWEY: But, JoAnn, I'd point out that in 9A, drop outs were accounted. And although it was a small study, I'd point out that there are a lot of drugs that have been approved by this advisory committee on less than 100 patients in a data set. Like flecainide for example. But in 9A, which is a relatively small number of patients, it was a very robust p value, the difference between placebo, 80, and 160 milligrams.

DR. CALIFF: Don't blame us for flecainide.

DR. KOWEY: And drop outs were counted as treatment failures.

DR. LINDENFELD: I wasn't born for flecainide.

DR. GRINES: I guess I'm still confused, then, as to why these patients did drop out. Because, we saw slides of talking about side effects, and how many dropped out due to side effects. And I guess I was assuming that if they didn't drop out due to side effects, they dropped out due to the fact that they

had a clinical event that was counted.

Now, is there a third category as to why the drop out rate was so high?

CHAIRMAN PACKER: Did people drop out for reasons other than lack of efficacy or adverse events?

DR. KOWEY: I'm sorry, what was the question again?

CHAIRMAN PACKER: Did people drop out for reasons other than recurrence or adverse events?

DR. KOWEY: Back up slide 205, please. This is the number of discontinuations by treatment group. This is in the outpatients and I can show it to you also for the inpatients.

The next slide, 206.

CHAIRMAN PACKER: So, I guess it is somewhere around, in the inpatients, about 5 to 10 percent. Is that about right?

DR. KOWEY: Yes.

CHAIRMAN PACKER: And this was administrative issues?

DR. KOWEY: I don't have those details.

John, do you know? Drop outs for other?

DR. WILLIAMS: The other category was a miscellaneous group. Either patients moved away from the center or they were protocol violators. So, that was the usual group of non-compliant study patients.

For the AE drop outs, most of them were for beta blocking side effects, bradycardia, weakness, dizziness, and so forth.

CHAIRMAN PACKER: We'll get into side effects later. We're just talking about how side effects influence the effect in an efficacy.

DR. THADANI: Is that the correct slide? I'm having a hard time following it now. You're saying there were 50 patients on placebo, 40 dropped out?

CHAIRMAN PACKER: Yes, don't forget. Discontinuation includes a recurrence here.

DR. THADANI: That's a --

DR. KOWEY: This lack of efficacy was 60, 35 of those 40 were lack of efficacy.

DR. THADANI: And the discontinuation-- you're including everything?

DR. KOWEY: Yes.

CHAIRMAN PACKER: Anyone have any other points about 05?

Mark.

DR. KONSTAM: Yes. You know, the issue about whether patients were started in hospital or out of the hospital, I guess if I understood in 05, patients with structural heart disease were mandated to be in the hospital. Those without structural heart disease were not mandated to be in the hospital. Do I got that right?

DR. KOWEY: That's right.

DR. KONSTAM: But could be in the hospital?

DR. KOWEY: Yes. A very small percentage of those patients were in the hospital.

DR. KONSTAM: What percent?

DR. KOWEY: It was less than 10 percent.

DR. KONSTAM: So, overall, over the entire population, what percentage was in hospital and what percentage was out of hospital?

DR. KOWEY: Well, can I have those two slides I just had. You can count the numbers.

DR. LINDENFELD: Twenty-three percent.

DR. KOWEY: I'm sorry, 27 percent.

DR. KONSTAM: Twenty --

DR. KOWEY: Twenty-seven percent in the hospital.

DR. KONSTAM: Twenty-seven percent in the hospital. Thanks.

CHAIRMAN PACKER: On that same --

DR. THADANI: I've got a question.

CHAIRMAN PACKER: Yes, Udho, hold on.

On the same issue, the outpatients were generally -- the indications without structural heart disease were generally viewed as outpatients. But when they were outpatients, they still underwent in all cases trans-telephonic monitoring. For how long? Can you clarify?

DR. KOWEY: When they were out of the hospital?

CHAIRMAN PACKER: Initiated, when they initiated on therapy as an outpatient, they underwent TTM for a certain period of time continuously during initiation of therapy.

John.

DR. WILLIAMS: TTM monitoring was done continually until they either had a relapse or they finished six months of treatment.

CHAIRMAN PACKER: No, no, no. It was done intermittently.

DR. WILLIAMS: During the outpatient initiation, they had -- they sent in telephonic monitoring, I think maybe about three days at the time of reaching steady state. We weren't getting daily -- a daily TTM. We have practice TTMs to teach them how to use the device and then they were -- during the initiation, we had more frequent TTMs.

CHAIRMAN PACKER: Again, I'm sorry, I just want to clarify the point. The TTM is recorded for a relatively brief period of time. People hook themselves up and send it in over telephone lines for a brief period of time.

DR. WILLIAMS: The TTM is recorded for just a few seconds. And then during follow up, it was every two weeks. And that's why when you have such a short period of ECG documentation, you don't pick up

a lot of asymptomatic occurrences.

CHAIRMAN PACKER: Just so I understand, that in the proposed labeling, when the concept of where therapy should be initiated is discussed and it says patients without structural heart disease can be initiated outpatient, outpatient with TTM or outpatient with daily ECGs, or outpatient without either?

DR. KOWEY: The way it was done in the trial was outpatient with both TTM and periodic electrocardiograms. The way I think it should be done in practice is with TTM. I'd probably, to be honest with you, Milton, I probably would do it more frequently in the initial phases than every three days. I commonly get one every day for the first seven to ten days the patient is being titrated at that dose.

CHAIRMAN PACKER: I'm sorry, Mike. Yes.

DR. CAIN: Peter, two questions which would also include all the studies. Atrial fib and atrial flutter are grouped together.

DR. KOWEY: Yes.

DR. CAIN: My bias would be that most of that was atrial fibrillation.

DR. KOWEY: Yes.

DR. CAIN: But just for the record, was that the case or were there differences among the trials where some trial picked up more of pure flutter versus atrial fib?

DR. KOWEY: No, in fact, Mike, we went back and looked at that very carefully because we were concerned about the same issue. The vast majority of patients in these trials had atrial fibrillation. And somewhere between 10 to 20 percent, and this was really consistent across the trials, also had atrial flutter. There were, for example, these were the patients that at least had some period of atrial fibrillation. So, the numbers, where it's less than 100, means that there were 10 percent for example in 9A that had only flutter. So, when you see 100 percent, that means that they had atrial fibrillation and about 10 to 20 percent of those patients across the trials also had some period of flutter. So, it was a typical AF population in all respects.

DR. CAIN: And the second is just a point of clarification about the duration of the trans-telephonic monitoring in NO5, what the definition of a recurrence was. So, specifically, if someone had symptoms and had 25 seconds of what looked like atrial fibrillation, was that counted as a recurrence or did you use the 30 second definition, or did it vary?

DR. WILLIAMS: The recurrence was diagnosed with ECG documentation of a fib or flutter, plus they had to have symptoms of a fib or flutter.

DR. CAIN: And the duration of the ECG strip that showed the fib and flutter was two minutes? Thirty seconds?

DR. WILLIAMS: No, there was no definition of duration but they had to have symptoms with it.

DR. CAIN: So, a failure could be someone who had marked symptoms of an irregular palpitation feeling in their chest. And yet the ECG strip could have shown 10 seconds of atrial fibrillation?

DR. WILLIAMS: Theoretically possible.

DR. PRITCHETT: Remember, Mike, that the -- it takes a little bit of time to get the device on.

It could be anywhere from a minute to several minutes to get the thing on. It isn't -- if you captured it, it's more -- and it lasted six seconds on the recording, the thing lasted more than six seconds.

CHAIRMAN PACKER: But on the other hand, I guess it's possible that they would have had a burst of palpitations and by the time they got the device on, nothing was recorded. And that wouldn't count at all.

DR. KONSTAM: If somebody had -- so this is in terms of following to the endpoints. If somebody had a trans-telephonic monitor routinely done, not because of any reported symptoms, and the patient was in a fib on this monitor, and still recorded no symptoms, how was that patient handled in terms of an endpoint?

DR. WILLIAMS: Without symptoms, they would be continued in the trial.

DR. KONSTAM: And they would not have been considered an endpoint?

DR. WILLIAMS: No, asymptomatic a fib was not an endpoint for the study.

DR. KONSTAM: But you tracked it. You do have asymptomatic. You do have ECG documented a fib.

DR. WILLIAMS: The number of asymptomatic documentation that we got from routine monitoring was a very small number. As you will see from the Kaplan Meier curves, the difference in the ends for asymptomatic plus symptomatic was very -- almost the same as for symptomatic.

DR. KONSTAM: But we just heard that for every asymptomatic not what we would have expected for every symptomatic recurrence of a fib, we would have, what did you say, 14 --

I'm struck by the fact --

DR. PRITCHETT: Captured by Holter -- captured by continuous monitoring, now. This is not trans-telephonic. This is continuous monitoring that you do for five days over the course of a month. You capture a lot more asymptomatic stuff than you do by sampling for 30 seconds every couple of weeks.

The every two week sampling is not a good way to measure the rate at which asymptomatic atrial fib occurs. It is a way to estimate the relative rate

that occurs in different groups.

DR. KONSTAM: Well, the two curves are almost identical.

DR. PRITCHETT: Yes.

DR. KONSTAM: So, this is what you're saying. Is that you picked up very, very few -- through trans-telephonic monitoring, you picked up very few episodes of a fib that was asymptomatic.

DR. KOWEY: Ed, is this something that we saw in the flecainide experience?

DR. PRITCHETT: Those data were conducted in the infancy of this technique and I think we did not look nearly as closely at that time at those data. So, I don't think we know what went on in the flecainide group.

DR. KONSTAM: But you still must have captured, even though those few, as endpoints because you kept track of them. And they were -- they do appear in those curves that we have that are called symptomatic or ECG. Is that right, that those patients were then just followed. Could they then, could those few patients have subsequently developed

an episode of symptomatic a fib?

DR. PRITCHETT: Of course. I mean, what happened, the trans-telephonic electrocardiograms are provided to the investigator so that the investigator knows that that patient had atrial fibrillation and can do something about it if he thinks it's important. In point of fact, most times that asymptomatic episode of atrial fibrillation resolved spontaneously and the patient goes on and has a symptomatic episode at some point later.

DR. KONSTAM: Let me just follow up on that, then.

If I'm an investigator and I've got a trans-telephonic monitor, and it shows that the patient's in a fib. Now, does that not bias me in terms of interpretation of the subjective endpoint of symptomatic a fib? In other words, when I speak to the patient next, maybe the next day or maybe my nurse calls him on the phone, isn't it more likely that I'm going to solicit symptoms of a fib because I know that that patient is in a fib?

DR. PRITCHETT: Are solicited in using the

trans-telephonic technique are recorded by the technicians who handle the calls at the time the patients make them. So, the patient calls in, transmits the recording, the technician says, what symptoms have you had, have you had any of these.

DR. KONSTAM: I understand. But then you just said that the investigator then has that information. And what I'm saying is couldn't it bias the likelihood that the next day in the physician's conversations with the patient or somebody else's, now we know that that patient is in a fib. It would seem to me they would be more likely to document a symptomatic endpoint in that circumstance.

What I'm sort of getting the feeling for is that the distinction between symptomatic and asymptomatic here is very murky. I mean, I think you were doing the trans-telephonic monitoring. The numbers, in fact, are almost identical. You say you picked up very few additional. But I'm wondering really, and we're dealing with a subjective assessment of a patient if they have symptoms of a fib. I call the patient up and then they say, yes, I -- see, I

have been having some palpitation. I don't know.

DR. KOWEY: Marv, does this help you at all? We just thought maybe if you look at the patients who were or were not taking beta blockers in addition to the study drug, and I believe that there area bout 30 percent.

DR. THADANI: I was going to ask you that question. Why was it two -- sotalol is a beta blocker.

DR. KOWEY: Well, it was a blinded study.

DR. THADANI: Yes, but 30 percent. I'm surprised at the start of the study beta blockers were not withdrawn. How often in practice --

DR. KOWEY: They are.

DR. THADANI: -- two beta blockers.

DR. KOWEY: If you know you're giving somebody a beta blocker, you don't use another beta blocker.

DR. THADANI: Yes, I'm surprised.

DR. KOWEY: But they may have been getting a low dose of the study drug or they may have been getting placebo.

DR. THADANI: No, but this was a dual response study, 05. Thirty percent of the patients. I know JoAnn asked the question on calcium channel blockers. But 30 percent on beta blockers.

DR. KOWEY: Right.

DR. THADANI: You would have thought they would have been withdrawn before they entered the study.

DR. KOWEY: Well, if you look at this, Udho, most -- There's a larger percentage of patients getting beta blockers in the placebo and in the low dose, as you would have expected, if that's the reason.

DR. THADANI: But you've still got --

DR. KOWEY: I'm not arguing --

DR. THADANI: -- 21 percent. So, you've still got 21 percent even in the highest dose. I think my feeling is beta blockers would never stop because the protocol was not design to withdraw the beta blockers. There happened to be -- there might have been post MI patients. And although sotalol has been used for them in European trials, they were never

withdrawn.

DR. KOWEY: Maybe this has boomeranged a little bit, but basically the reason I put this on-- if I could have the other slide back, the hazard ratio.

I was going to try to help Marvin. Now it looks like I've hurt you. But, if you look at the use of beta blocker, Marv, you see that if it were a beta blocker effect, then maybe people who were getting more beta blocker would have had a better outcome. I don't know. It's a way of looking at it.

DR. KONSTAM: Yes, it could be. But then again, the concomitant beta blocker use may have influenced the ability to exceed the dose.

DR. KOWEY: It's not a perfect answer. I'm just trying to help you to be comfortable.

But now I've made Dr. Thadani extremely uncomfortable and I don't know how to deal with that.

DR. THADANI: No, but I think in practice I don't use two beta blockers. If I see a patient who is in a fib and he happens to be in the beta blocker, if I switch him to sotalol, although not approved, but

I never have. It's very rare. I think only last week I saw a patient that was on both drugs.

So, the only thing could be that you could argue the other way around, the patients on placebo and beta blocker might have a less asymptomatic -- less symptomatic a fib because their heart rate could have been slower.

So, I was surprised that the study design was -- went through all the time and this drug was not withdrawn.

The other question I had that might be relevant, is if you look at the decay curve of recurrency survival, pick up, you know, 05 study, it seems like placebo decays very quickly and then flattens. Had you followed these patients for a longer time, all probably would have recurred.

DR. KOWEY: I think that's a fair statement.

DR. THADANI: So, if that is true, so really all we're talking about, symptomatic recurrence for a period of six months or eight months. And you follow them for -- maybe it's relevant because both

patients are symptomatic.

DR. KOWEY: Clinically, again, I think the reason why the claim was worded the way it was, is because we never expected antiarrhythmic drugs to be harmful. We expected it would be better. And so, we expect people on active therapy or on placebo to ultimately have a recurrence. It's the commonality. So, that's why the wording was the wording.

DR. THADANI: The other question is now a lot of patients in this study with structural heart disease. How many patients really had, say, a Class II, III, or IV heart failures? Very few if I remember correctly. Six, seven.

DR. KOWEY: There were a number of Class IIs. There were very few Class IIIs. I can go back to Study 05. If I could have the core slide.

CHAIRMAN PACKER: I just want to note that the sponsor is specifically requesting an exclusion on patients with overt heart barrier from any indications.

DR. THADANI: Yes, I think it was. That's why I asked this question, if I remember correctly.

CHAIRMAN PACKER: For study -- Do we have the slide? I don't know if we have it on the core. It was a small percentage. There was a very small percentage of Class IIIs.

DR. THADANI: So, they were excluded, if they had a heart failure.

DR. KOWEY: Yes, we don't have the breakdown on these slides but it was a very small number for Class IIIs. Most of them were Class Is and IIs.

DR. THADANI: I think that becomes relevant, too, now with the changing therapy for heart failure. These are going to take a role, and if they are in heart failure, they will not necessarily -- we don't have any data --

DR. KOWEY: No, no.

DR. THADANI: -- from this study and heart failure?

DR. KOWEY: No, we definitely do not. We don't have it anywhere. The only place where we have any heart failure patients in Class III was in the quinidine comparative study. This is the data from

004 that looks at the distribution. It's the same for 05.

CHAIRMAN PACKER: Tom.

DR. BIGGER: I just had a point of clarification about what was called structural heart disease in these studies. And was it the same for each of the studies?

DR. KOWEY: Yes, we have -- we can show you that. That's on a back up. We'll try to get it out for you.

Do we have the definition on a back up? What is it?

Here you go. This is the definition and it was the same across all the studies. If you had any one of those, you were classified as having structural heart disease.

CHAIRMAN PACKER: All right. Does anyone else have any comments on 05?

DR. GRINES: Did left atrial enlargement qualify as structural heart disease? No?

DR. KOWEY: No.

CHAIRMAN PACKER: Any other comments on

05?

I want to, before we break for lunch, try to get through the questions or issues on the other studies so that we can begin safety after the break. let me, in doing so, simply make note of the fact that a lot of the issues that we have brought up on 05 apply to the other trials. And therefore, we need not reiterate all of the, or revisit, all of these issues, the issues of informative censoring, the issues of trans-telephonic monitoring symptoms. We have covered these, I think, fairly thoroughly in the last long period of time.

And consequently, I think that we can assume that whatever concerns applied to 05, whether or not they've been resolved, will in fact apply, resolved or not, to the other trials. So, let me just ask everyone to, when they review the other trials, try to bring up issues unique to those studies and not reiterate the same issues.

I'm going to ask JoAnn to initiate the discussion of 04 next. But before, perhaps, doing that, it would be, I think, important to mention the

first issue that I think everyone has already identified from the FDA review which was the possibility of a treatment by center interaction for Center 29.

JoAnn, do you want to ask a specific question about that? And I only want to begin that way because it was highlighted in the FDA review.

DR. LINDENFELD: Yes, I think maybe the way to begin first is this issue that's highlighted in the briefing booklet about the actual intent for numbers of patients. We're told that the study was originally designed for 200 patients and somewhere increased to 349. The reason I want to -- and then address the site specific issue. Because I'm concerned not just that there was so much different in one site, but that the difference in those first 200 patients and the last 150, that specific site, I think entered a very large disproportionate number of patients in the last 149 patients of that.

So, maybe you could address all of that together.

DR. KOWEY: Dr. Marrott will address that

question.

DR. MARROTT: Mr. Chairman, with regards to the sample size issue on Study 004, somewhere in January of 1992, at a time point when about 110 patients or thereabouts had been entered into the drug, the sponsor, that is Bristol-Myers Squibb, the personnel that were responsible for undertaking the trial, that is the physician, the biostatistican, and the other support team, came to the conclusion from looking at certain other trials, for example, the control relapse information in the Coplan analysis, if you remember, there were six studies in the Coplan analysis. And they looked at the response of the recurrence rate in the control arm of the quinidine control evaluation meta-analysis as you may remember.

They also looked at the sotalol and the quinidine study, that is, Study H, and they looked at the results of Study 014 where the placebo response was 33 percent.

I think what has happened there, Mr. Chairman, is that there's been only a small fine tuning of the sample size for a different assumption

that was 30 percent initially at the start of the trail to 20 percent. So that the assumption at the start of the trial, if I remember it right, was 25 percent for placebo and 55 percent for active group, both d-sotalol and d,l-sotalol. Whereas, it was the other group 30 percent for placebo and 50 percent for sotalol based on the 014 for the placebo and sotalol. Based on the Coplan analysis for the standard -- sorry, the control group. And based on the age study, again, for sotalol.

Now, there was a perception with the division that something was not quite clear about this and then an analysis was done with the first 200 patients. But we did point out with the division at the time of the amendment of the protocol, we only had 110 patients recruited. And as you know from clinical trials that are done by pharmaceutical companies, if 110 patients are enrolled, possibly those 110 patients, they are not available in house.

So, I think that there was a fair assessment of what was going to be a better assumption with regards to placebo and with regards to the active

groups. So that is our response to the issue of sample size and the issue of the first 200 patients analysis.

I think there was a third one that Center 29 where you rightly point out that Center 29 we think by a play of chance, is performing very well for the active and very badly for the placebo.

And I would, if you don't mind, Mr. Chairman, request Dr. Fisher to please put forward his point of view.

CHAIRMAN PACKER: Before we do that, see if there's any additional clarification which is needed on the expansion of sample size. They are two separate. They're a little bit related but I think JoAnn's question was specifically on the expansion of sample size.

DR. MacNEIL: I think from the company point of view --

CHAIRMAN PACKER: Can you identify yourself, please, for the record.

DR. MacNEIL: Sorry, Dr. MacNeil from Bristol-Myers Squibb.

At the time we were conducting the study, people become aware of the fact that the original sample size was based on a treatment effect of 30 percent difference assuming that there would be a 25 percent placebo freedom of recurrence and a 55 percent freedom of recurrence for the active drug.

It was recognized from the meta-analyses that the estimate of people free from recurrence should have been higher based on what we knew from placebo. So, the recommendation was that we considered that the placebo effect would be 30 percent free from a recurrence and the active drug be 50 percent. And that's what led to the increase in the sample size. It was just felt that the study was under powered to show a difference. And we were blinded. We didn't have, you know, unblinded information upon which to make that judgment.

CHAIRMAN PACKER: Is the concern of the division the lack of documentation of this? I just want to see if I understand what the issues are because the explanation that you have provided is slightly different than the concern that has been

raised. And I just want to make sure we reconcile these so that we can move forward.

Abe, Dr. Karkowsky.

DR. KARKOWSKY: Abraham Karkowsky, Cardiorenal.

We read the protocols as they come in. This was an non-IND protocol. We saw no protocols. We have no record as to when things were done and when things were changed.

It's hard to retrospectively say what would have happened if this study would have found in fact 200 patients. Would they have continued to enroll patients?

CHAIRMAN PACKER: But they say they didn't unblind. We have to take their --

DR. CALIFF: Can I ask a question about that? And I've frequently wondered this. In these kind of small studies there's no DSMC. You're telling me there's no one who has access to the code or is monitoring the study?

DR. MacNEIL: The company does have access to the code but it's really -- it's restricted. It's

not available to anyone. So, it's basically locked up.

DR. CALIFF: Restricted to whom I guess is what I'm asking.

DR. MacNEIL: Well, it's the person who generated the randomization code. It's basically in the statistical department.

DR. CALIFF: So there's a statistician who's monitoring the trial?

DR. MacNEIL: Not in an unblinded fashion. In other words, the randomization code is generated and then in essence it's not available to anybody to review.

DR. CALIFF: And adverse events are not monitored by anyone?

DR. MacNEIL: Adverse events are monitored but they're monitored in the blinded way unless there's a specific reason to unblind. And then there has to be -- there's a formal mechanism by which there's a request made to the statistician for unblinding of a specific patient. But the statisticians themselves don't follow unblinded

events.

DR. CALIFF: Okay, so I'm not saying there's a problem here. I'm just trying to understand how it worked.

So, there were just like a safety committee, there was someone who was looking at the data as it came in. It was a statistician. There were no clear rules for when the statistician might say there were too many adverse events. And that was restricted purely to that statistician.

DR. MacNEIL: Well, let me clarify. The statistician generates the randomization code and then it is kept in a secure place. And the statistician doesn't otherwise look at any of the trial data. The clinical persons responsible for the trial review all of the adverse events as they are received on an ongoing basis. In general, these studies remain blinded despite the fact that there's a serious adverse event that might occur.

But in the unique instance, the investigator may request in order to manage the patients, to know what the specific drug was that the

patient was receiving. When that happens, then within the company there's a procedure by which the signatures of several individuals are involved in order to get the statistician to go back into the randomization code and tell specifically what that person was on. In an emergency basis, all of our drugs are labeled such that the investigator could unblind on site but we -- that would invalidate the patient and that we don't encourage investigators to do.

DR. MOYÉ: I think I'd just like to just ask you to elaborate like that in responding to my question. I understand that you have serious adverse event monitors to look at the individual case before they come in. And they have reporting responsibilities based on severity of event.

But let me ask you specifically, was there anybody in the company who was monitoring the trial on a per group basis? Anybody who's looking at placebo event rates, active group event rates, or efficacy for the first 110 patients? Was there anybody anywhere doing that?

DR. MacNEIL: No.

DR. MOYÉ: Thank you.

CHAIRMAN PACKER: Let me see if I can just clarify. I think you just said that the amendment that expanded the trial was made in January of 1992?

DR. MacNEIL: Yes.

CHAIRMAN PACKER: I guess the reason for the physician's concern is in the annual report dated July 7th, 1992, six months after the amendment, this study is still referred to as a 200 patient trial. In other words, if the decision had been made in January to expand the study, the question that the division has is why six months later the annual report does not refer to the expanded patient population?

DR. MacNEIL: I would have to say that was an error because the amendment does exist increasing the sample size.

DR. KARKOWSKY: We have the information. The sponsor sent us -- Berlex sends us through Bristol some information from Bristol-Myers Squibb as to the rationale for modifying their sample size. I can give that to you to look at it.

There was -- It did not seem like it was definitive that they would go to do, but it was clearly a discussion amongst people. We have no additional information. If it's important, DSI could go out and look at that information and convince everybody as to the timing of amendments, whether they received by all centers. And from the vantage point of the division, we can't do any more. And we will treat the information as if it is not any way unreasonable.

CHAIRMAN PACKER: And I just want one more clarification because it's also raised by the division when the discrepancy or an explanation was first sought during a meeting with the division. Apparently the division was told that the sample size was increased not because the expected event rates were adjusted, but because the initial intent was to do a comparison of d-sotalol versus placebo as opposed to a comparison of either treatment. The explanation you have just provided is different than the explanation in the divisional record. We just want to be able to make sure what the story is.

Did I say that correctly?

DR. MacNEIL: I don't know. The information we have, the discussion amongst the statisticians at Bristol Myers was mostly with respect to d-sotalol. Okay, as far as I remember, looking at the primary endpoints in the study, it was a comparison of d-sotalol with placebo and d,l-sotalol with placebo. So, I can't address your issue specifically but I would have presumed that it's d and d,l versus placebo.

CHAIRMAN PACKER: Maybe I can rephrase the question.

I don't think that anyone in the division, and I don't think anyone in the committee is saying that there is a problem. I think what we just want to do is clarify the actual sequence of events. And maybe I should ask.

Lem, if there were a problem, what would you do with the p values in order to make an appropriate adjustment? Because, it could be that the p values for this trial are sufficiently small that it just doesn't make any difference. I just want to be

able to clarify.

Let me just clarify the intent of my question is not to assume there's a problem. This is more of a hypothetical question as opposed to a question specifically. Lem?

DR. MOYÉ: Right. So, we're talking about a hypothetical circumstance here it sounds like, where--

CHAIRMAN PACKER: I just want to -- I want to emphasize that because there is -- the division is not saying that there is a problem. All, and you know we all want to be very, very careful here. My question is simply if there were in fact an expansion in the trial based on an interim analysis, what would one then do?

DR. MOYÉ: I think that if this interim analysis was not prospectively specified, and it was not in the protocol at the inception of the trial, that there would be a potential expansion of the sample size. Then we're looking at essentially letting the data from the trial determine the analysis plan. And I think that that has severe implications.

I think the best thing to do in that circumstance is to analyze the data as the investigators planned to collect it.

Then it's as simple as planning what you mean to do and then doing what you plan. And if the initial plan was to evaluate 200 patients, then the efficacy analysis for 004 would be solely on the 200 patients. To -- It is very -- I will say it is likely that you can get a subsequently randomized sub-cohort, which would have a different effect than that seen by the first 200. One reason would be your sampling variability, and I've seen that happen before. Another reason is that the patients who are randomized later. Perhaps they come from different centers. Perhaps they don't meet the exact same exclusion criteria. And so, that would be another reason why the effect might be different in one later randomized cohort than another.

CHAIRMAN PACKER: Tom and then Mark.

DR. BIGGER: Yes, if I understood it, that sounds right hypothetically. But that wasn't what was done here at all. The data from the trial wasn't

examined to increase the sample size. As I understood Mr. MacNeil. But, information coming from outside the trial, that the event rates they used to estimate the sample size were not the best estimates at the time they were reviewing the sample size situation. And the basis for decision to increase the sample size didn't come from the data inside the trial but from information coming from outside being reviewed into the cumulative. That's what he said anyway.

DR. MOYÉ: I don't dispute that. It was a hypothetical.

CHAIRMAN PACKER: It is a hypothetical question. Marv and then Rob.

DR. KONSTAM: Yes, let me just -- this is interesting because Rob and I were just on a panel yesterday where this very issue came up. And it came up from the perspective of an interim analysis was done. There was a concern that there was not sufficient power based on that interim analysis. There was no pre-specified plan in the protocol to expand the sample size. Nevertheless, that was the decision that was taken at the time of the interim

analysis to expand the sample size. And so, that was very clear that that had occurred. And the discussion took place in the room with several statisticians present, what was the level of penalty that should be imposed. And the consensus of opinion was a very small penalty. That it would not substantially influence the interpretation of the p value.

So, we can go back over the minutes of that meeting. But just in the interest of bringing consistency to this discussion, this is the way it took place yesterday.

CHAIRMAN PACKER: Why don't we move forward since we are not saying that this is an issue. Let me reiterate, we are not saying that this is an issue.

DR. CALIFF: Milton.

CHAIRMAN PACKER: Oh, Rob. I'm sorry.

DR. CALIFF: I think it would, from my perspective having been on the panel yesterday and having been outvoted eight to one on this issue, it would be useful, I think, to at least hear the cardiorenal perspective on this issue of engineering

clinical trials; that is, doing an interim analysis, looking at the unblinded event rates in the two groups, observing the observed difference, and then recalculating the sample size based on the observation. The two other Divisions yesterday said that it mattered a little bit but not much.

CHAIRMAN PACKER: Can I make a suggestion? This sounds like a great idea for a symposium. I think that we are ill-equipped to deal with this in any kind of definitive fashion today.

DR. FISHER: Just a quick aside, Rob, I have published a sequential method but one of the consequences is you can look at the unblinded data continuously, make decisions on how far you are going in such a way to preserve the type 1 error. I mean, there are ways of dealing with it now.

CHAIRMAN PACKER: Okay. JoAnn, we're going to go back to you on any other issues. Do you want to deal with the issue of Center 29?

DR. LINDENFELD: I know we're going to hear some discussion about Center 29 but the other concern I have about Center 29 is that they entered a

substantia by greater percentage of the patients in the study in the second half than in the first half. Not only were their results different, or more impressive at least, but they entered 20 percent of the patients in the 149 set and only five percent of the patients in the 200 set. Maybe we could hear -- ease our minds about both of those problems.

DR. FISHER: I haven't thought about the timing of enrollment but maybe we could get slide 178 out. As a general principle in analyzing data, we would like to include all of the data. We have to be very careful about excluding things.

Having said that, it's perfectly fair game to look for recruitment interaction. We all know certain situations where data are appropriately excluded. For example, investigator fraud, incredibly poor quality data of such that it is just virtually unbelievable, and so on.

In this particular case, the first point I would like to make is even if there is a certified treatment interaction, which I think is plausible looking at these data, it appears to be quantitative.

In other words, if you remove Center 29, in the remainder there is also an estimated favorable effect. Of course, you are losing a lot of power. If one center differs, there is an issue of what is a quote and what is the truth. I don't think it is necessarily clear they are a good or bad center and necessarily somehow is so unrepresentative we shouldn't consider it.

It's clear statistically that if the data are homogeneous, the best center is going to look a lot better than the average treatment effect. I mean, that's obvious. It's also totally clear statistically if things are homogenous and you remove the best center, you are going to underestimate treatment effect.

What we have here are three possible ways of dealing with things. The top is excluding the best site, 29. As you can see, when you do this, if you look at symptomatic AFAL statistical significance is lost, if you look at any occurrence, symptomatic or asymptomatic, if the log rank is just borderline and the median test statistic is better, I ask them to

throw out the worst site just to illustrate the point.

I mean, once you start playing this game, one great way to improve things is to say, "Well, gee, the worst site looks so bad we want to toss this out." If you do that -- I'm not advocating this but if you do this, you can see, of course, you have greatly improved things. No big shocker. Just like it's no shocker when you throw out the best point and things get worse.

If you treat things sort of symmetrically down below and move in the best and the worst, things are still statistically significant. This is despite the fact that, of course, if you're going to do this, you tend to lose statistical power because you are decreasing the sample size as you do things. I actually find this one a relatively easy part of the discussion. We ought to include all the data.

It's possible there is an interaction but it doesn't look to be qualitative enough. In other words, there's no good indication I can see that in some centers the drug works and in other centers it actually has an adverse effect. I think everybody in

medicine assumes that when we approve a compound it works better in some patients than others.

In other words, if this overall summary relative risk is not a true effect in every single patient but the continuity of human biology is such that we are willing to say, well it works overall. There may be differences and they are probably not that great.

DR. CALIFF: Lloyd, did you calculate the probability that a result as seen in 29 could have been -- what was the probability that could have occurred taking into account the overall treatment effect? In other words --

DR. FISHER: You mean if you only looked at that one clinic?

DR. CALIFF: No. If you take the overall effect and the total sample size, you ought to be able to calculate the likelihood that you would get one center that far in the extreme. Is it like 1 in 1,000 chance?

DR. FISHER: I hesitate to do that because it's a totally data driven thing where you look at it

and say, "Oh, my goodness. In this study it looks like we may have an interaction." I have made the statement and I intend to write a paper in the next few years, I've never seen a totally consistent clinical development program. Never. There are so many things going on. There is something weird. Well, how come you don't get the same dose response here as there, etcetera, etcetera.

I did do that using as a major, the spread of the largest clinic which will almost always occur in one of the few clinics. It's almost like a P value on that one site. That's at about a one in 100 level. That's why I say it's certainly conceivable to me that there is a quantitative interaction.

DR. CALIFF: I would have thought the main purpose of bringing this up would be to go look at the site and just make sure there is nothing funny going on there.

DR. FISHER: Yes.

DR. CALIFF: We've got some documentation that that was done.

DR. FISHER: I agree that is always very

prudent.

DR. THADANI: Before you leave that point, obviously the doctor in Center 29 has better healing power than other physicians obviously. We go for observations onward, but I was looking at the table provided from the center and --

DR. FISHER: I'm worried about the turkey.

DR. THADANI: I realize that.

DR. FISHER: The turkey is in 24 or it doesn't work. How do we keep the drug out of evidence?

DR. THADANI: If you look at the large centers -- I'm looking at Table 4 on the document I was sent by the Center, faxed to me on 4/23. I don't know if you have it or not. They look at large centers with sample size of 40, 42, 32, 30, 25, and 24 subjects, fairly large sample size. In that group the P value for Center 29 is 0002 and 00003, but none of the other centers approach really anything like it.

So if you exclude that center the significance literally disappears. I think we could

argue the center is very good. I don't know how you are interpreting it, the symptoms at that center may be very peculiar unless you audit the center.

DR. FISHER: As we can see from the log rank, I mean, the significance does disappear.

DR. THADANI: The question always comes up why is that center so peculiar which is driving the whole database. Plus we have heard, for the first 200 patients there is no significance. Then you have the next database which is highly significant but none of it is being driven by just one center which is obviously recurrence rated variable.

CHAIRMAN PACKER: Let me just make sure that we are not driving ourselves off a cliff here. The only reason that I know of that the Center 29 issue came up is not because -- tell me if I'm right-- Center 29 is so materially different than the other centers because we see that in clinical trials.

That is, some centers do have a greater estimated treatment effect than others. I think the only reason this came up -- correct me if I'm wrong -- is that Center 29 out recruited the other centers by

far after the 200 patient extension. If the 200 patient extension didn't exist, would Center 29 be an issue?

DR. FISHER: Milt, my impression was it wasn't that but it was the fact that a sizable segment of the improvement in the time to recurrence was at that center.

DR. THADANI: Milton, actually the question is raised because I'm reading what the FDA sent us, "Excluding the single study site, which is Center 29, the P value is no longer significant."

CHAIRMAN PACKER: No, but, Udho, it's not fair. You can take a whole bunch of databases and throw out the best site and the treatment effect disappears because you're not only throwing out the vector but you're throwing out -- you are reducing sample size. I don't know how many databases would stand that kind of assault.

DR. THADANI: I'm not saying to throw the samples out. I'm just saying it raises some issues that you've got excluding these 40 patients in the 360 patients. There's no benefit.

DR. FISHER: But it's not just reducing the sample size. You are biasing in the estimate against your study drug by taking out the best.

DR. KARKOWSKY: The initial protocol said they would look at investigator cross-site interactions. We had not seen that analysis. It is fair game to do an investigative cross-site interaction. The reason it was done is because we did not understand why the study size was increased and we saw a disparity in the first half and the last half of the study.

That was not data dredging. That was based on the only analysis we did. We don't have the facilities to data dredge. We have one statistician and she's dredging the stuff that is supposed to be dredging. Nevertheless, it did come up and then the question was why were those last 150 patients different? Now the protocol stipulated that they would do investigative cross-site interaction so we felt very comfortable looking at that.

Having found it we said let's take a conservative analysis which would be take out that

site that looks the most deviant. We thought that was a reasonable analysis. The things that might be determined are, (1) the study doesn't find anything; (2) the study may have found something but it's certainly less robust than we initially thought it was and that's why you guys are up there.

DR. KOWEY: Can I just make a suggestion that Rob already made which is I'm sure the sponsor would be very happy to have the site audited in detail to make sure there were no irregularities at the site. If there were no irregularities at the site, I think this discussion probably is moot.

CHAIRMAN PACKER: I assume the site has not been audited.

DR. KOWEY: No. It was not a sponsor study and it has not been audited. It's in Stockholm if anybody wants to take a ride.

CHAIRMAN PACKER: Okay. JoAnn, other issues on 04?

DR. LINDENFELD: This is just a general issue. Is this on? Yeah. Maybe you can just give me some insight if these are not beta-blocker effects

that are prolonging the time to atrial fibrillation, why is it that d-sotalol is not effective? As we talked earlier about some of the things we see beta-blocker effects. Are all of them beta-blocker effects? We don't know. I was just wondering if you could give me some insight into that.

DR. KOWEY: Actually, my feeling about this particular kind of drug is that having a beta-blocker incorporated into the molecule is an important aspect of the electrophysiological effect of the drug. It's a combination of effects which I think are important.

I don't know why d-sotalol wasn't effective in the study. I would have predicted that it should have had some efficacy. In fact, it did. It wasn't ineffective. It was just not as effective as the racemic one. I think that the drug works best when you do have some beta-blocking effect in addition to the Class III effect. I think it's a composite effect.

DR. KONSTAM: Can I follow on that? What percentage of the effect do you think -- I mean, you

made that statement so I guess it must be based on something. What percentage of the effect that we see here do you think is on the basis of beta-blockade?

DR. KOWEY: Yes. If I can have the first Kaplan Meier curve from study 004 that we showed which was slide 24. I don't want to be flip but I think it's probably about half way between here and here. This is what d-sotalol did as a pure Class III, this is what the combination drug did, and this is placebo. So it's probably an equal contribution of both parts.

I don't really know. I do know that when you use the drug at 80 milligrams twice a day it's a beta-blocker. I know when you use it at 160 milligrams twice per day it's more than a beta-blocker.

You are beginning to see Class III effect. We'll show you that later. Clearly since there is a difference between 160 and 80 in 9A, for example, you need to have both effects. Since there's a difference between d-sotalol and racemic sotalol, I think you need to have both.

DR. KONSTAM: I'll just point out what's

missing from this slide is a pure beta-blocker.

DR. KOWEY: Yes. That's right. There is no where in this database unfortunately anything that I can show you that is a pure beta-blocker study.

DR. KONSTAM: Can you just clarify for us non-electrophysiologists, you said that d-sotalol does not have beta-blocker effect. It's completely devoid of beta-blocker effect?

DR. KOWEY: Yes. A pure IKL blocker.

DR. KONSTAM: And with regard to the complement of electrophysiologic effects is it identical to d,l-sotalol or are there other differences?

DR. KOWEY: No. The d,l isomer's Class III properties are exactly the same as the d isomer's Class III properties.

DR. THADANI: Before you leave that point now on the -- sorry. The question is on d-sotalol. Looking at table 10 provided by the center, d-sotalol was not different than placebo in all 349 patients. The P value was .206 and d,l-sotalol is 0003.

DR. KOWEY: No. I'm not saying it's

sophistically significant. I'm saying that it's not the same as placebo.

DR. THADANI: The reason again I'm bringing the center into action, it seems again that Center 29 had a P value of 0003 and 0004 even with d-sotalol. I'm just wondering if the center is very peculiar, although Milton's point is well taken that one center can influence. It seems like a very peculiar center showing a marked efficacy with the two active drugs.

DR. KOWEY: Can I have the core slide, please, No. 54?

DR. FENICHEL: Actually, before --

DR. KOWEY: I'm sorry. Hold that a moment.

DR. FENICHEL: Hang on just a second, Peter.

DR. KOWEY: I'm sorry.

DR. FENICHEL: What we do know about that center is that the performance of d,l-sotalol was not all that different from that seen in other centers. What was remarkable in that center was the placebo was

different. The placebo performed especially badly. It wasn't that the active drugs performed especially well. So you would expect to see a marked increase in the apparent efficacy of both active agents.

DR. THADANI: So the question is could an investigator somehow have known what his placebo because it has symptomatic recurrence and he would say, "Okay, if you had symptoms, he could ignore it.", you know, I'm just not -- the investigator just makes me a bit uncomfortable with two active drugs by showing a very similar thing and placebo incidents were very low.

DR. FISHER: I just want to comment as a statistician with a lot of multiple comparisons, when you get your biggest effect, if they were all equal sample size, you expect it at a clinic where the placebo effect by chance is greater than expected and the active therapy is better than expected. That's all a valid part of the statistics taken into account in the total analysis.

DR. MARROTT: Mr. Chairman, I would like to make a couple of points. First is that in study

004 Center 29 when you look at the relapses for d-sotalol, the comment was made that study 29 seems to favor both d,l-sotalol and d-sotalol. That is not true because if you look at the 14 patients that were recruited by the center in the d-sotalol group, there were four relapses in the symptomatic category.

Then you look at any category and it was eight relapses in the any category. In fact, in the active group, albeit sotalol, there were eight relapses out of 14. I would consider that it wasn't like the investigator knew that there were some symptoms so it was an active group and the results came out because of the bias towards the active group. So, I don't agree with that comment.

The other point I would like to make is the reason we are making all this discussion is because the two groups, the d,l-sotalol group and the placebo group and fortunately for the sponsor are heading in the opposite direction. That is, whereas the active group has benefitted with less relapses, the placebo group has suffered with more relapses.

You know, if that would not have happened,

we would not have had this discussion because then we would have been dealing with only one part of the equation which is deviated from normal. Here what has happened is that by chance I suspect that the two sides have deviated on the opposite side.

I would also like to point out that as every reputable company does, Bristol-Myers Squibb and ourselves are not an exception, we go through the monitoring of sites very diligently and very seriously. We do this more so since this was one of the key trials of the company.

When we looked at the listings and we looked at some of the case report information, we could not detect that anything deviant had happened at the center. I can tell you that with the greatest degree of diligence that we have tried to be very objective.

I will add one more comment, that the number of patients who had structural heart disease was more in the placebo group but I can't elaborate further on that issue. I don't want to make any claims about that.

One more point, Mr. Chairman, very quickly. A point was made that the d-sotalol did not benefit but it has benefitted in study 9A so the data in study 9A does show that d-sotalol 200 milligrams BID does as well as the d,l-sotalol. Thank you.

DR. THADANI: Pran, the question I was saying to study this study. I did not say the other study. I was only referring to this database.

CHAIRMAN PACKER: Let me just see if I understand. Abe, just clarify. There was or was not a statistically significant treatment by center interaction in 04?

DR. KARKOWSKY: We did not see an analysis of treatment by center interaction.

CHAIRMAN PACKER: Okay. Has the sponsor performed such an analysis?

DR. KOWEY: No. It's not been done yet.

CHAIRMAN PACKER: Okay. And the division has not performed an analysis?

DR. KARKOWSKY: I certainly don't know how to do it. I've spoken to the statisticians and it may not be that easy to do.

DR. FISHER: The reason it wasn't done was there was so many sites with such small numbers of patients. At least the asymptotic statistics would be greatly endowed. There might be somebody somewhere who could have a program to do an exact analysis.

CHAIRMAN PACKER: Isn't the way that one deals with a small number of centers, a small number of patients, is to create pseudo centers where the centers are pulled?

DR. FISHER: Well, it was done by geographic region. There was no interaction. I said that's not what the agency is talking about because then you are to some extent washing out the 29 effect. The problem is doing this all post-hoc.

If you know you have a problem at a big center, then you'll be lumping almost everything else, or a huge number of everything else, into this one mega-center which is almost like saying the mean, which might have -- if somebody had written up in the protocol perspective, that might have some merits for looking at big centers. After you look at the data and see it's triggered by that, it's very hard to know

what would be the right thing to do.

CHAIRMAN PACKER: Alexandra?

DR. KAPATOU: Yes. Another point I wanted to make in this was that since we actually did a nonparametric analysis. The log rank test is a nonparametric analysis. There is no direct way of studying the treatment by center and direction except making tables like the ones I presented. If we had parametric model, then we could have put an additional term and that would have taken care of it.

DR. FISHER: Well, if we had bigger numbers there is a way to address it. The Cox model is semiparametric. It's nonparametric with time to event but parametric with respect to covariates and you could put in indicator variables for clinics and look at the sum degrees of freedom and interaction.

The problem here, as I mentioned, is the small numbers in many of the sites. If there were five centers all of which had 20 or more people enrolled, then I think it would be fairly clear how to attack it.

CHAIRMAN PACKER: Maybe I can ask Bob

Fenichel. Bob, we don't see treatment by center interactions on primary endpoints all that common but we have seen a few examples over the past five to 10 years of this observation. How has the division approached this in the past when a treatment by center interaction occurred?

Obviously if a treatment by center interaction occurred in a non-major trial or on the secondary endpoint, people probably wouldn't spend a whole lot of time talking about it. Just suppose something like that was seen in a major trial on its primary endpoint. What approach has division taken or has the policy been not clearly defined even in the past?

DR. FENICHEL: I think it's very hard to establish a perspective policy on this. I think some of what Lloyd has just said is pertinent that it's quite difficult when the outstanding center is indeed also the biggest center in which one also has the sort of systemic feel that, well, there's a time interaction in that the late arriving patients in this trial look different from the early ones. Well,

that's because -- that is because, in some sense of because.

This center became more active as the trial went on. This center was the biggest center and increasingly so as time went on. There are all these things confounded and the usual strategies are sort of worst-case analysis, if you like, where you say just throw it out. There's a small center that is the outlier and maybe it's because there has to be somebody who is the outlier.

Well, that's fine. We'll just throw it out and you'll see the results are kind of the same. You've lost a little power but it's all heading in the right direction. Here, you know, that doesn't quite apply.

Certainly the only recent experience with a dramatic effect that was somewhat similar to this was in one of the epolifibitide studies where there were dramatic region by treatment interactions -- region by treatment by gender interactions, three ways, that the stuff seemed to work a little bit better in men than women all over the place.

But then in Latin America it was actually worse than placebo in women. Well, what are you going to make of that? We don't understand it. We don't regulate drugs in Latin America. We regulate them here and so we just put it into labels and say, "Look at this. What do you think of that?" That's where it stands.

I don't know that some succinctly describable policy can be distilled from what we've done. Certainly it has never been set forth perspectively as a guide to our behavior.

CHAIRMAN PACKER: Mike. Mike has been waiting for a long time.

DR. CAIN: Can we have slide 24 put back on the screen, please? I just wanted to get clarification both from the sponsor and from the division about a point that was made earlier, and that was study 004 seems to be the only one in which we do have follow-up of individuals who dropped out of the study because of adverse effects. We do know the natural history then of what happened to those people.

The sponsor made a comment, if I remember

it, earlier that the data that are presented for study 004 takes into account that additional data. This has been a very key slide. If this is the perfect world of where we've taken into account follow-up of those people who were discontinued, then some of the issues we're talking about this morning are resolved. If it's not, then I would like to know that.

DR. KOWEY: Mike, this is slide 24 and let me show you slide 29 which is adding in all the patients who were discontinued or died during the course of the study. Again, this is the analysis that we have been talking about, the 05, all morning. Looking at the same kind of analysis, I won't say it's the worst case. It's the semi-worst case analysis, showing that these people died.

CHAIRMAN PACKER: But, Peter, just to make the point, although Michael's point is important because 04 did follow people all the way through, the percentage of people who are dropping out here is much smaller than all the others because it's six percent versus 29 percent.

DR. KOWEY: Yes.

CHAIRMAN PACKER: Consequently, even if one didn't get complete follow-up, and they did, but even if one didn't, the impact of a worst-case analysis here, even my proposed worst-case analysis, would be very small because the number of patients for whom data would be missing is very, very small.

DR. FISHER: The sponsor does have what was being asked for and it's on the slide including all of the follow-up data even after people discontinued and it looks the same.

CHAIRMAN PACKER: Any other issues on 04? I have one other question on 04. You showed, Peter, a subgroup analysis of patients above and below a creatinine clearance of 60.

DR. KOWEY: Yes. That's slide 28.

CHAIRMAN PACKER: Was there a interaction, a P value for the difference of the estimated treatment effect in the people above and below 60? Is there a P value associated with this?

DR. KOWEY: You have that as a backup. We have efficacy by creatinine clearance.

CHAIRMAN PACKER: Because the sense is,

and one usually sort of gets a poor man's estimate of an interaction by seeing to what degree the competence interval is overlapped. The competence intervals here don't overlap very much. The implication, if that were to be the case, was that this drug primarily works in a population which would be the smallest subgroup of this trial. That would be a very strange kind of conclusion.

DR. FENICHEL: Milton, do you think this might be just a concentration proxy because it does seem to work better in women? Not in every slide that Peter showed but in most where it was separated out by gender there was sort of a trend working better in women which may just be size.

Here it might be that the stratagem they used to correct creatinine clearance and reduce the dose did not completely correct for creatinine clearance and, therefore, the people with lower creatinine clearance or poor renal function were, in fact, getting more drug or a higher AUC anyway because certainly there is a strong tendency toward a dose response with the drug. I think this is all just a

proxy for that.

CHAIRMAN PACKER: I hadn't actually considered that because I guess I assumed that the algorithm they used corrected adequately. But if, in fact, it is a dose dependent phenomenon, it would suggest the possibility that the target dose in this call which was 160 BID, which is the highest recommended dose in the proposed labeling, is an inadequate dose. I don't want to go there.

DR. FENICHEL: Yes. I know. You're getting more adverse effects as you go up, too. It's a tradeoff.

DR. KOWEY: Let me just say, Milton, I think Bob's explanation is accurate because the exclusion was 50 CC per minute. You know as well as I do that there is a lot of error within that measurement. We're dealing with a very tightly defined patient population that probably works in people that did get more of the drug.

DR. FISHER: I just ask what happened in 005. If we could see slide 49. This suggests to me the other slide is a proxy for the multiple comparison

problem. I don't see that shown but we don't see the same thing here.

DR. FENICHEL: Well, it could be a different range of observed creatinine clearances so an effect would be amplified in one population and not so much in the other. I don't know. I don't think there is any explanation.

DR. FISHER: But then I would suggest that the agency, of course, can have them explore this further by looking at estimated creatinine clearance and going into it and body weight.

DR. THADANI: But wasn't the trial also different in the first study? He said the criteria was 60 ml, although some patients just happen to fall in because people were not very careful and didn't know how to calculate creatinine and they were 50s. This one brought it out in 40. That might be the difference.

DR. KOWEY: That's right. In that range of 40 to 60 they got it once a day.

DR. THADANI: So that could have the difference.

DR. KOWEY: Or they should have gotten it once a day.

DR. THADANI: Another thing I think looking at these trials, the side effect profile was much lower in all four while it was much higher because of the dose response design study in the 05. That might have practical implications because here you've titrated them.

DR. KOWEY: You'll see that.

DR. THADANI: That might be very relevant because if you have intent to treat here, it looks very highly significant. Yet, in the other one if you have intent to treat it falls apart because of the large dropout rate because of side effects.

DR. KOWEY: That's a possible explanation.

DR. THADANI: I think it's worth keeping it ín mind.

CHAIRMAN PACKER: Ileana.

DR. PIÑA: I want to come back to a point that Marvin was marking before and that, Peter, you alluded to, the beta-blocking effects of the drug may be more significant at a lower dose and as you go up

on the dose you start to get the QT prolongation. Actually, they should have data on this because there were comparative studies with atenolol and timolol when the drug was being studied for ventricular arrhythmia so there should be some comparative data on beta potency or beta-blocking effects to answer the question as to where would a beta -- obviously it would be theoretical as to where a beta-blocker would fit in there.

I have not reviewed the studies in great detail but I know that they exist and this was very early. Some of the doses are higher but some of the doses are at 160 and 180. DR. KOWEY: At the end of the presentation we'll talk about dose recommendations. We're going to show you some of the data relating to that question.

DR. THADANI: Isn't part of the data is by 80 milligram dose was not more effective?

DR. KOWEY: It depends on what study you're talking about. I know in A it was.

DR. THADANI: No. In the first study you show --

DR. KOWEY: In 05 it was.

DR. THADANI: It was marginal. It was not effective.

DR. KOWEY: Right. Borderline effective.

CHAIRMAN PACKER: I think the study that primarily supports the efficacy of 80 BID is dofetilide 345.

DR. KOWEY: Do you like that one?

CHAIRMAN PACKER: Rob?

DR. CALIFF: This maybe is headed to where I'm going eventually anyway.

DR. KOWEY: But, Milton, the reason I said 9A and you said 345 is we were talking about paroxysmal population in 05. You're right in terms of the robustness of the feedback. I'm sorry, Rob.

DR. CALIFF: We're picking apart each indívidual study. Are you going to show us any composites of the entire database? For example, this question about creatinine clearance. It seems silly to me to look at each individual study when you've got a provided database with a much larger sample.

CHAIRMAN PACKER: Are you going to be