going over safety as it relates to creatinine clearance?

DR. KOWEY: Yes.

CHAIRMAN PACKER: We'll get some of it then. But you want to know efficacy. Right?

DR. KOWEY: Yes.

CHAIRMAN PACKER: Do you have efficacy as it relates to creatinine clearance combined across the trunks?

DR. KOWEY: We have it for 04 and 05.

CHAIRMAN PACKER: Individual.

DR. KOWEY: Unfortunately, a lot of these other studies, Rob, were not in an electronic database so it's really hard to pull that kind of detail.

DR. KONSTAM: The problem with doing that is, as Bob is suggesting, which I concur, is if it's likely to be related to the levels and effect on levels, then it's an interaction between the renal function and the dosing regimen. Since the dosing regimes are different, you would have to really think about that a little bit.

I just want to say that I am concerned

about this creatinine clearance break in 004. Let me say it the way I see it. It looks like the treatment effect, which I think to me is more robust in 04 than it is in 05, is driven principally by the group with the low creatinine clearance, if you want to say it that way.

The only rationale that comes to mind to explain that is Bob's rationale that that's a group that the correction per dose didn't work perfectly so you wind up saying that it's conceivable then that it works only with where you have higher concentrations. We do believe that the adverse effect profile is going to be influenced by the concentrations.

DR. KOWEY: These are the data from 004 looking at the covariate adjustment by Cox or creatinine less than 60. Does that help you?

DR. FENICHEL: This is not the pertinent analysis.

DR. KOWEY: This is not the subgroup analysis.

DR. FENICHEL: No. This is a justified --

DR. KOWEY: This is a justified baseline.

DR. FENICHEL: That's right. If you had something that was driven by some little subgroup, then you might come up with a different result here and something might stand out. What you want is to take any of these various categories such as sex or age or creatinine clearance and show as you have in some --

DR. KOWEY: The next slide.

DR. FENICHEL: -- how it looks with people with low creatinine clearance and how it looks to people with higher creatinine clearance. You never have weight. Weight would be good. How it looks in big people, how it looks in small people. Of course, gender is kind of a proxy to that but not perfect.

DR. KOWEY: I agree. Both of these, I think, help a little bit. This one helps a little bit and the other one helps a lot. The subject analysis we showed you already.

CHAIRMAN PACKER: Any other questions on 04? If not, I think we need to re-energize. We're going to break for lunch. The study will talk about and take questions on after lunch until 3:45. We'll

reconvene at, let's say, 1:30.

(Whereupon, the meeting was recessed at 12:44 p.m. to reconvene at 1:30 this same day.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:33 p.m.)

CHAIRMAN PACKER: We will be starting in the next minute. Is the sponsor ready? We have an addition to the administrative issues for this morning so Joan will complete that at the present time.

MS. STANDAERT: Yes. For the record, in a memorandum I read earlier the exclusions were omitted. Two committee members were excluded from the discussions. That would be Dr. Roden and Dr. DiMarco. Thank you.

CHAIRMAN PACKER: Okay. Thank you. Before we start a discussion on dofetilide 345 I think, JoAnn, you had one other question you wanted to address.

DR. LINDENFELD: I do. Just a general question about both studies. As we talk about symptomatic recurrence, I want to clarify this point because I think there's a difference in -- I think I said this earlier but I didn't say it strongly enough -- there's a difference in a patient who has symptoms that are bothersome to a patient and the patient who

that just notices they have a rhythm change.

I wonder if there was any collection of symptoms that we might consider important more than occasional palpitations such as shortness of breath, fatigue, dyspnea at the time of atrial fibrillation is noticed? Or when we say symptomatic here, is all we mean is that the best we know is that the patient noticed a change in their heart rhythm?

DR. KOWEY: We actually have that on a back up -- what's the number?

DR. LINDENFELD: I know we have baseline symptoms but I haven't really seen --

DR. KOWEY: No. We have symptoms. 173? This is from 004. This is change from baseline to endpoint for 004.

DR. LINDENFELD: So there's no difference between placebo and sotalol? The symptoms were not different?

DR. KOWEY: That was an endpoint. That was looking at it from change from baseline to endpoint. This is the one. This is probably a better one. This is from 05.

DR. LINDENFELD: I sort of like the other one. Can we look at that again?

DR. KOWEY: Sure.

DR. LINDENFELD: The first one. If we take all the patients, there was no difference in these important symptoms from baseline to endpoint.

DR. KOWEY: No. There was a 13 percent reduction in the d,l-sotalol for any symptoms compared to nine percent placebo. There was a 14 percent reduction.

DR. LINDENFELD: But that's not significant. Is it?

DR. KOWEY: I don't think that there were P values calculated for these observations.

DR. LINDENFELD: You don't think it would be significant if it were probably.

DR. KOWEY: You are welcome to look at this if you want to look at the symptoms which I think is what you want is the other slide.

DR. LINDENFELD: The reason why I'm making this point is because as we talk about approving this drug for symptomatic atrial fibrillation, this doesn't

really evaluate symptoms as we usually think about them and study them; that is, shortness of breath, fatigue.

This evaluated whether or not the patient noted primarily that they had a difference. I guess we could look at that and you, if I'm wrong about that, can show me. So from what symptoms we have, at least we knew before there was no difference in the two groups, no major difference.

DR. KOWEY: Wait, wait, wait. The endpoint of the trial was the time to symptomatic occurrence of AF.

DR. LINDENFELD: Right. But I think there's been some confusion in here in the fact that we are ameliorating symptoms. In other words, there's a difference between symptomatic recurrence of atrial fibrillation which is not serious. It may have been in some patients. They may have had more shortness of breath and more fatigue.

DR. KOWEY: Here is the percentage of patients who had specific symptoms during their return to symptomatic atrial fibrillation flutter by dose in

05. This is the question you asked which is what was the symptom that they had at the time that they had their recurrence. This is it.

DR. LINDENFELD: And it doesn't look like to me there are any major differences.

DR. KOWEY: No, no, no, no.

DR. LINDENFELD: Okay. Make sure I understand.

DR. KOWEY: This is not an endpoint. This is just telling you what the symptom was when the patient had their recurrence.

DR. FENICHEL: JoAnn, suppose this were a mortality trial then you find that at endpoint everybody is dead.

DR. FISHER: If you look at the ends at the top there are different numbers experiencing the recurrence. See this at recurrence.

DR. KOWEY: You had to have a recurrence to get on this slide.

DR. LINDENFELD: At recurrence. Okay.

CHAIRMAN PACKER: Okay. I just want to keep moving and move on to dofetilide 345. Just to

clarify the record, Dr. Kowey indicated during the break that the information on dofetilide study 345 was actually obtained from the Internet. I don't know how many of you know that everything you see today can be accessed through the Internet. I guess that shouldn't be too surprising. You can access anything in the world through the Internet these days. I just wanted to --

DR. KOWEY: Including what happened at Center 29.

CHAIRMAN PACKER: Peter, it's not common for a sponsor to utilize another sponsor study to support approval. There are a lot of reasons for that. One is that most commonly sponsors don't do comparisons against drugs not approved for the indication that is being pursued.

DR. KOWEY: Correct.

CHAIRMAN PACKER: And also I think frequently a lot of times the studies that are carried out by a sponsor tend not to demonstrate that the competing drug works. Consequently, there is little enthusiasm to use it. I think the concern that I

have, and maybe the other members of the committee share it, is that when a trial is reviewed by the FDA, that has an active component that is being reviewed in the NDA and has the comparator.

There is a lot of attention given to the quality of a comparison for the active drug being considered and not necessarily a lot of attention being given to the comparator. In other words, checks of integrity, completeness, all the things that the FDA does are frequently not done, for example, in dofetilide 345 but sotalol arm because the sotalol arm isn't the arm on which a claim is being sought.

I guess one question that I have is to what degree can we utilize the sponsor's presentation in what may literally be for the purposes of today's discussion a study in which the integrity of the sotalol database has not been as carefully evaluated as the integrity of the dofetilide database in study 345.

DR. KOWEY: Can we ask Bob what his opinion is about that?

DR. FENICHEL: I was hoping you wouldn't

ask that. I think the answer is that this committee can use anything it wants. I have heard members of this committee refer to their vast clinical experience. Indeed, we recruit members of this committee in a slightly different sense of that phrase because of their vast clinical experience. So even if that experience is not explicitly referred to in your every remark, it is taken to carry the weight to a certain extent.

Now, so may you use 345 in supporting sotalol? Yes, you may. Is the FDA able to use 345 in supporting sotalol? I'm not really sure. I think the answer is probably not. What I'm drawing on is we certainly have experience with, say, competing sustained release products for common chemicals like verapamil, propriadin.

The question is, well, can the new sponsor make use of the animal toxicology data for the existing product? The answer is no, not without a right, presumably a purchased right, to refer to that data which is owned by the original sponsor or sponsors.

I imagine something like that applies here and that if there were some intended claim supported only by data from 345, I think that would be very problematic because that's the strict analogy to the animal toxicology case where there isn't anything that people know about verapamil in rats except from those studies that were done on rats.

Someone who comes along with a new sustained release form really doesn't have any intention of doing experiments in rats if he or she doesn't want to and doesn't have to. What in some sense we have done is they have to unless they can get right to reference the previous work.

Here it might be true that this is part of a big picture that there isn't some unique fact that can be found only in 345. If there is a unique fact only in 345, my guess is that this sponsor can't use it. I'm not sure that is correct.

CHAIRMAN PACKER: The reason for bringing this up is, (1) it's unusual and, therefore, we need to talk about it. It may or may not be relevant and the committee will probably make clear in its

subsequent comments how important 345 might be in their deliberation.

One concern I have is that it's difficult for us to ask you questions about 345 that you can answer. In fact, it's almost impossible for us to ask you the same kind of questions about 345 that we're asking about 04 or 05 or the other studies. I mean, if one were to ask about dropouts, completeness of follow-up, issues related to symptomatic or nonsymptomatic, it's hard to get those answers because my presumption is that the details of that, which are so important to our deliberation of 04 and 05 are known primarily to the sponsor of 345 and may not be known to either you or the committee.

DR. KOWEY: Let me just say a couple of things about that. First of all, I don't disagree with you at all. I also agree with Bob that if this were coming out of the blue as a totally novel concept, that we would be concerned and would not have presented it.

Two issues; (1) It is being used in this context to provide reassurance that a dose of 80

milligrams twice per day is effective. In fact, I could turn this argument around a bit that you are using about credibility of data and say that as a positive comparator it was the last thought on Pfizer's part that they wanted to show up the 80 milligrams twice a day. In fact, when they presented it to the advisory committee in January, I remember looking at it and thinking, "Okay." I passed it over. I didn't even think about it.

It was only after it was pointed out to me later that, gee, 80 milligrams twice per day did really well in that study. I think in reverse fashion, although I agree there are problems with validation, it actually provides me some reassurance that the observations that we've made in studies where we have an interest or this sponsor has an interest were made by somebody who really didn't have an interest. It is a novel concept and I agree with you, Milton. I don't remember ever having seen this before, this drug dofetilide is not yet approved.

CHAIRMAN PACKER: The concern I have is not its novelty. The concern I have is it is our

ability to interrogate the data and the issues with the same degree. I mean, our reflex would be to say, gee, that P value looks pretty small.

DR. KOWEY: Is there some way for the agency if they thought they needed to do that to interrogate the data on a more rigorous basis?

CHAIRMAN PACKER: The problem is --

DR. FENICHEL: If you buy the rights to the data from Pfizer, I'm sure he'll do it.

DR. KOWEY: I don't have a check with me but I'm sure --

DR. FENICHEL: Look, I think that is a real problem but what I would recommend to the committee is I don't think this is different from the problem that arose with Center 29. I don't think it's different from the problem that arises implicitly all the time in looking at files, which is to say, well, maybe these results will not survive audit. Maybe the agency was convinced after looking at the data. But then when we send the DSI person around to the site, he finds that the patients were made up or whatever.

The committee should proceed with the data

on its face. There may be questions that cannot be answered by the sponsor because of peculiar circumstances here. There will be other questions that are similar to the questions that always arise in terms of audit not having been done. Of course, that's true.

I think as regards the rights to this data, if that ever becomes pivotal in trying to establish some otherwise unsupported fact that the sponsor wants to assert about sotalol, I think that's going to go ultimately to -- it's not going to be my opinion. It's going to be something that the FDA general counsel deals with. The way to deal with lawyers is not to ask them what to do. It's tell them what you want to do and then see how they will allow you to do it. That's the same thing here.

DR. FISHER: Could I ask Bob a hypothetical? What would happen if sotalol in 345 actually looked harmful or it had a lot of adverse event data. You could not explicitly consider that? I mean, that would be a horrible thing to happen.

DR. FENICHEL: Well, you're right. I

don't know what the answer is. I think the answer is that in that setting this would be like the sponsor is obligated under law to inform FDA of whatever it knows about the drug. Very often people tell us, "Well, here is some literature of some guy's study reported somewhere. We don't have the data and we don't know very much about it but we found it so we're passing it on."

Most of the time that stuff doesn't amount to much. Sometimes it is. Well, sometimes it's stuff like adverse reaction. Here is a report from some minor journal somewhere of an adverse reaction to our drug. We don't even know if it's true. We don't know very much about it.

Sometimes on the strength of that we tell the firm, "Look. This sounds suspicious. You ought to study that." The firm goes back and studies it. We do collect adverse things and we are able to consider them in that light.

You know, I suppose to carry your hypothetical to the extreme, suppose that 345 were very large and what it had demonstrated had been not

that sotalol 80 milligrams was pretty good, but rather that 80 milligrams of sotalol killed everyone who took it. Well, what would we do with that? That would be very tough. We would have to deal with that. That's not at all like the current situation.

CHAIRMAN PACKER: Okay. I think we have at least noted the issues. I think we have addressed the issue as much as we can. I would ask the committee that to the extent that 345 influences any of your votes or deliberations, you should make it clear so that it is clear to the division. If it's irrelevant, that's fine. If it's relevant, please make clear that it is relevant. It's just that we can't really do a whole lot about asking the sponsor questions about a study they didn't do.

JoAnn, I think you had one more question before we move on to the next thing. You're fine? Okay. We'll move on to study 014. JoAnn.

DR. LINDENFELD: We're told that three subjects were entered twice into 161. Is that correct? I was wondering if you could tell me what the study looks like without those patients who were

considered twice, or did it make any difference?

DR. KOWEY: The company will address that.

DR. LINDENFELD: I don't know if it helps. Page 69 of our briefing document says that three of the subjects were withdrawn and then re-enrolled. It seems like an unusual --

DR. MARROTT: We will check by the board and come back to you on this question.

DR. LINDENFELD: And then just clarify for me subject dropouts were followed, not followed?

DR. MARROTT: They were not.

DR. LINDENFELD: They were not found just as in 05.

DR. KOWEY: Is that correct?

DR. MARROTT: That is correct.

CHAIRMAN PACKER: Just to clarify, about 20 percent of the patients had AEE's and didn't have follow-up. Is that about right?

DR. KOWEY: That's correct.

CHAIRMAN PACKER: Any other questions --

DR. KOWEY: It is actually 15 percent. Do you want to see it?

CHAIRMAN PACKER: No. Any other questions from any other member of the committee on study 014? Okay. Let's move onto study 9A.

DR. LINDENFELD: One question on 9A. Let me see if I got this right. The time to recurrence of arrhythmia meantime was six days with placebo and 13 and 18 days in the two sotalol groups. Is that correct?

DR. KOWEY: Give me one second and we'll put the slide up.

DR. LINDENFELD: Just a rough idea if that is correct.

DR. KOWEY: It's slide 54, please.

DR. LINDENFELD: I guess maybe other people want to comment on this. It brings up what is statistically significant and what's clinically significant in terms of -- I know these are recurrent arrhythmia so maybe this makes more of a difference.

DR. KOWEY: Yes. Remember this had a fairly arcane running so that we were collecting data by frequency of occurrence. It was stratified by the amount of time the patients were watched. In

addition, the analysis was also adjusted for that period of observation. This is clearly a group of patients who have very frequent arrhythmias judging from the placebo time to relapse.

Because there was such an enriched patient population, P values for the differences between the groups are significant. Not only for d,l-sotalol but also for d-sotalol. Clearly it was a different patient population.

DR. FENICHEL: Peter, let me take off on something in JoAnn's question and that is, of course, each of these trials was analyzed as a survival trial. If this were literally survival and the endpoint was death, one might say they all died within a couple of weeks. Does it really make that much difference?

Then, of course, it is recurrent arrythmia and what we see in each of the trials going back to, I think, the flecainide trials is that the analysis has been a survival analysis with the assumption that the Poisson parameter, if you like, that the time to recurrence to the first recurrence is somehow typical and representative of the subsequent time between

recurrences which is a plausible thing to assert.

But I don't know, and maybe Ed Pritchett wants to speak about this, because I think this is a conceptual issue in this area. Is that well validated that this kind of analysis is, in fact, predictive of what would happen over the course of months or years of continuing therapy.

DR. PRITCHETT: There are several lines of data that support that. First, we know that in individual patients that the individual occurrences, serial occurrences of a symptomatic supra ventricular arrythmia constitute a Poisson process as you said.

Secondly, we know that in a group of patients -- by the way, these two observations were published in the same paper in Circulation in 1981 -- in a group of patients if you measure the time to first event and then the time between the first and the second, the distributions are identical. They sit right on top of each other.

Finally, you may recall from the flecainide program where in that program there was an attempt to measure to record four events during the

follow-up period and the primary analysis was timed to first event. If you look at the average time between events for four events and the ratio between the flecainide and the treatment group, it came out to be the same as for the time to first event. The time to first event is a good estimate apparently of what this does to the rate of recurrences over time.

DR. THADANI: On this study on the recurrences, by how frequent ECG is monitored? Is it Holter or again just the transmission of 25 seconds? Because if it is not Holter, as you said, the Holter shows 10 to 12 times more than this one. How much reliance can one place if it's not the Holter?

DR. MARROTT: It's not Holter.

DR. THADANI: So it's just transtelephonic monitoring. As we have heard, the reliance that could vary from incidents 12 times less than the Holter. How much reliance with a sample size so small one can't compare anything on it? Is it possible that if done more frequently you'll have more episodes than other groups?

DR. KOWEY: It's certainly possible. By

the way, the endpoint here, the ECG documented recurrence of atrial fibrillation. It doesn't necessarily mean that it has correlated its symptoms.

DR. THADANI: Sure. It could be just on that 20 second recording which is negative and the event could have been positive.

DR. KOWEY: That's right.

DR. PRITCHETT: I might just comment with respect to, as you just said, the important thing is that this is a symptomatic outcome. Also with respect to the treatment effect here, I think Peter pointed out this is a very, very active group of patients with a median recurrence time of six days.

What you see with the 80 milligram dose is a doubling of the median time and then the 160 a tripling by the standards that the committee has used in the past which said that the minimum useful effect would be a doubling. This certainly meets that.

CHAIRMAN PACKER: Abe?

DR. THADANI: It's only a nine week study and the frequency of monitoring could have been two or three times.

DR. PRITCHETT: No, no. The patients were called in when they had a symptomatic event.

DR. THADANI: It was only a nine week double-blind study.

DR. PRITCHETT: At the median time of event the placebo group was six days, it could have been a lot shorter than nine weeks and all the useful information would have been captured. This is a very, very active group of patients.

DR. KARKOWSKY: What I would do is like to make a couple of things clear. The first thing is that the analysis for the overall study if one includes discontinuation as having bad outcomes I don't think makes statistical significance. That's point number one.

Number two, the a fib flutter subgroup was never p specified as a subgroup in this study. No. 3, that in this group if you look through the study there were people who had arrhythmias classified as either a fib and a flutter, a fib and atrial tachycardia.

Number three, one could have dissected the group to decide that the a fib group included those

people, didn't include those people, or include some of those people. If you look at the numbers, and if you have one placebo patient or two placebo patients who didn't have recurrences, the P value would have probably gone away.

CHAIRMAN PACKER: Maybe we should ask a question. In general we think that looking at subgroups of studies are interpretable if the overall study was positive. Was the overall study -- we don't know the results of the overall study.

DR. KOWEY: We showed you the intention of treatment on slide 53 for all patients. This is for all patients.

DR. CAIN: Ed, can I ask one follow-up to your question -- to your comment and that was if there is a doubling and tripling in this population group, the confidence that that doubling and tripling would be applicable to other patient groups, how far can one stretch that as opposed to the data simply being specific for this particular population.

DR. PRITCHETT: I think that how generalizable the data are depends on how

generalizable the entry criteria are. One of the things that made this group so active was the screening that was done when they set up that screening period to say put patients in the one-week bin or the two-week bin which developed a very enriched population of patients.

I believe that those numbers would likely hold up if the entry criteria were related sort of to the type of patient, not just -- in other words, I don't think you have to screen your patients and see whether they have one episode per week or three weeks in a row to obtain this benefit.

DR. KOWEY: Michael, do you want to see the inclusion/exclusion criteria?

DR. CAIN: It's okay.

DR. THADANI: On that issue of paroxysmal a fib which is happening so often, I personally would have liked to have seen the frequency of episode rather than just -- I realize the study was designed for the first episode, but if a patient is getting 10 episodes on a 24-hour Holter or 20 episodes and then that information is available, that would be very

useful to realize that not only you're reducing the onset of the first episode but are you reducing the number of episodes. These patients are obviously bothered with recurring symptoms. Any data they have?

DR. PRITCHETT: Well, No. That is very closely related to the question that Michael Cain answered. What we know is that --

DR. THADANI: In this population was there any data?

DR. PRITCHETT: Well, it wasn't done in this study. What we know in general about patients who have recurring arrhythmias are that when you put them on observation and measure time to first and then measure time between the first and the second that that number is the same. And from the previous clinical trials program done with Flecainide presented to this committee in October of 1989 and published in Circulation by Geoff Anderson in 1991, we know if you follow people to the fourth event and then look at the average time interval between events compared with the median time interval, that those numbers are nearly the same.

There is a substantial empiric body of data that tells you that measuring treatment effects by looking at time to first event is a good way to estimate long-term effects.

The best study done to try and follow patients for multiple events was the bidisomide study conducted by Ciro which was published in Circulation in 1995 which recruited 1,200 patients with atrial fibrillation and 200 with PSVT, and we tried to follow patients for a full year no matter how many events we had.

What we found is you could keep them in the trial for a couple of events before they demanded to be taken out if the drug wasn't working. While it's a nice idea to say let's follow patients until they have eight events or let's capture every event over the course of a year, in practical terms that's very, very difficult to do. No one has been able to do it successfully.

CHAIRMAN PACKER: Okay. If there are no other questions on 9A, let's move on. I guess the only study remaining is study H. This is the open

label comparison of quinidine and sotalol. Any questions? Okay. Are there any questions at all on any other issues related to efficacy? Are we in a post prandial lull? Let's proceed to safety, please.

DR. GRABOYS: There's three groups of patients. This may be extraditable to I think all of the studies but there are three groups of patients here that are missing in terms of being able to make a decision about risk benefit.

Two have already been alluded to. One is the octogenarian population. We are increasingly seeing people in their 80's who are presenting with atrial fibrillation. We question then in that population what kind of data do you have to support safety in that population.

The second is women, particularly in view of the fact that QT prolongation seemed to occur more commonly in women with sotalol, and the fact that has already been alluded to, women seem to be under-represented in the data.

The third is the African-American and Black population in which you see that 99 to 100

percent or even 90 percent in some of the studies are all white. How do we then interpret that in terms of, again, safety utilization in the Black population.

DR. KOWEY: Tom, I'm going to address, in the safety presentation, I'll talk about age and gender. I do have some other backup slides that I'll show you on age and gender if you want to see them. Unfortunately, many of these studies were done in Scandinavia.

A couple of these studies, as you've heard already, were done in countries where there are no African-Americans, and so the database, as you point out correctly, does not contain them. It is something I'm sure that the sponsor would consider doing in a post-marketing effort.

CHAIRMAN PACKER: Okay. There being no further questions about efficacy, let's move on to the presentation. Rob, yes?

DR. CALIFF: Just one question. This is a mixture of studies not all of which were done specifically for marketing for this indication. Out of the universal study looking at sotalol for atrial

dysrhythmias, is this 100 percent of those studies?

DR. KOWEY: The only studies that we have in the database that we did present to you for efficacy where G, which was a subpopulation study of MSPT cohort and then the two Stige studies which were really not done specifically to look at these studies. Stige II sort of was but it was stopped very early and there was no useful data.

DR. THADANI: There are no other studies which have been done, have negative results not published or not presented or not shown here?

DR. KOWEY: I'm sure there are studies that have been kind of not published but not by the sponsors.

DR. THADANI: There is no end date on those studies?

DR. KOWEY: No.

DR. THADANI: All the end dates have been--

DR. KOWEY: There are compassionate use studies but they are not --

CHAIRMAN PACKER: Any ongoing trials at

the present time?

DR. KOWEY: No.

CHAIRMAN PACKER: Let's move to safety.

DR. KOWEY: I asked Milton and he agreed so I'm going to hold him to it. I only have few slides on dosing recommendations, so I'm going to cover these last two topics. Neither of these areas are nearly as long as the efficacy discussion so we should be able to get through it fairly quickly.

This is the composite of the clinical information we are going to use for the safety presentation, 2,184 patients. I'll be pointing out that there are four studies that are in an electronically pulled database that you've already heard about this morning, 05, 004, 014, and 9A.

We have safety information for the most serious adverse events in the unpulled and I'm not going to be discussing specifically issues in the compassionate use studies, although I will present you a bit of information about the most serious adverse events in the total database.

I do want to point out, Milton, that we

are going to show you data for deaths and torsade only from the 345 study of dofetilide. This will be grouped basically into three parts of this presentation. The first part is to look at the most common adverse events. This will be, as I said earlier, from the pulled database.

I have a discussion of clinically important adverse events from a larger database. Then I'm going to present supportive studies showing no access for structural heart disease. One is the post-MI Julian study which the agency felt very strongly that we should show you today, an old sotalol study. Then the ICD study that was recently completed and the results are currently in review.

Again, I want to make sure that everyone understands that we will be using different denominators for the safety discussion. For the most common AE's we'll be using a pulled placebo controlled database. We will be showing you data from the double-blind phase of these four pulled trials. So we will have 415 patients in the sotalol arm and 282 patients in the placebo arm for the most common AE's.

For heart failure, stroke, and myocardial infarction, we have data from the controlled phase of eight controlled studies. That's the four pulled and the four older studies for an end of 656 and a placebo group of 358. We've added in for death and torsade data from the dofetilide of 137 patients in placebo and in the sotalol arm. That's where these numbers come from.

This is the most common adverse events in the clinical trials. This is looking at the pulled placebo controlled trials. And I think the numbers speak for themselves. You probably would expect for a beta-blocker to see fatigue and dizziness, bradycardia, dyspnea, and palpitations as adverse events in the d,l-sotalol arm at a higher frequency than in the placebo arm. These are the discontinuation rates; in the d,l-sotalol arm 17 percent compared to five percent in the placebo arm.

I'm now moving into more serious adverse events. You are going to see this kind of format on several of these slides that will be coming up. We have put the studies on the left-hand side that

generate the information. The d,l-sotalol placebo, a comparator if one is in the study or one is included in these particular studies. That would be d-sotalol or quinidine.

And this is for deaths in the controlled phase of the eight controlled studies; the dofetilide trial, 245. Again, we are adding these numbers. This is the percentage of patients who died in the program, 0.5 percent compared to 0.4 percent in the placebo arm. These are the numbers for d-sotalol and quinidine.

These are the patients who died in these trials. In the d,l-sotalol arm three of the deaths were in study 014. These three patients received doses of the drug which were in excess of the dose that we are recommending for this particular patient. You notice that there are no deaths in 05 or 04.

There was one death, as I already mentioned to you, in H which was a myocardial infarction in a patient who got 160 milligrams per day. The cause of death, like I said, was myocardial infarction. In the placebo arms, in 004 there were

two deaths, as I have already mentioned. Both patients have structural heart disease.

This is torsade in the controlled phase of the eight controlled trials and dofetilide trial 245. The total is four for 0.5 percent, placebo arm 0.2 percent, none in the d-sotalol, and one in the quinidine arm. I want to emphasize that in this entire data set all these patients who had suffered torsade, there were no deaths.

These are the torsade cases themselves. This is, again, the controlled phase of the controlled trials. Study 014 was where three of the sotalol related torsade events occurred. These are the number of days that the patient had been on the dose that led to the torsade.

I want to point out this little cross here. That patient required a cardiovert. These three patients had self-terminating torsade.

In this group of controls, again, I mentioned earlier that there was one patient we studied each who developed torsade and that person required a cardioversion. The patient in 004 had

received a placebo and developed torsade, actually had torsade, or taken the marketed anti-arrhythmic drug after stopping placebo. So this is a torsade experience in controlled clinical trials.

I want to show you an analysis of the back end torsade in the controlled phase of the eight controlled trials and a dofetilide study segregated on the basis of dose in the study. This is within the recommended dose for this indication of 320 milligrams per day. This one, this is in excess of 320 milligram dose. There were 62 patients in the controlled phases of controlled trials who received a dose greater than 320 milligrams.

There were 734 patients who received the dose that we are recommending. This is death. There was 4.8 percent in this group, 0.1 percent in the less than 320 milligram group. In the placebo the death rate was 0.4 percent. This P value is Fisher's Exact test comparing these two columns. Not comparing placebo, comparing this column with this column.

This is the torsade rate, 3.2 percent for patients who received greater than 320 milligrams.

There was 0.3 percent in patients receiving less than 320 milligrams. This is the placebo rate which was a little tiny bit less. This is the P value with the difference between that group and that group. This is important because of recommendation of dose for this indication.

This is heart failure in the controlled phase of the eight controlled trials. Here we do not have a dofetilide information so at the end the smaller 656 patients, 1.5 percent in the d,l-sotalol group. You can see it's 0.8 percent in the placebo group, 0.6 percent for d-sotalol, 1.3 percent for quinidine.

This is stroke in the controlled phase of eight controlled studies. d,l-Sotalol, 0.9 percent; placebo, 0.6 percent; d-sotalol, 0.5 percent; quinidine, 2.3 percent.

This is myocardial infarctions in the controlled phase of the eight controlled studies; 0.5 percent for d,l-sotalol, 0.6 percent for placebo, 0.6 percent for d-sotalol, and there were no cases in the quinidine group.

This is a slide now from the entire safety database, not just from the eight controlled studies, showing the overall incidents of death, torsade, heart failure, stroke, and myocardial infarction in the entire database including the compassionate use studies in the open label experiments following the controlled phase and these are the percentages. Remember that for death and torsade, the data includes patients in the dofetilide trial.

I would like to point out that there were 28 cases of torsade in the entire database. Of those 28 patients there were two deaths and torsade.

I very briefly want to run through the two supportive studies for no excess mortality and structural heart disease. Again, this was an agency request and this one is a study which has just recently been completed and I'll do this briefly.

The Julian study was a post-myocardial infarction study very much in the genre in the early 1980's of beta-blocker trials after myocardial infarction. The goal of this study was to evaluate the efficacy of sotalol in reducing all-cause

mortality reinfarction following acute myocardial infarction. There were 456 patients, the usual age group enrolled five to 14 days after MI. The primary endpoint was all-cause mortality and reinfarction.

We are only going to show you data for all-cause mortality there's been some question about the way that the reinfarctions were quantitated. We have those data if you want to see it. A statistical test and it was a one-year study which was published in Lancer.

Persons, as I said, who had a recent myocardial infarction were randomized to a very, very novel dose of sotalol, 320 milligrams delivered as a single dose in the morning compared to placebo, double-blind treatment for 12 months. For those patients who could not tolerate 320 milligrams a day, they could have their dose reduced to 160 milligrams per day but in the protocol specifically indicated that that was for patients with bradycardia less than 50 beats per minute.

This is patient characteristics. There were mostly males in the study. This is the history

of coronary arteries. There is hypertension prior to the acute event. I want to point out that during the infarction a substantial number of patients had had heart failure, an increased cardiothoracic ratio, relative hypotension. There's a relatively even split at both ends of the study as to anterior, interior infarct.

This is the Kaplan Meier. Well, this is the cumulative mortality total for the study for d,l-sotalol and for placebo. There has been some discussion about the early mortality that was seen in the d,l-sotalol group. I want to point out that at no time during the first 10 to 30 days of this study was there a statistically significant difference between the two groups in terms of mortality and there are many explanations that you can discuss as to why that may have happened.

But in any case, the study showed that there was not only no excess mortality with d,l-sotalol for a one-year time frame, but in fact there was a reduction in mortality although it by no means met any kind of statistical significance.

The second study, the so-called ICD study, was a test of the hypothesis that d,l-sotalol would be effective in place of the placebo preventing all-cause ICD shocks. As many of you know, patients who have defibrillators are prone to frequent device disrupt causing a significant amount of morbidity and, in some cases, mortality.

Population of patients with 202 patients with ICD's who were implanted for the indication of life-threatening ventricular arrhythmias. I'll show you a breakdown of that in a moment. The primary prespecified endpoint was time to first all-cause ICD shock with that after randomization. And it was a Kaplan Meier survival curve with a log rank test.

As I said, these are patients with life-threatening ventricular arrhythmias. The randomization was stratified for ejection fraction. Patients were distributed by ejection fraction greater than and less than 30 percent. In the presence of renal insufficiency in this study, the find is a creatinine clearance between 30 and 60 cc's per minute. Patients received the once daily dose similar

to what was done in 05. Patients less than 30 cc's per minute were excluded. The therapy was continued double-blind for 12 months.

And in the sotalol arm of the study -- well, in both arms of the study there was the opportunity for changing dose which was done blindly.

This was the inclusion criteria. These were patients who were undergoing first implantation or placement of an ICD within three months of enrollment. For those patients who had had replacement, it was necessary for them to have had at least one shock during the preceding six month period in order to be certain that these were not simply quiescent patients.

Tiered therapy ICDs were used in all cases and all devices had electrogram storage and logging of shock and other types of cardio pacing episodes for us to be able to retrieve the information and make a judgment as to whether or not the shocks were appropriate.

I would also point out that predistress

testing was carried out in this cohort to guarantee that shock energies were at least 10 joules below the maximum ICD ouput. This is fairly standard clinical practice for ICD input.

These are the baseline characteristics of the patients in the placebo arm and in the sotalol arm, even number of patients. This is male being two percent, age matched. I would point out that a number of these patients had undergone coronary interventions. A substantial number of these patients had previous myocardial infarctions. There was a small percentage of patients who had Class II New York Heart Association.

I would also point out that as a typical ICD patient population, a third of the patients that had aborted sudden death, two-thirds of the patients had ventricular tachycardia either symptomatic and/or inducible in the physiology laboratory.

This is the primary three-step spot analysis for the ICD study upon the first all-cause shock or death internalization with the intention to treat analysis. This is the true value for the

observation and difference between sotalol and placebo.

If one relied on the investigator's interpretation of the electrograms to determine whether or not the ICD shock was appropriate for VT/VF -- that's the first shock was appropriate for VT/VF. These are the data. The P value is 0.007.

Finally, this is all-cause mortality and intention to treat analysis or placebo, 4.6 percent, and for d,l-sotalol, 2.6 percent. There were no sudden deaths from this clinical trial.

This is just to make you aware of the fact that when we look at the study based on the stratification of less than and greater than 30 percent ejection fraction, there was consistency of the results across those two strata.

I will conclude from this entire safety discussion that doses between 80 and 160 milligrams twice per day are safe. In fact, in study 05 and study 04, where they were the doses used, there were no deaths and there were no extensive torsade. Discontinuation due to adverse events, as we've seen

before lunch, is dose related, but when titration is permitted, it maximizes the benefit to this ratio.

The incidents of death, torsade, and other serious AEs in the entire database as well. It appears, therefore, justified that in patients who have structural heart disease, outpatient therapy may be safely undertaken.

I just want to make, Milton, if I may, just the three or four slides on the characteristics of dosing recommendations because this does have to do a good deal with safety. This gets to a question that we discussed earlier, and that is the electrophysiologic and pharmacodynamic effect of this drug, vis-a-vis its affect on electrophysiologic parameters and then on efficacy. These are data from the randomized dose ranging study 05 looking at heart raté QT and QTc. Heart rate is illustrated on the slide in pink and you can see that with increasing dose of the drug, there is a progressive fallen heart rate. But there is also a more profound increase in the continued interval if one gets the 160 milligram dose, which, again, in these patients for the most

part was taken twice per day and with a renal impairment was taken once a day. If you examine the information regulating QTc to the dose response in study 05, the pink bars are change. This is delta now PTC in milliseconds. Our presumed study states from baseline and QTc. And as you would expect, as you increase the dose you increase the effect on QTc. The green is a Kaplan Meier estimate of relapse-free intervals, a relapse-free rate at 12 months showing a progressive effect by dose.

Based on all this information, we would make the following recommendations about dose. First, as in the clinical trials, it is extremely important that careful attention be paid to identify and correct the risk factors for coarrythmics effects of sotalol which include hypokalemia, tachycardia, and QT prolongation, either a congenial or acquired on the basis of use, for example, of other drugs which come on in the interval which are well described.

Sotalol may be initiated on an outpatient basis, as I said, about structural heart disease, but doses greater than 160 milligrams twice a day, or once

a day in patients with renal dysfunction, are not recommended. The titration is an extremely important part of using sotalol. It's the way we use it in clinical practice. It's the way it was done in several of the clinical trials.

And we think that the data adequately supports these recommendations. Treatment should be initiated with 80 milligrams twice per day. We have data from study 345 and study 05 which provides, we think, comprehensive evidence that the drug works at that dose and has a good safety profile. Remember, in study 345 there were no deaths and no torsade, and neither were there in study 05.

Study 05 provides evidence of efficacy and safety for 120 milligrams twice per day, which should be the second step in the titration process. Many physicians routinely go to 120 milligrams twice per day even if the patient has had no recurrences with 80 milligrams twice per day on the principal that this may be the most effective dose.

And then, finally, for patients who do not respond to 120 milligrams dose, study 004 suggest that

d,l-sotalol at 160 milligrams twice per day is effective and safe.

That concludes my comments.

CHAIRMAN PACKER: Peter, could you just go back one moment.

DR. KOWEY: Can we go back?

CHAIRMAN PACKER: Yes. Statement No. 1, you say study 05 provides evidence for efficacy and safety at this dose?

DR. KOWEY: I would say that there is a better effect but not statistically significantly better effect for 80 milligrams in 05.

CHAIRMAN PACKER: First of all, I don't think there was anything that one could talk about at 80 milligrams versus placebo in study 05.

DR. KOWEY: Can we go back at least two slides? Okay, I agree. The reason I said it is because there are patients who will respond to an 80 milligrams twice per day dose. We don't know how to preselect those patients necessarily, but I think, as I said in clinical practice, we usually start at 80 milligrams twice per day.

CHAIRMAN PACKER: I'm sure 80 milligrams twice per day is effective with people of creatinines of 4. I'm joking.

DR. KOWEY: Or for people with small body size, as Bob was talking about earlier.

CHAIRMAN PACKER: The issue here is not to question the recommendation of where to start but to question your conclusion that that starting dose is effective or has been shown to be effective instead of the 05.

DR. KOWEY: Okay. I will concede, Milton, that most of the efficacy data for 80 milligrams has to come from 345. But we do have safety data from 05 and that was a compound sentence that said safety and efficacy. So, maybe I can hide behind that.

DR. THADANI: Also, I think you can't say some of the patients respond; so did the placebo patients, 28 percent, so that's a nonstatement.

DR. KOWEY: Well, again, it depends on how much confidence you place in study 345.

DR. THADANI: I realize that but there's only 2 percent difference. I think Milton's point is

very valid.

DR. KOWEY: I have to concede that was overstated.

CHAIRMAN PACKER: Why don't we begin with JoAnn in the conventional way.

JoAnn, questions about safety?

DR. LINDENFELD: Just to start off, could you show us a list of the drugs that were excluded in these studies? I guess the question is were they the same. I know anti-arrythmics were excluded. And that ties in with verapamil. It just said in the protocol there was a list of excluded drugs. Just for the purposes of how we use these drugs, do you know what that included? Erythromycin, bactrim?

DR. KOWEY: Yes. The investigators were instructed in the protocol to exclude the use of any drug that prolonged the QT.

DR. LINDENFELD: Could you just show us a list of that so we --

DR. KOWEY: We don't have a list of the actual slides.

DR. LINDENFELD: So any drug that might

prolong QT but there was the specific --

DR. KOWEY: That was specifically an exclusion criteria.

DR. LINDENFELD: And approximately how many were there on there, 30, 20? Was there a large number?

DR. KOWEY: I'm sorry?

DR. LINDENFELD: There were a fairly large number on that list?

DR. KOWEY: Of drugs? Oh, yes.

DR. LINDENFELD: That the investigators looked at.

DR. KOWEY: It's a big list.

DR. LINDENFELD: Again, that doesn't take away from the efficacy but there's a large group of drugs that these older patients might be taking that interfere here.

DR. KOWEY: Absolutely true.

DR. LINDENFELD: Just to be sure, I understand that even in the 004 study that dotiazam and verapamil were required to be withdrawn prior to the use of sotalol so that those drugs were

specifically excluded because that gets back to the risk of bradycardia and there is a fairly substantial risk of bradycardia. What I wanted to ask was, do we know was that primarily following conversion to sinus rhythm, the bradycardia?

DR. KOWEY: Yes.

DR. LINDENFELD: Okay. Many of those were classified as serious adverse effects. Is that correct?

DR. KOWEY: Which? I'm sorry, JoAnn.

DR. LINDENFELD: The bradycardia.

DR. KOWEY: Yes.

DR. LINDENFELD: A number was quite serious.

DR. KOWEY: A number of them were classified as serious. Yes.

DR. LINDENFELD: And in terms of adverse effects --

DR. KOWEY: Do you want to see the percentages?

DR. LINDENFELD: That would be great.

DR. KOWEY: Can we have the common adverse

events greater than 6 percent slide in the core?

DR. LINDENFELD: I just want to emphasize here that the safety things will include not only the QT prolonging drugs but drugs that may cause bradycardia.

DR. KOWEY: Here it is. Actually, you know, I take it back a bit. This is greater than 6 percent incidence bradycardia. I take back what I just said. It's actually a small percentage that were considered severe.

DR. LINDENFELD: And then can you give us some information about specific subgroups, the ones we know are high risk for torsade?

DR. KOWEY: Yes.

DR. LINDENFELD: Heart failure, female gender, age greater than 70. Specifically, I wondered LVH wasn't specifically included but let's get back to the group Tom talked about, the African-Americans with LVH who might be considered high risk. Do you have some specifics for those groups?

DR. KOWEY: I don't have LVH but I can show you a lot of the other stuff.

DR. LINDENFELD: Was LVH excluded? I didn't see that as one of the --

DR. KOWEY: No. It was not excluded. There were a smattering of about 20 or 30 percent of the patients in the trials that had hypertension so LVH was not an exclusion.

Can I have backup slide, please, No. 361. This is population less than and greater than 60 in the controlled phase of the controlled trials. These are the deaths in the greater than 65 and less than 65 group. Heart failure, stroke, torsade. There was more dizziness in the older patients and there was more bradycardia in the older patients.

DR. GRABOYS: Peter, those over age 65, what was the average age? We need to know about the older population.

DR. KOWEY: I'll tell you, Tom, I don't have the data but I can tell you that there was not a large number of very, very old in the study. The octogenarians that you were talking about, I'm afraid there really weren't very many in the trial. I don't know exactly what the number was.

DR. LINDENFELD: Do you have torsade by gender of creatinine clearance?

DR. KOWEY: Yes. Which way do you want it? You want gender first or you want creatinine clearance first?

DR. LINDENFELD: Either one first.

DR. KOWEY: Okay. How about if we do gender. And do you want torsade? This is torsade by gender and treatment in a controlled phase of the controlled class. This is female, male. This is comparative data with quinidine and there's some d-sotalol, a very small number of patients. What was the other one, JoAnn, heart failure?

DR. LINDENFELD: Creatinine clearance.

DR. KOWEY: Creatinine clearance. We can do that. Can I have 367, please. This is creatinine clearances greater than 60, less than 60. This is torsade, deaths, heart failure, stroke. There was more bradycardia in the patients who had well preserved creatinine clearances and there was more dizziness in patients with low creatinine clearances.

DR. FENICHEL: You know, I don't see how

this is interpretable really because suppose that the people in the trials generally all had creatinine clearances that were in the range of, say, 55 to 65. Well, then what you'd find is the people -- and the threshold, I think, was to cut the dose at 60.

Well, then all of a sudden the people who all essentially had the same creatinine clearance, the ones with the slightly lower creatinine clearance were actually getting a much lower dose so it looked like it was much safer in that group. I think this is hopelessly confounded.

CHAIRMAN PACKER: I think it's also hopelessly confounded by the fact that none of the ADCR people corrected. Consequently, elderly people could get more side effects on placebo than younger people. That wouldn't be too surprising. So that I think that in order to really interpret this one has to adjust for the corresponding incidence in the specific subgroups in the placebo group.

DR. KOWEY: Can I have slide 296. This is the placebo group, Milton, and this is the d-sotalol group. This is the breakdown for creatinine

clearance. I can do this basically for whatever parameter you would like.

CHAIRMAN PACKER: I think this actually, sort of, makes a point. Look at dizziness. If you compared only the sotalol group, you might expect that there was not a lot of difference in dizziness above and below 60. If you compare it to the corresponding placebo group, which is less than 60 on sotalol, less than 60 on placebo, there is a substantial difference in risk of dizziness which is not present if you do a placebo correction on the group with more normal renal function, something which one would never have picked up if one only did a comparison above and below 60 in the sotalol group.

So if you--One, I think one should always do a placebo correction, and second is that this would indicate that dizziness is an issue in the group. Much more of an issue than not in a group with more borderline, you know, functioning. The group with normal renal function, literally there is no increase in dizziness.

DR. KOWEY: Everything you said I

completely agree with. That's why we analyze the data for common adverse events with placebo in the controlled phase of the controlled trials because you had placebo information.

CHAIRMAN PACKER: Bradycardia is not differentially distributed.

DR. KOWEY: That's what I was just going to say. So you can that with the placebo correction, it's really not an issue. I can do that if you would like. I have data for other subgoups, but I think what you'll see is that it comes out as a wash in many of these studies.

CHAIRMAN PACKER: Does anyone want a specific subgroup not--that they haven't seen for this kind of placebo corrected data. I think that we would like to spare all of use having to see every single permutation and combination of these.

DR. KOWEY: Did you want to see gender?

DR. THADANI: You might show gender in QTc. I thought my reading, if I remember correctly, QTc was more prolonged in men than women. Am I correct?

DR. KOWEY: I can show you data on that on slide --

DR. THADANI: Am I reading it wrong? I thought--

DR. KOWEY: I'll show you slide 320.

DR. THADANI: Torsade is the opposite around. No, I realize this doesn't go together.

DR. KOWEY: These are data male versus female, male in yellow and female in orange. This is change in heart rate. You can conclude anything. I mean, you can look at these and decide what you think. This is QTc data and this is QT uncorrected for 80, 120, 160 milligram dose groups in study 05.

DR. THADANI: There's less prolongation in woman of QT and QTc, which--You know, normally we talk about incident is torsade greater in woman. My indication would have been that QTc is more prolonged in those groups.

DR. KOWEY: For reasons that are not clear to me -- you are right, by the way, that torsade is more frequent in women. You are also right that you tend to get more QT prolonging effect in women. We

didn't see either of those in these data. I suspect part of the reason is because we were at the low end of the dose. If we had gone higher on the dose, we may have seen that effect.

DR. CALIFF: And, I might add, at the low end of the number of patients.

DR. KOWEY: Yes. Also true.

DR. THADANI: Also probably the beta-blocker has different effect. Doesn't it?

DR. KOWEY: Yes.

DR. THADANI: Where you find the QT because other drugs don't have beta-blockade.

DR. KOWEY: But these are the bases that we want to use, and that's the data on the QT.

CHAIRMAN PACKER: Michael and Ileana after.

DR. CAIN: Just one methodologic question. The QT measurements that are reflected in these data were made off the 12 week ECG?

DR. KOWEY: Yes.

DR. CAIN: Because someone earlier had said you were also measuring them off of the

transtelephonic.

DR. KOWEY: The transtelephonic was used as an indicator that the patient had to come in for a 12 week so that these data we're seeing here are from 12 weeks.

DR. PIÑA: I'm having a bit of a time figuring out why the ICD trial was shown under the safety considerations. Since it was and there were patients entered who had ejection fractions of below 30 percent, were they dosed differently? Were they dosed in-hospital versus outpatient?

DR. KOWEY: The majority of the patients in this study were in the hospital. The majority, I don't know what the percentage was. All of them--that's a good majority--were all in the hospital for initiation of the drug, but there was no dose adjustment by ejection fraction. There was a dose adjustment by creatinine clearance but not by ejection fraction.

DR. THADANI: But that's a VT population. Right? ICD.

DR. KOWEY: You know, to explain to

Ileana, her first question was, "Why did you see that? Because you really like it?" I think, first of all, it's the first study that has ever been shown. I mean, it's a little bit extraneous but it's the first study that shows that there is a benefit to using the drug as adjuvant therapy in ICD patients.

But, in addition, the question that a lot of you have been asking is if you give this drug to patients who don't have good ventricular function, does it have an adverse effect? Well, the FDA wanted us to show you the Julian data, which we did, and this is another group of patients who have bad ventricles. That's the reason why the data was shown. That's the only reason why the data was shown.

DR. THADANI: What were the incidents of torsade in that ICD group? Because here you showed that sotalol far less often so there's no incident of torsade.

DR. KOWEY: If you can tell me an ICD patient from an electrogram whether something is torsade or polymorphic--

DR. THADANI: We can't tell.

DR. KOWEY: --then you have to really tell me how to do that.

DR. THADANI: How many were polymorphic versus monomorphic VT?

DR. KOWEY: I don't have a breakdown. I do not have a breakdown. Do we have a breakdown of poly versus mono VT?

DR. WILLIAMS: There was one patient that had torsade diagnosed from a Holter. We had in the protocol a requirement for a Holter at one month. Protocol required a Holter recording at one month, and one patient had a polymorphic VT documented on that Holter QT prolongation which was called torsade. The patient was taken out of the study and was on placebo. We had another patient who from the electrogram --

DR. KOWEY: While you are talking, John, can I have slide 357, please?

DR. WILLIAMS: The electrogram suggested torsade but I'm not sure if you can diagnose torsade from an electrogram of an ICD.

DR. KOWEY: One of those patients was a placebo patient and one of these patients was a d,l-

sotalol patient, but to tell you the truth, I mean, it's possible that some of these discharges could have been for torsade.

DR. THADANI: But you were able to interview. That's the good thing about the ICD. You can go back and integrate the --

DR. KOWEY: Yes. It was done.

DR. THADANI: That means the incidence of torsade mostly is asymptomatic in patients, unless they die, that might have important implications. Now you are showing me that QTc in women doesn't change very much. Why you won't admit these patients in the data of cost containment for hospitalization realizing that adverse effect could have happened up to 10 days of therapy, not necessarily 24 or 48 hours. If you're going to see it, even in structural heart disease if you feel comfortable that's there's no torsade in that, why you won't admit the patient at all.

DR. KOWEY: I hope I didn't misspeak.

DR. THADANI: One of your slides said nonstructural heart disease patients can be started outpatient.

DR. KOWEY: Nonstructural.

DR. THADANI: Why nonstructural heart disease? With the incidents so low why are you recommending that? Why can't you make a bold stab that you're not going to hospitalize anybody and give a drug and monitor them just on ICD.

DR. KOWEY: There was torsade and there were deaths in patients who had structural heart disease in this database. So we're not horribly comfortable with saying that you can start the drug out of hospital. In 05 and 04 there were no events in patients that received the low end of the dose. That's the basis for that recommendation, but I think that's an arguable point. We can argue that as a clinician but I'm not sure that the data would support either way.

DR. THADANI: You're suggesting I start a patient on 80, send them home and bring them, and back before I do 160 or 120 rehospitalize them?

DR. KOWEY: In my practice patients that have structural heart disease, they are rehospitalized for every step in the titration. I know that sounds

difficult and it is always difficult for the patient but it's the way I practice. Yes, the answer is yes.

CHAIRMAN PACKER: Dr. Karkowsky.

DR. KARKOWSKY: A quick point. I expected Bob to offer the usual agency disclaimer. We haven't reviewed the ICD study neither for efficacy or safety. So to the extent that's pivotal and requires an FDA review, that needs to be deferred.

CHAIRMAN PACKER: Thank you. Marv.

DR. KONSTAM: Yes. I'd like to comment a little bit about the issue about the Julian study and the ICD study. I want to make the point, and I feel fairly strongly about this, that actually I'm not helped in the least by these studies. I made the same point with regard to the dofetilide data set in Diamond studies.

The issue is you have a population that is targeted for the approval, for the indication, and a very different population for which you are making some comment vis-a-vis survival. And you are doing it in the context of the drug that is fairly complicated that has antiarrhythmic effects, proarrhythmic

effects, and beta-blocker effects. And when you look at what's--

I think the ICD study is particularly problematic. I won't even go there. I think with regard to the Julian study, a post-MI population where it looked the incidence of mortality was overall was about 8 percent, far more than we expect in the population that is going to be targeted by this indication. And a population in whom we know very well in hindsight that they are going to be benefitted by the beta-blocker effect and a fair likelihood that they are going to be benefitted by the antiarrhythmic effect of the drug as well.

And in contrast, the population that is being targeted by the indication being asked for here where in the absence of, well, I think much less likelihood, significantly less likelihood of benefitting from the beta-blocker effect per se in terms of survival, and certainly no rationale for likelihood that they are going to benefit from the antiarrhythmic effect of the drug again with regard to survival.

But, you know, a concern, and that's what the concern is that I don't think is allayed by those other trials, that there will be some small but significant excess mortality perhaps in the 1 to 2 percent range from the proarrhythmic effect of this drug. I think that the solace that has been taken, and I think this was particularly relevant in the dofetilide data set and equally relevant here with the Julian trial. I actually take absolutely no solace from the findings of those two studies that you showed at the end.

DR. KOWEY: Let me just make two comments. No. 1, it was the agency that really wanted us to show the Julian study but we didn't mind doing that because, to be perfectly honest with you, Marv, as a clinician if I'm going to use a drug on somebody with a beat-up ventricle for atrial fibrillation and I know there's a study out there that randomized 1,400 patients with beat-up ventricles, and if anything the drug showed a positive effect, not a negative effect, and this is true in spades for amiodarone, in spades, I'm much more likely to use that drug than another

drug.

You can argue you shouldn't use any drug. You can argue that maybe you need some other experience, but the fact is you've got to use a drug in many patients and would you rather use a drug for which there is no mortality data or would you rather use one where there is some data that shows that's it's at least neutral?

DR. KONSTAM: Well, I have to say we could get into this in all sorts of directions but I don't look at it that way. What I'm looking at is I just really want to ask a question and let's just focus on the question. Is there a potential for excess mortality in the target population here under consideration and what is that level of excess mortality? That's really the question that I need to figure out. I'm going to say to you I am not helped in the least about that question from that study.

DR. KOWEY: How about the data that we showed you in the less than 320 milligram group where there was less mortality in those patients than in the placebo ones in the trial? Did that compel you?

DR. KONSTAM: In which population?

DR. KOWEY: Can we have the core slide?

DR. KONSTAM: Okay. In which population?

DR. KOWEY: In the population we're looking at here. Can I have the core slide?

DR. KONSTAM: That gets into -- that's the next set of data. I'm just focusing on the Julian.

DR. FENICHEL: May I say why the agency thought the Julian study was pertinent? I don't mean dispositive but certainly pertinent. That is suppose the Julian study had come out the other way? Suppose in this relatively fragile population compared to your usual run of atrial fib patients, d,l-sotalol had been extraordinarily toxic and had resulted in increased mortality across the board? That would certainly make one very nervous.

DR. KONSTAM: Bob, I don't disagree with that.

DR. FENICHEL: Well, okay. But if you say that here was a randomized controlled trial, one of whose possible outcomes was very bad, then that result is informative. Now, the fact that it was not very

bad, is it fabulously reassuring? Do we have any reason whatsoever to believe that the life-giving effect that one may read into this, unexamined by FDA studies in that population, should be expected to occur also in the AF population? Of course not. In that respect it doesn't help.

But as a means of looking for proarrhythmic effects in a population which has demonstrated in the past its capacity as mind canaries, if you like, who detect those effects, I think that is perfectly find if, once again, it survives FDA review which it has not seen yet.

DR. FENICHEL: But it's also a population in which I would construe has more of a potential for benefitting in terms of survival from the antiarrhythmic effect. I guess just the bottom line about my feeling is I don't object to looking at the data for the reasons that you indicated. If there were something worrisome, we've got to look at it to get worried, but all I'm saying is that the absence of seeing something worrisome does not reassure me.

CHAIRMAN PACKER: Michael.

DR. CAIN: I think the additive part is that it is neutral at best. It's an old study, but I think one has also been faced with the clinical scenario that if you have someone who is recovering from an infract, the beta-blocking effects of sotalol did not achieve the statistical significance in improving mortality.

If you now had a post-MI patient who had atrial fibrillation in 1999, could you be doing he or she a disservice by putting them on sotalol and not putting them on a primary beta-blocker that has been shown to have a favorable effect?

DR. FENICHEL: Oh, I wouldn't for a minute use those results as the basis for a post-MI claim, which is not being requested.

CHAIRMAN PACKER: Let me see. I don't think anyone here is saying anything that is different than anyone else. I think that the definitive database, if you want to be reassured about outcomes, would be an outcome study in patients who are specifically targeted for treatment. Given the event rate in such individuals, which I think is probably,

especially if you include those without structural heart disease, is an event rate which is much lower than the post-MI or ICD trials.

We're talking about trials of substantial numbers of patients. I'm not saying that should or shouldn't be done. Clearly summation of the mortality data from the existing trials is difficult to interpret because the number of events is so small the confidence interval is stretched to eternity.

Consequently in the absence of -- in an effort to provide some data, just some, they said, "Well, you know, we did these trials for another purpose." They didn't do it for atrial fib. It's clear they didn't do it for atrial fib. They are putting this forward and I don't think they are putting this forward to say that this should be persuasive that there is no excess mortality in atrial fibrillation.

I think they are putting it forward to say that, "We did these trials and we want to tell you about them. They are the only long-term outcome trials we have." Maybe they are hard to interpret and

maybe they are reassuring but I don't think they are uninformative. They've got to be informative. They've got to do something.

DR. CALIFF: I want to speak out in great opposition to Marv here and his feelings about this meaning nothing. To me this is much more meaningful than a 1,000 patients put in atrial fib trials with 10 pages of exclusion criteria to take out most patients who are actually going to get the drug in practice. To me this is much closer to the segment of patients where most of the action in terms of cause of death is going to be. This is very important data to me and I would hate to not see it shown.

I do agree it is not definitive. The best thing would be 3,000 or 4,000- patients with atrial fib that represented the true population including 80-year-olds that are likely to be treated with the drug when it gets in practice but we never get to see that in these meetings.

CHAIRMAN PACKER: Abe.

DR. KARKOWSKY: Let me bring up one more study which may or may not be relevant and that is the

Sword study. Now the Sword study people got d-sotalol and not d,l-sotalol and people here are getting d-sotalol, too, but just having an l-sotalol to counteract it. To the extent that one has comfort, one can diminish that comfort by looking at the Sword study if one believes that is relevant.

CHAIRMAN PACKER: Can we address the issue of Sword and the issue of the Julian trial head on in the following way? I mean, you mentioned, Peter, that there is an early apparent increase in mortality in the Julian trial. Admittedly the dose is 320 milligrams once a day and it's an atypical dose.

Maybe others can comment on this but there is a dose dependent prolongation at QTc interval up to 21 milliseconds with this drug at a dose of 160 milligrams BID which is within the recommended dosing range. In the past when we've seen databases of drugs that increase QTc by 21 milliseconds, there's a fairly good torsade signal in those databases with 21 millisecond increase.

DR. THADANI: Is it really, Milton?

CHAIRMAN PACKER: Yes.

DR. THADANI: I thought you had to be, you know, chained from baseline by x percent above 520 and 20 milliseconds you start with 420 and only go to 444.

CHAIRMAN PACKER: I was looking at the dofetilide database and there was a 20 millisecond increase with dofetilide, I think, at their highest dose. They had a torsade signal at 500 milligrams.

DR. FENICHEL: Milton, this is a little bit of a digression but what Udho has raised is something that people don't understand about this. It may be worthwhile. What we have seen with bad actives has been on average QT prolongation, exactly as Milton has said, of on the order of 20 milliseconds.

If you look at cisapride it's 21 milliseconds or 18 milliseconds. If you look at terfenadine at doses of 200 milligrams, which was higher than were recommended for that drug. It was 23 milliseconds or something like that. And across the board there really aren't drugs in common use that raise the average QT an awful lot.

And the reason is that, of course, there is highly varying susceptibility to QT prolongation

and the average of 20 milliseconds reflects a few outliers who are people who are hypokalemic and people who are women. People who are hypokalemic who start out with long baselines and who, therefore, somehow, unjustly perhaps, seem susceptible to further prolongation, and so forth and so on. But 20 milliseconds of average prolongation is plenty.

Now, who are the people who get into trouble? They are not, by in large, the people whose prolongation is 20 milliseconds, so that was the issue that I think Udho spoke of.

CHAIRMAN PACKER: Yes, but I think that's the point. The 21 millisecond average increase here represents a fair number of people who have more than 30 millisecond increases who, at least based on the experience with other drugs that have average increases of 20 to 22 milliseconds, usually produces a barely recognizable signal of torsade.

I guess what I'm asking is: one, what was the average increase in QTc with d-sotalol at the dose that increased mortality in Sword, and if it was 20 milliseconds or 22 milliseconds, is the reason that

we're not seeing that signal here because the beta-blocking properties of l-sotalol?

DR. FENICHEL: Well, you know, Craig Platt is here and I'm diffident about speaking about Sword but my recollection is that there were five cases of torsade in all of Sword. I mean, there was a hugely increased death rate in the patients who were treated with d-sotalol in that trial but there were only five identifiable cases of torsade, some of which were in the placebo group.

CHAIRMAN PACKER: I'm just curious. So the drug didn't kill people because of --

DR. KOWEY: Can I have slide 338, please? This is an analysis that was done of the early deaths in the Julian study. I don't know whether you read about all this but there was a tremendous amount of interest. In fact, Ronnie Campbell, the late Ronnie Campbell, chaired at least two meetings in which there was a very, very intense examination of the death that occurred early in the Julian study. This is the total deaths that occurred in the sotalol and placebo groups.

Inflectors, by the way, were people who had a abrupt change in their course on sotalol and, therefore, were considered to be people that would probably have something bad happen from the drug. That's the best I can explain that. It's a very complicated definition.

But if you look at what they thought the mode of death was, it was very interesting. The electrical deaths that you would have thought would have been likely because of such a large dose of sotalol, 320 milligrams is a single dose, which does have a very high C max and should produce a good deal QT prolongation didn't occur except in the placebo group. There were more what they thought were mechanical deaths in the patients who were receiving sotalol.

CHAIRMAN PACKER: The only problem is that I can't believe -- you can't tell how people die. I mean --

DR. KOWEY: Well, you know, we're looking at a study that is 16, 18 years old and --

CHAIRMAN PACKER: No, no, no. Oh, please.

I'm not asking you to do better than this. What I'm asking is, and I guess this was raised by Bob Fenichel's question, there's a database with d-sotalol raising concerns. d-Sotalol increased QTc. Let assume for a moment an increased QTc of about 20 to 25 milliseconds.

DR. KOWEY: Okay.

CHAIRMAN PACKER: This drug at 160 BID, which is in the recommended dosing range, increases QTc 20 to 25 milliseconds, doesn't appear to produce the same torsade signal, and in a patient population of the Julian study was not associated with the same increase in mortality.

That indicates to me support for Marv's hypothesis that there may be two countervailing influences here. One a beneficial one which is limiting the clinical consequences of a prolonged QTc interval and maybe reducing mortality hiding an adverse signal. I hope I expressed that accurately.

DR. KONSTAM: Yes. But, you know, I want to ask another question taking that around the primary safety gate is set and, you know, we're saying there's

a low torsade signal and a low deathrate. Tell us about the time frame associated with this experience. In other words, we can't really tell from this in terms of the ends. What is the median time of exposure, what is the total number of patient years or what have you? What is the median exposure time that we're looking at in terms of the denominator for the effect?

DR. FISHER: Maybe while you are getting it, I can insert one thing. Answering JoAnn's question on 014 about the three people who were entered twice. Because they started from or they had to get into normal sinus rhythm, actually those three people were only counted once in the original analysis. But since then, the sponsor has re-run it without those three people at all, and the log rank P value goes from .017 to .030. And it was not significant as you consider discontinuations, and that is still true. It goes from .275 to .334. So basically things are the same.

DR. GRINES: I have a question about the differences between d-sotalol.

DR. KONSTAM: Wait a minute, can we get the median time?

DR. KOWEY: Did you want that, Marv, in Julian, or did you want that --

DR. KONSTAM: No, no. I am not interested in Julian. In the primary data set.

DR. KOWEY: Can I have slide 277, please? Thank you. That was fast. This is number of patients by duration of exposure in weeks.

DR. KONSTAM: Can you explain that more?

DR. KOWEY: I am sorry. The top is double blind and the bottom is double blind and open label combined.

DR. KONSTAM: Right.

DR. KOWEY: This is less than 320 and greater than 320. And this is any Sotalol and this is placebo. So this is one week of exposure, 4, 12, 24, and 56. It is the percentage of patients -- the percentage expressed as the number of patients in the group.

DR. KONSTAM: Okay. So most of the patients -- I mean I don't know how to -- I mean what

this study does. I mean, I guess the easiest way to express this, I think, would be to look at the median time of exposure. So that when we have a denominator in there of the number of patients, how many patient months are we actually talking about here. I get the feeling it is very short median exposure. You know? It seems like most of patients are taken care of with the 4 week group.

DR. THADANI: Between one month and four months.

DR. KONSTAM: The four-month group. So we are talking about -- you can't lose -- the four-week group. It is weeks, right? The four-week group. The four-week. All right. So we are talking -- do you know the median time?

DR. KOWEY: I don't have it in front of me. But we can see that. We have got it somewhere in here.

DR. KONSTAM: I think it is very important when we are talking about one percent death rates and not all one percent death rates are the same. Certainly a one percent death rate over a four-week

exposure is not the same as the one percent death rate in a typical survival study. So just to make that point.

DR. THADANI: In that context, could he show the death rates to the time too or what? I know there were only two deaths. Did they occur early or late?

CHAIRMAN PACKER: But the numbers are so small, what are you going to do with them? I mean, how many ways can you cut four deaths?

DR. KONSTAM: I think that is the point. I think the point is the numbers are really small and not in the least reassuring, therefore.

CHAIRMAN PACKER: Tom?

DR. KOWEY: To put this in some perspective, Marv. You weren't on the committee when other antiarrhythmic drugs were approved for this indication. But the flecainide data base was substantially smaller than this data base. And for flecainide, there was a mortality MI study that actually went in the wrong direction. And flecainide was approved for a defined patient group at a defined

dose. So it is a little bit inconsistent to be saying that this is a tiny number of patients. It is not a tiny number.

DR. KONSTAM: No, I know.

DR. KOWEY: It is actually a substantial number and there is a mortality study -- two of them in fact -- that go in the direction of benefit.

DR. KONSTAM: Peter, that is -- I understand. You are getting into questions of interpretation. I just want to say I don't -- I mean, I am not reassured by any of that. I mean, I guess I am just trying to say if you want to make a case that sotalol is associated with no excess mortality of importance, I am only making the point that I can't conclude that at all. That is all.

DR. KOWEY: But, Marv, if you can tell me what antiarrhythmic drug you can conclude that for --

DR. KONSTAM: I am not trying to argue that point.

DR. KOWEY: No. But it is a problem with every single antiarrhythmic drug we have for AF because, as Rob said earlier, we don't have 3,000

patient studies in the appropriate patient population. What we have is a defined data set, and then you have some other studies tacked on. I agree it is not perfect, but it really isn't all that bad compared to what we have seen in the past.

CHAIRMAN PACKER: Cindy?

DR. GRINES: I guess I wanted to just point out -- I know you don't want to hear about the Julian study, but they did treat them for 12 months and actually the withdrawal rate, according to the article, is around 25 percent of the patients receiving sotalol and 21 percent of the placebo. So that withdrawal rate isn't quite as high as the ones in the a fib trial. And I just wondered, if we are going to talk about d,sotalol and the Sword trial, I guess maybe I need some clarification about how it differs from the d,l variety. Because it seems in the atrial fibrillation trials that d,sotalol was not effective at reducing the incidence of a fib. And I don't know enough about the two preparations.

DR. KOWEY: Well, one is -- one contains a beta blocker and is an IKL blocker. That is

sotalol. And one is an IKL blocker, which is a common garden variety antiarrhythmic drug.

DR. GRINES: So the d,sotalol is just an antiarrhythmic drug?

DR. KOWEY: It is just an anti -- it has no beta blocker.

DR. GRINES: And the d,l is the beta blocker?

DR. KOWEY: Yes.

DR. GRINES: Okay .

CHAIRMAN PACKER: Or the d,l is both.

DR. KOWEY: Both.

DR. GRABOYS: Peter, you know I think we are going over this in such picayune detail because it is not simply using an antiarrhythmic drug in terms of using an antiarrhythmic drug and acknowledging the toxicity of the drug and excess mortality. We are talking about using an antiarrhythmic drug that is potentially toxic for a population that is soft in its indication for the use of the drug. For me to take or to use this drug in a patient, in a 75-year-old patient, because I am hoping that maybe they will have

less palpitations at 6 months than with placebo they had less palpitations at 3 months, it makes me very concerned and we get back to "first do no harm." And that is really why there continues to be a lot of this discussion.

DR. KOWEY: I would say, Tom, that in clinical practice if someone merely has a few palpitations now and again, I think that it is probably wrong to use a drug that has a powerful effect on repolarization to treat them. Especially if it is in a group of patients for whom there appears to be some excess chance of harm. I don't disagree with you. But there is a universe of patients who have atrial fibrillation that is very symptomatic and they want to have it treated. They want to have those symptoms reduced. And in order to do that, we have to use an antiarrhythmic drug. The question is in the antiarrhythmic drugs we have available, where does this fit in? There is a definable patient population for whom this drug may be useful. It is just that it is not -- it is not the universe of AF. It may not even be the majority of AF. But it is a definable

patient population. It has been defined in the clinical trials. And I think that to say that this drug can't be used for anybody with AF because we are concerned about a group of patients at the end of the spectrum of risk, I don't think that is right. That is where the rub comes in.

CHAIRMAN PACKER: Marv?

DR. THADANI: Can I ask a question of Bob Fenichel here? You might remember when we discussed the aspirin issue -- going off the track here. Aspirin was recommended for approval on the basis of separate trials, which is a Scandinavian -- Sotalol plus aspirin versus Sotalol plus placebo. Do you recall? I can't remember now what the incidence of torsade was. Because they had a 3,000 patient population. It was a very neat study. They were not on anything else.

DR. FENICHEL: No one who doesn't use Holters has any idea of the incidence of torsade. You can't find torsade in a spot check population. Torsade comes and goes. So I don't remember the study, but unless they did that, they don't know how

much torsade there was either.

DR. THADANI: But could you also say that torsade based on the -- I realize the IC data, people don't like it. But we may not necessarily care, like you said. The reason the incidence that Milton was pointing out in some studies is higher is because they did the Holters. And in this study, they never did the Holters, so you never know the true incidence of torsade. It may be much higher than the reported incidence sometimes that you read in the literature as 4 to 6 percent.

CHAIRMAN PACKER: Udho, I don't think you are quoting me correctly. The torsade signal comes from clinical events not from Holters. So that the --

DR. THADANI: Not --

CHAIRMAN PACKER: No, not from Holters. Not from Holters. It is from clinical events. There is a discernible signal. I think in many antiarrhythmic drugs -- I think Bob outlined some of the examples. At 20 millisecond increases, you are getting a signal for lots and lots of drugs.

DR. THADANI: I don't -- Milton, I think

I have seen Holters and patients don't complain of anything and they have 40 seconds. So it looks like polymorphic as it moves around.

CHAIRMAN PACKER: It may be. But that is -- but --

DR. THADANI: I think you pick up more on a Holter than on a random transtelephonic monitoring. So I think the incidence probably is underestimated.

CHAIRMAN PACKER: No, no. But the data bases that Bob Fenichel cited were clinical event data bases. Unequivocally. They were not -- the risk identified with those drugs was based on clinical events, not on Holters. Not Holter-detected asymptomatic torsade.

DR. THADANI: On the Vaprodil data base, I remember when we were doing those studies, we had Holters. And on aspirin buffered Elvaclo, we had PVCs. We put Holters on and we stopped the study because there were a couple of -- very few deaths, but I think there were some incidences of torsade which was higher. So there is some data there.

DR. FENICHEL: Even depodril. Deprodil is

probably the worst proarrhythmic drug around. It is approved as second line therapy only. And I think the number of identified arrhythmias in the preclinical -- in the preapproval data base was -- you could count it on your hand. It was very, very few. You know, it is very hard to find these signals. We care about these signals, but that doesn't mean there are so many of them that they will show up in samples of this size.

CHAIRMAN PACKER: Marv?

DR. FISHER: Marv, can I make one quick comment just for your information? From the slide up there, you can get an underestimate of the average exposure, which is 12.6 weeks. So it probably is around 16 to 18, I would guess, from --

DR. KONSTAM: What's -- I am sorry, I don't understand.

DR. FISHER: This is the average exposure of the people in the sotalol group. You are talking about numerators without denominators. You know, what is the death rate for --

DR. KONSTAM: Right, right, right.

DR. FISHER: I am just giving you a rough

idea of the --

DR. KONSTAM: 16 to 18 weeks?

DR. FISHER: That is a guess. A mathematical under bound. But it is certainly correct to 12.6.

DR. KONSTAM: A question about the dosing, Peter. What is the evidence that 160 mg bid is better than 120 mg bid?

DR. KOWEY: The 9A study had a better outcome in patients that were at 160. And in addition, the 004 study had two-thirds of the patients on 160 mg.

DR. KONSTAM: Right. But it didn't have a 120 mg dose.

DR. KOWEY: And if you are just talking about efficacy, and we don't want to get back to where we were this morning, 160 beat 120 -- I am sorry, 160 had a higher number of patients event-free at 12 months in 05. So it was in one parameter better than 120. In the other parameter, it was less good than 120. But 120 was an effective dose in 05, and was significantly better than 80.

CHAIRMAN PACKER: Does anyone have any other questions about safety or dose response? Can we move on to a conclusion of the sponsor's presentation?

DR. MARROTT: Mr. Chairman, members of the Advisory Committee, and Dr. Fenichel, Dr. Kowey has presented with clarity a balanced overview of the clinical data and the potential of sotalol for treating patients with atrial fibrillation.

I guess no clinical data base is squeaky clean, and the sotalol data base is certainly not an exception. However, it appears that the efficacy data from studies presented point in a similar direction. All are positive and significant to varying degrees. This is true whether patients have chronic or paroxysmal atrial fibrillation or structural or no structural heart disease. In the latter group of patients, the data suggests that outpatient administration can be safely undertaken.

The risk from serious adverse events is present as with any other antiarrhythmic drug. But it is extremely low. We recognize that safety is of paramount importance when treating atrial fibrillation

or flutters, arrhythmias which in the majority of patients are not life-threatening. The sponsor bears the responsibility for providing conditions that will minimize the safety risks, and we would like to discharge this responsibility diligently.

We have discussed the possibility of a risk management program with the FDA. The three key objectives of this program shown on the slide are to differentiate our product when used in atrial fibrillation or flutter and when used in ventricular tachycardia or fibrillation.

Second, to provide patients with atrial fibrillation valid information and support. This is in keeping with the current notion that patients should understand their treatment and be allowed to have a greater say in their health and well-being.

And third, to ensure that the healthcare professional is better informed and better educated. We will continue to develop this theme and discuss our ideas with the FDA. This concludes the sponsor's presentation. I would like to thank you, Mr. Chairman and members of the Advisory Committee, for your

attention and for the courtesy you have given to us. Thank you.

CHAIRMAN PACKER: Any other comments or questions from any member of the committee?

DR. CALIFF: There was some discussion about post-marketing surveillance data related to sotalol. Is that going to be discussed?

CHAIRMAN PACKER: There were post-marketing surveillance data that were summarized in the briefing document briefly.

DR. CALIFF: Yes.

CHAIRMAN PACKER: It hasn't been formally presented. Did you have any questions about it, Rob?

DR. CALIFF: Well, it seemed confusing. I didn't know what to make of it. But there seemed to be a lot written about it by the FDA.

CHAIRMAN PACKER: Most of the comments are in the FDA review -- some of the supplemental reviews the committee received within the last 10 days.

DR. CALIFF: And to me it is very important because we don't know a lot about post-marketing surveillance, but the public believes that

there is some way that we can tell if drugs are safe or not once they get on the market through this methodology. Here we have a drug that has been used for many years. It has been used a lot for the indication being sought here and we have post-marketing surveillance data. And the question is it of any value?

DR. KOWEY: We can present a few slides if you want to see them. Dr. Jin, do you want to hop in and show some information?

DR. JIN: Okay. Slide 381, please? Okay. Post-marketing adverse events recorded did not show anything really surprising than what you have seen from clinical trials. The most common adverse events were fatigue, weakness, wheezing, shortness of breath and bradycardia. But the most significant ones probably or the ones of concern were torsade, VT, VF, cardiac arrest and syncope. They are presented on this slide. In this five years -- six, I am sorry -- six-year period from 1993 to 1998, FDA has received a total of 46 case reports of torsade, VT/VF, and cardiac arrest. And Berlex laboratory had received 28