case reports because some of the cases we reported to the FDA directly. And 10 of these 46 cases died.

Based on our marketing research data from IMS and from other sources, we estimated that roughly about 2,000 person year exposures of Betapace in this six-year period. And this is presented in a rate of per 100 person years. So that means the reporting rate of domestic torsade, VT/VF and cardiac arrest is about 2 per 10,000 person years of exposure. So it is very rare. But obviously we don't know the under-reporting rate and the spontaneous report is subject to the under-reporting. Not every case is reported to us or to the agency.

For foreign cases, there were 27 cases in FDA it has said. We know of 72 through Bristol-Myers, because it is marketed by Bristol-Myers, and we don't have denominator information to provide a reporting rate of adverse events.

Can I skip the next one and go to the third slide, 383? The other significant adverse event from post-marketing reports is bradycardia. Again, FDA has said there were 43 case reports of bradycardia

and 8 of these cases died. And actually 5 of these 8 cases are included in the torsade slide I just presented. Again, Berlex received 32 case reports of bradycardia. And the adverse event recording rate of bradycardia is 2 per 10,000 person year exposures. So both show that the reporting rate is extremely rare. And I guess nobody can really tell you exactly the magnitude of under-reporting to give you an incidence rate of torsade or bradycardia from the commercial use of the product.

DR. THADANI: Do you know what the death rate will be in a similar patient population who is not on the drug? Because the event rate looked very low. So is there some data available? I am sure there are some population-based studies available to show that.

DR. JIN: I do see that for torsade I saw about one-third would die not on this product.

DR. THADANI: But without this product, if you took the same patients, what would one see?

DR. CALIFF: So, Udho, what you are asking is what seems like just a -- I mean, it makes you

wonder why we go to all this trouble. What you end up with is a numerator with no denominator. And even the numerator doesn't have a denominator for the likelihood that the numerator would ever be reported. So what -- Bob, maybe you can tell us what value -- I mean, we are evaluating clinical trials done in highly selected populations, not representative of patients who will actually be treated. Then we put the drugs out there. Some information comes in and we can count up the things that come in. But we have no earthly idea what the denominator is or what the control population would have been. Is this any better than just how the doctor feels on that day about the drug? Or what is the value of all this?

DR. THADANI: I don't think it is valuable.

DR. FENICHEL: Well, I think data like this are extremely hard to interpret. I think we collect these looking for unusual events -- events whose rate compared to the background rate can be defined so that it is much more interpretable, although still difficult to see TTP or agranulocytosis

or fulminant hepatic failure or something else whose background rate is on the order of 1 in 100,000 or 1 in a million. When we look at death, which in an ordinary middle-aged population occurs at the rate of 1 percent per year, and in an ordinary elderly population occurs at higher rates than that. And in a population with substantial organic heart disease, it is even higher, perhaps into the 6 to 8 percent rate. I don't know what to make of this.

CHAIRMAN PACKER: Okay. All right. Thank you very much. Any final questions? Okay, thank you. We will proceed to the questions. Question 1, atrial fibrillation/flutter may be associated with disabling symptoms or with no symptoms at all. Whether or not it is accompanied by symptoms, atrial fibrillation is associated with an increase in the risk of stroke. Without regard to the data about sotalol, what sort of data should be required with respect to any drug for atrial fibrillation? Is deferral of relapse into atrial a fib sufficient, or must some more immediate patient benefit, for example reduced symptoms or reduced incidence of stroke, be part of any approvable

claim?

The question here focuses on what constitutes an approvable package for a claim for atrial fibrillation. JoAnn?

DR. LINDENFELD: I think that at least recently we have considered deferral of relapse as a reasonable basis for a claim. But I do think this whole study brings up that ideally what it would be nice to see is if that change in the incidence of atrial fibrillation results in some measurable symptomatic outcome -- exercise capacity, symptomatic benefit, fatigue. I think that would be ideal in this study. And we don't really know that from this study. That was the point I was making earlier about actual symptoms. We don't really know that at the end of the day the symptoms were different.

CHAIRMAN PACKER: Yes. I am just trying to -- can you hold that thought for a moment? I am trying to figure out how we get from A to B. Because if you have a patient who has a paroxysmal atrial fibrillation and so they are enrolled in trial when they are in normal sinus rhythm. And they are

arbitrarily reevaluated at a fixed point in time after or during the course of double blind therapy. Also in normal sinus rhythm, it would be hard to know how one evaluates exercise tolerance or symptoms or fatigue or anything because they are in the same rhythm. I guess ideally one would -- well, I don't know ideally what one would do. How do you get from A to B? How do you actually evaluate something that is a transient recurrent intermittent event that you are trying to put a symptomatic measure on, aside from the symptoms that the patient would report while they have the event.

DR. LINDENFELD: Yes, I don't know how to do that either in the paroxysmal arrhythmias. But I think in the patients who relapse into chronic atrial fibrillation, it would be nice to know if the percentage is higher of those who remain in sinus rhythm. Do they actually feel better than the ones that have reverted to atrial fib. And that is a measurable outcome. So in that fairly large group of patients at least that would be measurable. I don't know that I know how to do it in the paroxysmal. I

doubt quality of life would really capture that.

CHAIRMAN PACKER: All right, Udho?

DR. THADANI: Then you could do that by giving a diary. That would be one way. If you really believe in exercise tolerance, you can put them on a pedal speedometer and see how the patient walks every day.

CHAIRMAN PACKER: When would you measure exercise? When they are in sinus rhythm?

DR. THADANI: Well, in a day how much distance they walked. Because a lot of paroxysmal a fib, at least some of the patients I see in coronary disease are induced by exercise too. So if you could have a daily record. I mean, I could give you an idea, but it is an impossible task. And I think if you really believe in the -- since the question is combined with strokes and symptoms, one way would be to have put one patient on say Coumadin, and then another patient group with a paroxysmal a fib not on Coumadin and see the stroke difference rate, which will be a tough issue.

CHAIRMAN PACKER: You can't do that. Your

patients are on anticoagulation.

DR. THADANI: But most of the time now what we are doing is we put patient on anticoagulants and after six months if you see them in sinus rhythm, they are taken off. And I think there are ways you could do the trial. The question is open. So I am just giving you some of the issues one could address. But it is tough to document it in a trial.

DR. GRABOYS: I don't think the Coumadin issue is germane at all. The standard of care now with an increasingly elderly population is that regard -- once they have declared themselves in having AF, the standard of care mandates that they be on anticoagulants period.

CHAIRMAN PACKER: Marv?

DR. KONSTAM: No, but there is another side to this coin, which is that if you believe, as I happen to believe, that there is something good about being in sinus rhythm. So take that as a potential useful endpoint. But then ask the question, however, is there something adverse going on simultaneously. So I think one of the issues really here is are there

-- is there something about this drug that is driving adverse effects on symptoms, which would make it -- if you were concerned about that and I think we ought to be concerned about that -- then you would want to measure symptoms across the population to at least reassure yourself that that is not going on. So I understand that doesn't directly address the question of symptomatic a fib, but it is another point.

CHAIRMAN PACKER: Okay. But let's directly address the question. The question says what constitutes an approvable claim. What data base constitutes an approvable claim? Who on the committee would suggest that an approvable claim require evidence for reduction in the risk of stroke? Anyone? Who would require an improvement in exercise tolerance? Who would require -- and stop me when I get to something you like.

DR. THADANI: You are talking about paroxysmal a fib now or chronic a fib?

CHAIRMAN PACKER: Even in the chronic a fib studies, they are cardioverted.

DR. THADANI: But say if you don't

cardiovert and the patient is in a fib?

CHAIRMAN PACKER: That is a different claim.

DR. THADANI: No, no. I realize that. You are talking about if he stays out of the a fib, he benefits. But if he is in chronic a fib, the exercise tolerance might go down and it could even slow the heart rate and you could improve the exercise tolerance. And I think you probably have to dissociate between chronic a fib and paroxysmal a fib on that issue.

CHAIRMAN PACKER: Michael?

DR. CAIN: I think for the way that they have defined paroxysmal and chronic for this study and for the question that you are asking, it doesn't matter. You are talking about someone who has been in atrial fibrillation for some period of time and is now through whatever mechanism in sinus rhythm. And now what you are trying to judge is do you feel better or worse in sinus rhythm than the way you feel should you happen to go back into atrial fibrillation. And so I think for the way that it is being defined here,

chronic and paroxysmal groups are essentially the same thing.

DR. KONSTAM: That is right.

CHAIRMAN PACKER: Okay. Let me see if I got it. If a sponsor comes to this committee with a data base that shows a reduction in time to first symptomatic atrial fibrillation, is that okay? Anyone thinks -- does anyone think it is not okay?

DR. PIÑA: Did you just put the word symptomatic in there now?

CHAIRMAN PACKER: No. The episode is symptomatic. The episode is symptomatic. The concept that the differential here is that the episode is symptomatic, but under usual clinical trial methodology, one assesses symptoms at a fixed point in time. They may or may not be in atrial fib. It is hard to know how to assess that if they are in normal sinus rhythm. You are not actually addressing the question. You are actually addressing a safety issue rather than an efficacy issue under those circumstances.

DR. FENICHEL: Milton, let me clarify the

question and also respond to something that Marvin said much earlier in the day, raising a whole new version of the question. The idea when the question was written was could one submit a claim -- would it be an approvable claim to come in with data consisting entirely of electrocardiographic measurements? In other words, to show that the actively treated population had better looking electrocardiograms than the group treated with placebo and independent of any demonstrated effect upon symptoms or upon the risk of stroke. So is this a -- is that laboratory finding, if you like, sufficient, or does it need to be accompanied by some clinical benefits such as the patient says he feels better. Despite all the other miscellaneous unrelated effects of the drug, it is still so much nicer to be in sinus that he is willing to put up with the diarrhea and vomiting or whatever it is.

Now the other side of the question which Marvin raises, which I had never considered, is not so much is the electrocardiographic victory sufficient, but Marvin raises the question, as I understand his

point earlier today, of is the electrocardiographic benefit necessary? Suppose that through rate control or some other means, the patient was made to feel so much better despite ongoing or perhaps even increased fraction of time in atrial fibrillation because he is flipping in and out but he does it at such a low rate or in such a numb state that he does not object to it. Is that okay? Because he does feel better, even though electrically he is worse. Now as I understand what Marvin brought up earlier is he said, no, no, that would not be acceptable. The symptoms are indeed a surrogate for the real benefit, which is an electrical benefit. Well, that is a respectable point of view too. So I guess the two questions are or would be is the electrocardiographic benefit sufficient? That was the original question. And the new question prompted by Marvin is the electrical benefit necessary?

CHAIRMAN PACKER: Rob?

DR. CALIFF: Yes. As far as the electrocardiographic benefit, I think that is a nice scientific benefit, but not one that is germane to the

public health. So while I would like to see that as part of any effort, and certainly since we are attempting to base our eventual clinical benefit on science, I think it should be a part of the protocol. But essentially I don't think people are taking drugs because of their electrocardiograms. They want to have their symptoms alleviated. So for me, the critical things are that there be some demonstration of improvement in symptoms and that there be enough patients representing the kinds of patients in whom the drug will be given to rule out any plausible unacceptable increase in risk of bad things happening. And I think in order to do that, what I would really like to see being done would be to push the research community to do more inclusive studies, particularly in atrial fibrillation. I really agree with Tom. We need to be including people over age 80. We have this term therapeutic orphans now for children because randomized trials have not been done in children and therefore we don't know how these drugs work. But I think the elderly now are in exactly the same situation. And the trials need to be larger. When

you are looking at trials of 100 patients in each type of atrial fibrillation, it is going to give us some nice information. But that should be a subset of a larger study that can really allow us to estimate even by Marvin's strictly sticking to the atrial fibrillation group of what the real risk is.

CHAIRMAN PACKER: Ileana?

DR. PIÑA: Rob, are you saying that if the drug doesn't convert a fib into sinus but the patient doesn't have symptoms anymore because they are feeling better and maybe their rate when they are in a fib is slower, which is something that Bob was saying, it is okay and they don't have to demonstrate efficacy by keeping the patient in sinus? In other words, is being in sinus rhythm better than being in a fib, even if you don't have symptoms?

DR. CALIFF: Well, I think in this case we are fortunate that we have a methodology that will tell us about the ECG and can be done in a smaller sample size than what it takes to have an adequate safety data base. So I think we can do both here. But Marvin was actually raising the converse of that,

which is that they may be worse. They could still be in atrial fib and not know it because you may be tempted not to take your anticoagulant drug. But here again that is where an adequate safety data base in a population that was really at risk of having strokes, for example, would be very helpful in knowing whether it was better or worse. But being symptomatically better, I think, with a slower rate, to me that would be a nice thing to have as long as it didn't increase your risk that something else bad happened.

DR. THADANI: On paroxysmal, there is a trial ongoing. NIH is doing a firm trial just to address that issue. The patients in one is very controlled. The other one is keeping them in sinus rhythm post cardioversion. So I think those issue are very relevant and they are looking at outcome in a very large sample size. So the symptoms are important because we get patients reporting with rigor and they fail, who are ending up having oblation of their AV node just to get rid of the symptoms. So I think it depends on how symptomatic a patient is. I think that is very critical. If the symptoms are mild or the

symptoms are bad enough that he would need hospitalization. So I think the question is being addressed in a very large NIH trial.

CHAIRMAN PACKER: Yes. It is not the question --

DR. THADANI: It is not the relevant issue here.

CHAIRMAN PACKER: It is not the question we are talking about. The analogy here, although Bob Fenichel hasn't made it, is probably the analogy of how this committee and the agency evaluates antianginal drugs. The data base for antianginal drugs -- and I understand we haven't seen one for a long time -- is that there are two kinds of data bases. One is a symptomatic data base and the other is a physiologic data base -- a prolongation of exercise tolerance or a prolongation of time to a specific ST segment depression. The Agency -- Bob Fenichel, please correct me if I am wrong -- has taken the point of view that reduction in symptoms per se is insufficient because one might achieve that with morphine. That one requires both a -- well, I should

say one requires a reduction in the -- it requires the physiologic response and it would be nice to have the symptomatic response, would that be correct?

DR. FENICHEL: No. No, that is not right. The basic claim is the symptomatic claim. You need to have a lot of evidence of the symptomatic claim and then you need to have what I think would fairly be described as merely supporting evidence of the anti-ischemic claim. So it is not strictly analogous. Well, what you said is right, but it is strictly analogous. In other words, what you would -- as I described it, yes, it is a two component claim and it is a symptomatic claim. It is not an outcome claim, for example. But there is this physiologic or electrophysiologic component which is necessary. It is a non-ischemic component. The situation here, and indeed that is the analogy which I think the original question was meant to draw out -- is this something where you could simply get a drug approved for ischemia in the case of antianginal drugs? And of course that is an acceptable indication in some parts of the world. In Europe, the drugs are approved as

anti-ischemic. And a demonstration of symptom relief or exercise improvement or something like that is not required. Well, we don't do that. The question here is this like angina, where you need symptoms and the cardiogram should go in the right direction? Or is the model, Marvin's model, where the electrocardiogram is really the disease and the symptoms are a surrogate for true patient factor, that is a fairly radical idea. But it is not --

DR. KONSTAM: Since this is my model, can I kind of refine it a little bit?

DR. FENICHEL: Yes.

DR. KONSTAM: I think you set up the discussion just I think in the right way, Bob. But let's maybe focus on it from the perspective of an efficacy claim. And I guess take them in two steps. So, first, just the ECG, which is the way the question is posed. And let me give you my answer to that. It is I would be accepting of that on the grounds that -- and we discussed this at length around elfedalide, and there were some very persuasive arguments made and I personally accepted them that if you knew that a drug

kept somebody out of atrial fibrillation. And I personally would accept that from a perspective of efficacy. And I can justify it on the grounds of the stroke story. You know, not everybody can take anticoagulation. There are a variety of reasons. But I think that to me is sufficient to say that that could be a claim for efficacy. So that is my opinion about that.

With regard to the other side of it as you have raised it, I would refine really what I really want to say here. I actually would be accepting of an efficacy claim for, as the sponsor has set it up, prevention of symptomatic atrial fibrillation, accepting the fact that some of that is going to be contributed to by rate control and some of it may be contributed to by preventing the a fib. On the grounds that that is preventing symptoms. So I can accept that. I guess where I am going to get into issues around it is when we get -- when we move from the question of efficacy to the question of approvability. Because to me it makes a big difference if we wind up concluding that the way this

drug works is by reducing heart rate when the patient is in a fib. Then that makes me look at the data set very differently and it makes me say, well, we have other drugs that do that. And so when we get to the benefit/risk ratio, to me it shifts it. And that is really -- it wasn't so much to say that I couldn't accept that as an efficacy endpoint. It is just that I think that the mechanism is important in looking at the totality of the question.

CHAIRMAN PACKER: Okay. Let's -- this is not a specific issue or question about sotalol. So why don't we just go down the committee and phrase the question as follows. Should the primary basis for the approvability of a drug for atrial fibrillation be the ability to suppress symptoms? Should the primary basis be the ability to suppress ECG recurrence of the arrhythmia? Or are both -- or should both be required? In other words, the first possibility is that symptoms are very important and the ECG evidence is supportive. The second is ECG is important. Suppression is important. And the symptomatic relief is supportive. Or do you feel that both are required?

Bob, would that answer the question?

DR. FENICHEL: Yes, that is it.

CHAIRMAN PACKER: Good. Lem, why don't you start -- we will start -- oh, I am sorry, JoAnn, our primary reviewer, tell us what you think.

DR. LINDENFELD: I think EKG evidence is sufficient without symptoms. I think symptoms would be supportive.

CHAIRMAN PACKER: Okay. Lem, while we --

DR. MOYÉ: I would say both.

DR. BIGGER: I have a different answer. I would say either. Either by itself without the other.

CHAIRMAN PACKER: Okay. We didn't include that, but one could. Would anyone change their answer based on that possibility? No. Okay.

DR. GRINES: Actually, I might change my choice if you had either.

CHAIRMAN PACKER: Okay. Tom?

DR. GRABOYS: I would like to see both.

CHAIRMAN PACKER: Marv?

DR. KONSTAM: I'd say either.

CHAIRMAN PACKER: Okay. Michael?

DR. CAIN: Either. And the scenario would be that you could have somebody who is dizzy all the time but the drug puts them in sinus rhythm. Although they are still dizzy, they are in sinus rhythm. And that would be either.

CHAIRMAN PACKER: Ileana?

DR. PIÑA: I would go with either.

CHAIRMAN PACKER: Udho?

DR. THADANI: I would go both, especially based on the past experience. You could suppress PVCs and patients could die. So if the patient is both symptomatic and the ECG is better, are you going to say that drug is effective? So I will go for both.

CHAIRMAN PACKER: Okay. I would vote for both as well. Let me just say that, Joan, from what we have outlined, there is a slight preference for either for the committee. Let me just say that I think it is important to, although both Tom Bigger and Michael Cain don't officially vote, this is more of a general question. And, Bob, you are getting a little bit of a mixed message here, but I think you are

getting a sense of where the committee stands.

DR. FENICHEL: Yes. That's fine.

CHAIRMAN PACKER: That means the committee feels the way it does today and would be anxious to look at other data bases tomorrow. Okay, question number 2. It is also a generic question. I am not going to read the question, but we all know the issue of drop-out rates and the issue that we talked about of informative censoring. Let me --

DR. FENICHEL: Milton, I think that question was really adequately discussed.

CHAIRMAN PACKER: Fine.

DR. FENICHEL: And since this doesn't bear upon the specific drug, I think we can skip it now.

CHAIRMAN PACKER: Fine. I think it would be fair to say, Bob, that the committee was unanimous in indicating what they thought was the right path to follow. Number three, most of the patients in -- question 3 deals with paroxysmal atrial fibrillation/flutter. There are two studies. There is study 05 and there is study 9A. And considering both study 05 and study 9A, did these trials have specific

features that might render them more or less than normally persuasive. This really actually, JoAnn, gives you an opportunity to highlight the issues that are of concern or basically highlight the major strengths or weaknesses of the trial that would lead you to think that one should put more or less weight on them.

DR. LINDENFELD: I think study 05 was a reasonably good study with the one problem that we discussed that question 2 would have addressed, this drop-out rate. And I think there is some concern that the drop-out rate here was among people who would have been most likely to revert to atrial fibrillation. I think the second study, 9A, isn't very persuasive, just very small numbers. So I wouldn't put much weight on that. I think that overall these studies are -- particularly 05 is a reasonably persuasive study. Once again, I think the specific features of concern are the very short follow-up, the drop-out rate, which we discussed, and then I think also this just is not really terribly representative of the population of patients we would treat.

CHAIRMAN PACKER: Okay. Any -- what we should do is find out how the committee feels. Bob, let me just ask -- a distinction is made here because the sponsor made the distinction between paroxysmal atrial fib/flutter and a chronic atrial fib that has been converted to normal sinus rhythm. I think I heard Michael Cain earlier suggest that that distinction is somewhat artificial and impractical. Can we -- if that is the case, then the distinction between 3 and 4 is totally artificial. Does the Agency believe that these are distinct indications? Because some of us might feel that they are not distinct.

DR. FENICHEL: I think the best solution for those of you who do believe they are not distinct is to cast the same vote on each question. I think we do have products approved for one condition and not the other. So at least at one time or another we and you must have been convinced that they are distinct.

CHAIRMAN PACKER: Okay. Why don't we rephrase -- I think we have all discussed the issues related to 05 and 9A. I think that one could ask the question 3(A) in the following manner. And that is,

let us ask whether one finds from 05 and 9A, can one conclude from looking at these, given their strengths and weaknesses, that there is an effect on sotalol on recurrent paroxysmal atrial fib, and whether you would consider that data to be persuasive for that indication. Because that is really what we are asking here.

DR. THADANI: Are you going to take a vote whether people on the board here believe paroxysmal is different than chronic?

CHAIRMAN PACKER: No.

DR. THADANI: People are obviously -- you said they might be the same. But --

CHAIRMAN PACKER: All right, Bob?

DR. THADANI: Do you want us to vote on that yes or no, just to know how many people on the panel differ them? Yes? No?

CHAIRMAN PACKER: No.

DR. FENICHEL: First of all, I think it is a religious discussion and it is not going to get anywhere. Secondly, I think that to the extent it could be made a rational discussion, I don't think it

can be made rational separate from the drug at hand. So one might -- the committee members might vote that, oh yes, they are the same as regards sotalol. But that might give the wrong impression to those hearing the discussion because the same committee might, with equal rationale, believe that they were different when considering the next drug that comes along for the same general area of indication or indications. So I just don't think it is a useful discussion.

DR. THADANI: But, Bob, they really are different because the patient --

DR. FENICHEL: Look, I don't think it is a useful discussion.

DR. THADANI: But they are different. Chronic a fib don't go into sinus rhythm by definition.

CHAIRMAN PACKER: Yes, they do because --

DR. THADANI: After cardioversion or something.

CHAIRMAN PACKER: They are converted. Anyway, I think the question that is before the committee with 3A evolves into do you consider the

data with sotalol in paroxysmal atrial fibrillation to be persuasive. You can -- that is really the question. I don't think it is the identification of the issues because we spent a lot of time identifying the issues. I think the question is do you consider it persuasive. You can use any criteria you want to answer that question. And I guess if you wanted to, you could say a little bit or a lot. I don't want to restrain the range of responses. So, JoAnn, do you consider the data supporting an effect of sotalol in patients with a history of paroxysmal atrial fibrillation and flutter to be persuasive based on studies 05 and 9A?

DR. LINDENFELD: I think we often talk about this as do we consider this similar to a single reasonable trial, and I would say I consider this as these two together. I don't really consider 9A. So I think I would be -- I think this is as persuasive as a single significant clinical trial.

CHAIRMAN PACKER: Can I suggest the following? Because I think that the previous format that we have used, which is equivalent to two trials,

between one and two trials, one trial, et cetera, there are certain situations where that becomes particularly useful. This is sort of different than that because we sometimes use that scale when we have one very, very big study and we are trying to gauge the level of persuasiveness. Here we have got 8 studies of varying degrees of issues. So I think one sort of has to look at the totality of the data base. And so I think that is why the usual scale is avoided here. Is that true, Bob? And consequently I think -- you can still hedge your bets. But rather than say one or two, do you consider it to be persuasive to support an effect of the drug?

DR. LINDENFELD: I would consider it normally persuasive.

CHAIRMAN PACKER: Normally -- I like that. Normally persuasive. Lem?

DR. MOYÉ: I would consider it unpersuasive. I think that study 05 is fatally flawed because of the problem of drop-outs. And 9A is essentially a subgroup analysis. So I would say no.

CHAIRMAN PACKER: Okay. Tom, we are going

to ask you to vote. Joan will not officially record the vote. But I think it is important for everyone to hear how you feel.

DR. BIGGER: Yes. I think they are reasonably persuasive.

CHAIRMAN PACKER: Okay. Cindy?

DR. GRINES: I agree.

CHAIRMAN PACKER: Tom?

DR. GRABOYS: No, I don't think they are persuasive.

DR. KONSTAM: I don't know how to quantify it. I think they are a little bit less persuasive than I would like them to be. I don't know how to quantify that any more than that. And I think that the concern that is driving Lem really all the way to say it is useless doesn't drive me anywhere near that far, but it does raise concerns in my mind.

CHAIRMAN PACKER: I guess here is the way to judge the question. Assuming that the committee were to vote that the drug were approvable, and that is a much more globally comprehensive question, would you include in the concept of what the drug was

approvable for those with a history of paroxysmal atrial fibrillation? I mean, that is really the question.

DR. KONSTAM: Well, that is more complicated. I mean, you know if -- I am not sure how to answer that. I mean, if we really were looking at these two things as different entities, then I would have a lot of problems. Because I would be left with this data set as the only evidence and I would not feel that that in and of itself would be sufficient just taking 05 as the single trial. So I guess I am going to be stuck unless we say that these are sort of one condition that take different forms.

CHAIRMAN PACKER: Okay, that is fair.

DR. KONSTAM: And I am happy to do that. So in that light, I think the answer would be I think that the studies, particularly 05, is useful and would move me -- would under those circumstances move me toward an approvability.

CHAIRMAN PACKER: I understand. I understand and the intent of the question is not to create a black and white situation.

DR. KONSTAM: Right.

CHAIRMAN PACKER: The intent, in fact, is to gauge it. And I think you have accurately portrayed your feelings about it. Michael?

DR. CAIN: Again, I would lump them together for the purpose that both groups of patients, paroxysmal and chronic were in atrial fibrillation and are now in normal sinus rhythm. And it separates that from the chronic persistent, which means no matter what you do, you cannot restore sinus rhythm. If you lump them together, then I think 05 is normally persuasive in the group of patients that have been studied and discussed, with the footnote that there are still several groups of patients that have not been included.

CHAIRMAN PACKER: That actually is a specific question later on. So we will highlight it at that point in time. Ileana?

DR. PIÑA: I share Marv's concerns about 05. And with that caveat, I would say I am somewhat persuaded.

CHAIRMAN PACKER: Udho?

DR. THADANI: I think 05 we discussed the problems because of intent to treat versus drop-out issues. And I think that is a concern, although the data is going in the right way on the whole. And again, the problem with the subgrouping in the other study. So I am marginally persuaded, but the evidence is not as strong as I would like to see. But there is a suggestion it is going in the right track. So marginally persuaded.

CHAIRMAN PACKER: Okay. I guess I agree with what the -- the way the committee is actually emerging is they feel there is evidence for an effect on paroxysmal atrial fibrillation, which is less than the kind they would like to see. But they believe that in effect does exist. They would not like to conclude an effect doesn't exist. And I think that Michael Cain said it probably best by saying that the decision might be easier if one were to consider paroxysmal and chronic together as a combined data base, but that is for -- I think we will discuss that in just a few more minutes. Bob, I think this will become more clear in just a few minutes. JoAnn, did

they identify a dosing regimen that convincingly defers relapse into atrial fibrillation?

DR. LINDENFELD: I think 120 mg bid was the minimum dose that convincingly does that.

CHAIRMAN PACKER: Okay. Does anyone -- would anyone suggest a different answer? Would anyone suggest 80 mg bid? Would anyone suggest 160 mg bid? Would anyone agree with 120 mg bid?

DR. KONSTAM: Yes.

CHAIRMAN PACKER: Okay. I just want to make sure you are awake. Okay. JoAnn, did they identify a regimen that convincingly alleviates symptoms or reduces the incidence of stroke?

DR. LINDENFELD: Well, the answer to stroke is no. I think symptoms -- the symptomatic recurrence as an isolated symptom, yes.

CHAIRMAN PACKER: Okay. Would anyone disagree?

DR. KONSTAM: Yes, I would.

CHAIRMAN PACKER: Marv?

DR. KONSTAM: You know, I mean in the sense that I think -- I guess calling this symptomatic

consideration. The sponsor is suggesting outpatient use for patients without structural heart disease and inpatient initiation in patients with structural heart disease. JoAnn, what do you think?

DR. LINDENFELD: I am not comfortable yet starting this drug as an outpatient for several reasons. One, I think there is still a reasonably small number of patients, 349 in 04 and 25 percent of 05, which is a small number. But also we have discussed over and over again the population that will actually be treated, and those are older people. And I think expecting -- seeing the risk of taking an extra drug, I just am not yet comfortable with the safety of this drug as an outpatient. So I would say no to that.

CHAIRMAN PACKER: Okay. Anyone would disagree with JoAnn? Okay. Then it is the consensus of the committee as well as Marv Konstam, who also said that all patients should be hospitalized for treatment. So it would be in-hospital initiation. Any other comments? Okay.

DR. THADANI: Also, I think it would be

a fib is a little bit different than saying -- I don't know how to -- this isn't going to sound right. Saying that it alleviated symptoms of a fib in the sense that I think what the investigators were really detecting was palpable a fib. In other words, patients who knew they were in a fib. And I think that that is somewhat different from saying that they were experiencing a limiting symptom from the a fib. So I would -- I guess I would question that this is clearly an effect on symptoms per se.

DR. LINDENFELD: I totally agree with that. This is just symptomatic atrial fibrillation but not other symptoms.

CHAIRMAN PACKER: Okay. So the proposal that has been put forward is that symptoms here -- that there should be no claim for symptomatic relief. The symptoms here are a marker for recurrence and consequently evidence for a drug effect. Is that correct? I just want to make sure what you are saying. Okay.

DR. KONSTAM: I can accept that. I mean, I don't really have a problem with the term

symptomatic a fib. I just think it has a little different meaning than what we are usually looking for when we talk about symptoms.

CHAIRMAN PACKER: Yes. I mean, symptomatic a fib here is the name of a disease.

DR. KONSTAM: Right.

CHAIRMAN PACKER: As opposed to for the reduction of symptoms in patients with atrial fibrillation.

DR. KONSTAM: Right. A subtle point.

CHAIRMAN PACKER: We are saying -- and let me make sure that everyone is in accordance -- that the disease being treated here is symptomatic atrial fib. That was the entry criteria. And that the reduction of symptoms is evidence for a drug effect but not evidence for a claim for reduction in symptoms. Is that fair?

DR. THADANI: Yes. I think the table we saw, the overall symptom rate was not much different -- the totality of the symptoms. So I think if we are talking about symptomatic a fib, we should separate it from the totality of the symptoms. Because I didn't

see any significant P values.

CHAIRMAN PACKER: I think you are agreeing, Udho, right? You are agreeing. Okay. Let us move on and address exactly the same questions, and then I am going to take the liberty of trying to get a consensus of 3 and 4 together. The studies under consideration are those that randomize patients after being converted from chronic AF. The studies are 004 and 014. And, JoAnn, do you consider, considering all the weaknesses and strengths of these studies, that the evidence this drug has an effect in preventing or reducing the risk or extending the time to recurrence in patients with a history of chronic AF that have been cardioverted, do you think that you consider the evidence that sotalol has such an effect to be persuasive -- normally persuasive?

DR. LINDENFELD: Normally persuasive, yes.

CHAIRMAN PACKER: Normally persuasive. And why don't we start at the other side for this question. We went this way. Udho?

DR. THADANI: Yes, I think the 004 study is pretty persuasive. I will go along with the vote.

CHAIRMAN PACKER: Ileana?

DR. PIÑA: I agree.

CHAIRMAN PACKER: Michael?

DR. CAIN: I agree.

CHAIRMAN PACKER: Marv?

DR. KONSTAM: Well, I guess the only thing -- 004 is the study that was extended, right?

CHAIRMAN PACKER: Yes.

DR. KONSTAM: So I guess just in terms of the answer to 4A -- I mean, there is a feature that raises questions and I am not sure how much that should affect things.

CHAIRMAN PACKER: That is why you get paid big bucks.

DR. KONSTAM: Yes, right, big bucks. So I guess I am in statistical limbo about this. Because I have heard very different advice from different statisticians about this point. And digesting all that, I am going to still say that I am persuaded by the study.

CHAIRMAN PACKER: Tom?

DR. GRABOYS: I agree.

CHAIRMAN PACKER: Okay. Cindy?

DR. GRINES: Agree.

CHAIRMAN PACKER: Tom?

DR. BIGGER: I agree.

CHAIRMAN PACKER: Lem?

DR. MOYÉ: I don't agree. I think 014 has the same lethal flaw that 05 has. And I think 004 is much too small and doesn't have the -- it is not as all inclusive of important demographic subgroups as it should be to be persuasive. So my answer is no.

CHAIRMAN PACKER: The lethal flaw you identify in 004 is not the informative censoring, since that wasn't an issue. I just want to make sure that we know what lethal flaw in 004 you are referring to.

DR. MOYÉ: No, 014 had the lethal flaw.

CHAIRMAN PACKER: I am sorry.

DR. MOYÉ: 014.

CHAIRMAN PACKER: Does 004 have a lethal flaw?

DR. MOYÉ: No. 004 -- the problem I have with 004 is that it is small and that it does not

include -- it is not all-inclusive of the demographic subgroups I would like to see in order to base a decision. That is going to affect many communities.

CHAIRMAN PACKER: Okay. My vote is that it is persuasive. JoAnn, do you want to identify what dosing regimen you believe has been shown to have an effect which is being discussed in question 4?

DR. LINDENFELD: Well, I think this was a dosing regimen, I believe, of 80 bid up-titrated to 160 bid. And so I think that would have to be the recommendation. It is hard to identify a single dose out of that.

CHAIRMAN PACKER: I am sorry?

DR. LINDENFELD: This was a regimen that started off at 80 bid going up to -- wasn't that correct, 160 bid?

CHAIRMAN PACKER: Yes.

DR. LINDENFELD: So there was a single regimen that was tested rather than a specific dose.

CHAIRMAN PACKER: All right. A dosing strategy that was tested. So I guess we would need to be empiric here and say it was the dosing strategy

that was evaluated in the trial.

DR. LINDENFELD: Right.

CHAIRMAN PACKER: Okay. And I assume that the answer that everyone has to 4C is identical to the answer they provided for 3C. Does anyone disagree? Okay. Now let me --

DR. THADANI: You know on the stroke issue -- because one other concern one has is I don't think everybody was on anticoagulants. When I was reading it, some 40 percent or 50 percent of the patients were. So I don't think you can address the issue at all not knowing the details of how many -- you know the sample size is small.

CHAIRMAN PACKER: No. JoAnn said to question 3C that there were no data whatsoever on stroke.

DR. THADANI: Oh, okay. So the same applies.

CHAIRMAN PACKER: And in fact the response of the committee to 3C was there was no data that showed it alleviated symptoms. What it did was prevented a disease called symptomatic atrial

fibrillation.

DR. THADANI: Okay.

CHAIRMAN PACKER: Okay. I think we clearly enunciated that principle in 3C, and I think we are reiterating that principle in 4C. Okay. Let me just -- I want to get two more questions here which are to be inserted between 4 and 5. To what degree, if any, are your opinions on 3 and 4 influenced by the results of dofetilide 345? It is not asked. But I think the Agency probably would like to know because there is an operational issue which is important here. The question 3 and question 4 did not ask you to consider dofetilide 345. So, okay, you answered 3 and you answered 4. Now the question is do you need dofetilide 345 to get to where you want to go based on your answers to 3 and 4, and the answer could be it doesn't matter or it helped a little or it helped a lot. JoAnn?

DR. LINDENFELD: It helped a little.

CHAIRMAN PACKER: Okay. Udho?

DR. THADANI: I think it helped a little because I am still not convinced that we know the true

incidence of torsade in the absence of Holter monitoring. I think we got a very in-random sequencing of the data base. I am not sure I can be very -- you know, the incidence of torsade might have been underestimated.

CHAIRMAN PACKER: Are you sure you are answering the question?

DR. THADANI: Well, the question is are you sure with the --

CHAIRMAN PACKER: No, no. This is an efficacy issue on atrial fibrillation and the question is did 345 influence you in a material manner. And the possibilities are no, a little, or a lot. The efficacy. There is no torsade issue here.

DR. THADANI: I think a little.

CHAIRMAN PACKER: Ileana?

DR. PIÑA: It helped me very little simply because it was going in the right direction.

CHAIRMAN PACKER: Michael?

DR. CAIN: No real help.

CHAIRMAN PACKER: Marv?

DR. KONSTAM: Yes, I am -- I would have

answered these questions identically had I not seen 345. So in that light, I will say not at all.

CHAIRMAN PACKER: Tom?

DR. GRABOYS: Not at all.

CHAIRMAN PACKER: Cindy?

DR. GRINES: It helped a little.

CHAIRMAN PACKER: Tom?

DR. BIGGER: Yes, it helped a little because a small dose had a definite efficacy signal.

CHAIRMAN PACKER: Now, Lem, you can actually use this as an opportunity to change your vote because the real question being asked is to what degree are you looking at 345 in a meaningful fashion. I think you have already said for questions 3 and 4 that you are not persuaded. So you could say that if you included 345, you would be persuaded.

DR. MOYÉ: I am appreciative that at this last meeting I can attend that the chairman gives me an opportunity to change my mind. I think I will decline.

CHAIRMAN PACKER: Okay. All right, you can't say I didn't make the offer. And personally I

think that Marv has said it the way I would feel about it, which is that I would have voted the same way without 345. But in all honesty, it probably helped a little. Okay. Let me see if I can clarify one other issue before going on to 5. One concern that I have -- this is to Bob Fenichel -- is that physicians might get the impression that sotalol is a treatment for chronic atrial fibrillation in patients who remain in chronic atrial fibrillation. I have -- I must say I have a major concern about that. And in fact this is a treatment for patients in normal sinus rhythm. And the proposed wording that the sponsor has in my view does not make that clear, which is why I tend to favor Michael Cain's suggestion that the distinction between paroxysmal and chronic atrial fibrillation here is more of the history of the patient as opposed to the state that the patient is in at the initiation of therapy or the intent of therapy. The state that the patient is in is normal sinus rhythm at the initiation of therapy and the intent of therapy is to prevent recurrence. And the only difference between 3 and 4 is whether their previous history of atrial

fibrillation was intermittent or continuous. And because of that, my sense is that what we are really talking about is that this is a treatment for patients in normal sinus rhythm with a -- and I hate to say this -- either a history or recent history of atrial fibrillation or flutter as opposed to paroxysmal or chronic. And I just wanted to make sure that I got a sense of the committee that Michael Cain's view on this, which is that the distinction here is somewhat artificial, and therefore the two data bases can be viewed as being mutually supportive, is the consensus view here. Because I understand, Bob, there is a history of making these distinctions. But the intent in fact is to treat patients who are in normal sinus rhythm. The risk I see here is that if the wording of the indication includes for the treatment of chronic atrial fibrillation, that patients who are in atrial fibrillation will get this drug to either convert them or for some unbelievably undefined goal, which I think is a significant risk.

DR. FENICHEL: Well, we know certainly that an awful lot of the quinidine that is used is

used in patients who have been in atrial fibrillation for decades and physicians say when asked, oh yes, well quinidine is used for atrial fibrillation. So, of course, the risk you are alluding to is a serious one. And in my fantasy, we get the labeling wording right and that solves problems. But that is a different world. So I think we are going to work on getting the labeling right to send the message that indeed this is for people who are now in sinus rhythm but who have histories of one thing or another. I think there is -- well, the reason that this distinction has been made in the past is not that it is to be given either -- that other drugs are to be given either to people in chronic fibrillation or paroxysmal fibrillation, but rather that drugs have tried to demonstrate efficacy in patients of both kinds and have succeeded in only one. So what are you going to do? Well, you've plainly got to label it for the one.

CHAIRMAN PACKER: I think the key operational distinction here, and I will just try to reach a contrast with dofetilide, is that if I

remember correctly, the sponsor of dofetilide was actually seeking a claim and provided data that in the doses that they were recommending that there was -- that they would use the drug for conversion.

DR. FENICHEL: That is correct. We have pharmacological conversion labeling for -- well, for ibutolide and for quinidine certainly and submitted for dofetilide.

CHAIRMAN PACKER: No such claim is being requested here. And in the only study to evaluate it, the doses used are outside the recommended range. So all of this, I think, underscores the concept that this is a drug to be given in patients in normal sinus rhythm for the prevention of recurrence. This is not a treatment for atrial fibrillation. This is in somewhat contrast to dofetilide that actually had presented the committee a conversion data base with the intent that the drug could be used for a conversion at the same doses that it was used for the prevention of recurrence. I think the distinction here is important. Tom?

DR. GRABOYS: Yes. See what you have done

though is you have raised the issue, the fundamental issue, which is the translation from what goes on in here or what goes on in the office when Dr. Kowey is managing a patient in the umpteenth degree perfectly is different than translating it into the community. And the concern that we have is being this is not going to be used for an indication as a life-saving event where you are willing to accept some risk. We are back to the same fundamental issue of how the physician in the community is going to be dealing with this. And the fact that I frankly don't trust the physician in the community in terms of managing these patients, regardless of how much so-called educational material they are going to try to give that physician.

DR. THADANI: Milton, also I think perhaps one of the issues could be the wording could be completely changed. Because the trials we have seen from my point of view would be to delay rather than use the word prevent. I think prevent is the wrong term here. We should use the word delaying the reversion to atrial fibrillation after a patient in a fib has been converted to sinus rhythm.

CHAIRMAN PACKER: The sponsor has already incorporated that concept in their proposed labeling.

DR. THADANI: So that might be easier. That means you have to convert the patient into sinus first before you start the drug. And then all you are doing is claiming a delay of reversion into a fib.

CHAIRMAN PACKER: I think that the sponsor has already incorporated that. I think the committee is in favor of the emphasis on the use of this drug in normal sinus rhythm. And, Tom, I wish we could address your concern in a meaningful fashion. But we probably -- unless you can come up with a specific suggestion, that dissociation is commonplace, not only -- and does not only apply to this drug. And I don't know how to fix the problem.

DR. PIÑA: I have a question.

DR. GRABOYS: We have got the only other scenario --

DR. PIÑA: I am sorry, I have a question of the sponsor. You have a lot of numbers of patients already being treated for atrial fibrillation with this drug. Do you have any in-house data as to how

many of those patients are being given the drug for conversion versus keeping them in sinus rhythm? I mean, you showed a large -- a very large use of this drug in the community.

DR. KOWEY: As a point of fact, Ileana, they do not have any data. All I can tell you is that in clinical practice, this drug is rarely used for conversion to sinus rhythm. And the reason is because it rarely works. At the doses that we are recommending, it just simply doesn't have enough of an effect. Where it is used, however, which is a little bit different than what you are talking about and which has not been studied in all honesty, is it is used in a fashion where the patient is loaded with the medication in the hospital in atrial fibrillation and then are cardioverted on the drug to sinus rhythm. That has not been studied in the clinical trials we have presented today. But that actually is probably -- if you are talking about the way doctors use the drug which is not what you are talking about, that is the way doctors use the drug, the way you are not talking about.

CHAIRMAN PACKER: Tom, I am wondering if we can address your concerns in part by suggesting that whatever approved labeling -- and I don't want to wordsmith this too much, but I think that some guidance here is appropriate. Maybe the indication section should say this drug is not a treatment for atrial fibrillation and should not be given to patients with atrial fibrillation. That is probably too strong. I am trying to figure out how to phrase it.

DR. THADANI: You could say unless they have been converted to normal sinus rhythm. Because you are not going to use it for a fib. And also I think you could go further to allay Tom's fear. If the patient has a first recurrence, the drug should be stopped. Because that is how the studies were done. If the patient had a recurrence, the patient was withdrawn. And that is not an intent to treat. So you could say, okay, you start a drug if the patient is in sinus rhythm and paroxysmal and continue it. When the first recurrence occurs, the patient is out of the drug or if the patient is in chronic a fib, you

cardiovert him and put him on the drug and if he has a relapse, the drug should be stopped. Because if there is a relapse, why do you want to continue it? And I think that would be an important thing. I know we have not done it, but that would be one way to avoid indiscriminate use of a drug which may be questionable to use once the patient is in a fib other than controlling the rate.

CHAIRMAN PACKER: Tom, you raised the concern and I think we all share your concern. Does the proposal that I just made go somewhat to addressing your concern or would you modify it in any way?

DR. GRABOYS: No. I am going to have difficulty approving this drug based on the points that I have already raised.

CHAIRMAN PACKER: Are you trying to say --

DR. GRABOYS: The fact is that this population will all end up in atrial fibrillation. All you are doing is delaying it, as has already been mentioned, or deferring it for a few months. And you are deferring it under the concept that somehow I am

going to feel better for those few months. But ultimately they are going to end up in AF and AF will be the rhythm of choice and you are going to control their rate and they are going to feel better.

CHAIRMAN PACKER: Okay. Why don't we do this. The appropriate time to discuss this at length would be after question 8. So let's go on to question 5. JoAnn, what do you think is the likely incidence of QT prolongation and torsade in various populations if the patients are treated with sotalol using the dosing regimens suggested by the clinical trials?

DR. LINDENFELD: This is a broad question in various populations, but I think that if the drug is used as specified in these trials and these doses in these patients, the incidence will be low, probably under 1 percent. I just think several people have made the point that this is not necessarily the population or the doses in which it will be used or the doses for creatinine clearance.

CHAIRMAN PACKER: Okay. A question for Bob Fenichel, is that a good enough approximation?

DR. FENICHEL: Yes.

CHAIRMAN PACKER: Okay.

DR. KONSTAM: Can I chime in, Milt?

CHAIRMAN PACKER: All right.

DR. KONSTAM: I mean, again, I just don't know the answer to this question. And the thing is that we can't answer this question without reference to the time frame of our observation in this population. So I am not sure what the median time of exposure that we have in terms of our data set is, but it is relatively short. It is measured in weeks. And so I think if you were going to ask the question of what is the incidence of torsade -- all the caveats that you mentioned, JoAnn, I fully agree with. But I would just add to that the time frame in that we don't know what it would be in a year or two years.

DR. THADANI: But surely the incidence of QT is not small. QT interval prolongation is dose response related.

DR. KONSTAM: Oh yes, QT prolongation is a lot more than 1 percent.

DR. THADANI: So I think there are two separate questions here. The incidence of torsade is

small, but the incidence of QT is proportional to the dose. So if you look at the 05 study or even 04 when you dose titrated, you are saying average QT prolongation is 21 or 22 seconds. That is the mean value, so there are a lot of patients falling outside. So I think the QT prolongation is uniform. That is what the drug does. While the incidence of torsade is small. So I think my reading is there is a dissociation between the two phenomenon. And I am also more puzzled now the more I hear about QT. Women show less prolongation and have a higher incidence of QT in general. So I am more confused than ever what the real relationship is.

CHAIRMAN PACKER: Ileana?

DR. PIÑA: Yes. I think that more than dose, it is probably serum concentration which varies according to renal clearance. So that the higher -- I mean the lower the renal clearance, the longer the QT. But that is part of the drug effect as well. So you are going to live with it if you approve the drug this way. And I think we just have to be cognizant of the fact. But I still think that the rate of torsade,

at least if dosed appropriately as recommended, continues to be small.

DR. THADANI: Also, I think since the question also addresses population, there is some discomfort. We don't have a large sample size in patients with a diminished LV function. In the first study, the disclaimer was 60 -- a creatinine clearance of 60. In the second study, it was 40 to 60. But the sample size was so small in all that we are using or the ones that we are dosing. I think we would like to really see a bit larger sample size to be sure than in these patients, even in the once daily dosing. Say if you used 160, you might end up having more prolongation of the QT than one could be reassured from this smaller data base.

CHAIRMAN PACKER: Okay. I think what we have right now is -- just reading everyone's comments, the following conclusion. That the incidence of QT prolongation is dose dependant and has, in fact, been described and quantified in the existing trials. And I think what has been added in general is that of course the incidence of torsade has been defined only

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in the patients who were treated and has not been defined in the patients who were not treated. So the incidence, I guess, JoAnn, of less than 1 percent applies to the patient populations that were adequately represented in the clinical trials. Does anyone disagree with that conclusion? Okay. Does sotalol cause significant side effects other than QT prolongation and torsade?

DR. LINDENFELD: Yes I think it causes side effects we would expect from a beta blocker -- bradycardia, fatigue, exacerbation of heart failure.

CHAIRMAN PACKER: I don't think anyone disagrees. Any other side effects anyone believes should proceed?

DR. THADANI: What about the age group? You know, there was some concern about dizziness in people who were above 65. I think we should mention that because again the sample size might be small and Tom brought up patients who are 70 and 75. And you don't want them to have syncopal attacks or something or whatever. So I think probably we need more information on that.

CHAIRMAN PACKER: Okay. Let me just -- for the record, Dr. Califf had to catch a plane, but he voted yes on questions 3 and 4 for persuasiveness and also agreed with the committee on the dosing issues and on the symptom and stroke issues. Any other points on 6?

DR. BIGGER: Well, just the bradycardia can be very severe and cause hypotension and even death. So it shouldn't be -- it should get a little bit of a highlight.

DR. THADANI: Milton, on that question I think also probably raise the issue. Because I was surprised in these trials that Digoxin was allowed and most other drugs as background therapy. We know that especially in patients with a fib, if they are dig- plus another beta blockers, sometimes -- especially when they are in a fib, the rate really goes slow. And I have seen pauses of three to four seconds, especially with the two combinations. From the data base, since the trial was done on background Digoxin on most of the patients, are we going to recommend that Dig must be used or what? Because I know it

won't come up in the questions until the bradycardia is used. Because none of the trials -- I think they wanted the Dig background. And the problem is they rated this background so that the patients don't have too many symptoms. I don't know why. Because I was a bit puzzled. I know Dig controls the rate in some patients, but not in all. So would you have to say this drug should be only used in patients who despite Dig remain symptomatic?

CHAIRMAN PACKER: That is question 9, Udho.

DR. THADANI: But in the bradycardia issue, can you dissociate the two?

CHAIRMAN PACKER: We will bring it up in 9.

DR. THADANI: Okay.

CHAIRMAN PACKER: Okay. Number 7, do there appear to be differences in safety and efficacy between d,l-sotalol and available therapies. I think the Agency -- the division emphasizes that it may be hard to make this assessment because there are no direct comparative studies or there are very few

comparative studies. It is still relevant to ask the question whether the risk/benefit relationship for this drug differs materially from what one might think or one might deduce would be the risk/benefit relationship for other drugs. I assume that that comparison, Bob, is to be made for drugs that are approved for the indication.

DR. FENICHEL: Well, I think it would be problematic if there were a drug which -- well, I don't think it should be limited to stuff approved for the indication.

CHAIRMAN PACKER: Okay. That is fine.

DR. FENICHEL: Well, I think people might think, well, there is another drug even in the pipeline that the rest of us haven't heard about. And I can imagine that people might think, oh well, there is this secret drug which is so much better and it would be a shame to have this one out. Well, that is a respectable point of view. Or people might think they know something about dofetilide, even though of course it is not approved but it was discussed at this meeting just a couple of months ago. And so I don't

think people should limit themselves to approved therapy.

CHAIRMAN PACKER: Okay. JoAnn, 7A? From what you can deduce, do you think that sotalol is markedly more or less effective than other treatments? The word available here is to be converted to the word other.

DR. LINDENFELD: Other. Given everything, I think that sotalol is equivalent to other available therapy.

CHAIRMAN PACKER: Does anyone disagree? Okay. 7B. Does sotalol appear to be more or less proarrhythmic than other therapy?

DR. LINDENFELD: Compared to other drugs that cause torsade, I think sotalol appears --

CHAIRMAN PACKER: Other drugs for the treatment -- for the prevention of recurrence of atrial fibrillation. This is not a treatment for atrial fibrillation.

DR. LINDENFELD: I think the rate of torsade is equivalent or the same.

CHAIRMAN PACKER: Okay.

DR. GRABOYS: Is that what you are focusing -- is that the definition you are looking at as proarrhythmic or torsade rather?

DR. LINDENFELD: Yes, I think torsade is the same if you want to include bradycardias as proarrhythmias.

DR. GRABOYS: You are saying with regard to available therapy.

DR. LINDENFELD: I guess I was counting --

DR. GRABOYS: You are not saying available therapy of beta blockers and calcium channel drugs.

DR. THADANI: Quinidine and --

CHAIRMAN PACKER: Yes, I think --

DR. GRABOYS: That needs to be clarified.

DR. LINDENFELD: We should clarify that, yes.

DR. KONSTAM: I think that is the critical thing. And this is where the mechanism comes in. Because what is this drug and how is it working and what is it doing? And we believe that a significant portion of the drug's effect is beta blockade. We are not exactly sure how much. But I am not sure we know

for sure that it is anything other than a beta blocker. And so obviously I think if we're comparing it to another beta blocker, it is far more proarrhythmic. So that is where the quandary comes in.

DR. THADANI: But surely here we are not asking about indications to control the rate, right? A beta blocker --

DR. KONSTAM: Yes, but Udho -- I guess we don't know really how much of the effect in terms of preventing recurring symptomatic a fib is an influence on heart rate when the patient goes into a fib.

DR. THADANI: I think perhaps would it be reasonable to insert something by that that the rate has to be controlled and other drugs should be used? Because beta blocker has been approved to control the rate in a fib, right?

DR. LINDENFELD: I think if we compare it to drugs that we would use to prevent recurrent atrial fibrillation, and given the drugs we would use to prevent it, I would consider the risk of torsade to be equivalent.

CHAIRMAN PACKER: Yes. I don't think we have to make this too complicated. I think that compared to drugs that block the AV node, this would be more proarrhythmic when compared to the drugs that we use to prevent recurrence of atrial fibrillation, which I think is what is being asked here.

DR. KONSTAM: But beta blockers, I am sure, prevent recurrence of symptomatic atrial fibrillation. I don't know if it has ever been studied quite that way.

DR. THADANI: But they are not approved, though, for that.

DR. KONSTAM: I understand.

CHAIRMAN PACKER: I don't think we can get from where we are to -- you understand the problem. We don't have any data base.

DR. KONSTAM: Right. Right. I also want to just -- can I just add that even with reference to this issue in terms of other drugs that prevent atrial fibrillation recurrence per se, I concur with your thought although I just don't feel that we have the data.

DR. LINDENFELD: No.

DR. KONSTAM: Even to say that.

DR. CAIN: And I think the only other caveat is that if you take propathenone and flecainide, they are indicated and used, I think, because of CAST, hopefully exclusively in people without structural heart disease, where as at least sotalol here there is some people who have had structural heart disease who have received the drug. So I think that comparison between propathenone and flecainide in people without structural heart disease and sotalol without structural heart disease versus with structural heart disease, we don't have the full story on that.

DR. THADANI: Milton, available means approved?

CHAIRMAN PACKER: No. We went through this already.

DR. THADANI: We said approved, right?

CHAIRMAN PACKER: No.

DR. THADANI: Because then I think I want to make a little --

CHAIRMAN PACKER: The operative word here is other.

DR. THADANI: Yes, I think I want to make one comment. The incidence probably is higher than what is reported with amiodarone. Because available therapy -- they are using a lot of amio for prevent of recurrence of a fib. And if I look at the literature data base, the relapse rate of maintaining sinus is 60 or 70 percent. Again, not an approved indication. But amio is the only drug which doesn't cause torsade. Because we have used amio in patients who have had torsade on type 1A and other drugs. So if you are putting a -- when JoAnn said it is the same as others, the only exception I will put probably is amiodarone. I don't know if the committee members would agree or not. But that is at least my experience from the literature data.

CHAIRMAN PACKER: Tom and Marv?

DR. KONSTAM: No, I just think Udho made a good point.

CHAIRMAN PACKER: Okay. Let me just make sure that I understand. The consensus here is that

maybe with the possible exception of amiodarone and with the possible exception of beta blockers if they were to work for this condition, that d,l-sotalol is not any better or worse compared to other drugs for prevention of recurrence in terms of its proarrhythmic effects. Is that what the committee feels? I just want to ask one question. Just so that I understand. The dose that appeared to be a reasonably effective dose here was 120. If you -- I didn't see a lot of proarrhythmias at 120. Am I missing something? I mean, I would almost be tempted to think about the possibility that it looks the same as others if you get up to 160 bid or higher. But is there a dose that is effective here that is less proarrhythmic, or is that a conclusion which absolutely just can't be reached from the available data? Cindy?

DR. GRINES: I agree that it looks like the torsade is dose-related in that I was struck also by the low incidence of torsade in the proposed dosing. But I think there are just so few patients that we have to conclude that it is probably equivalent.

DR. CAIN: And I think, Milt, the other thing is the type of patient. We are excluding people with large infarcts and congestive heart failure, which are the ones that --

CHAIRMAN PACKER: Right. And those were not excluded from the dofetilide data base. Okay. So is everyone comfortable with comparable with plus or minus amiodarone and plus or minus beta blockade? Okay? You've got it. All right.

DR. THADANI: Plus or minus heart rating lowering calcium blockers. Like we still use --

CHAIRMAN PACKER: That is a different indication.

DR. THADANI: No, no. The beta blocker is the same to control the rate. A different indication, yes.

CHAIRMAN PACKER: A different indication. Okay. Is -- are there non-proarrhythmic side effects that are more or less prominent with this drug than with other drugs that would be used to treat the same condition? JoAnn?

DR. LINDENFELD: I think there are some

non-proarrhythmic side effects that are more common. But I think if you take all non-proarrhythmic side effects that this drug has a reasonable side effect profile.

CHAIRMAN PACKER: Comparable?

DR. LINDENFELD: Comparable, yes.

CHAIRMAN PACKER: Comparable?

DR. KONSTAM: I mean the bradycardia. Tom Bigger made the point. I mean the bradycardia is more than certain other drugs that are available.

DR. LINDENFELD: But other drugs have, for instance, more diarrhea and more --

DR. THADANI: Less GI side effects than quinidine, I guess.

CHAIRMAN PACKER: I guess the question is is the non-proarrhythmic side effect of this drug so clearly distinguishable from others that you would use it as a factor to sway your opinion as to whether this drug should be made available? I think the answer or the sense that I got from your response, JoAnn, is no. What you gain with one, you lose with another?

DR. LINDENFELD: Correct.

DR. THADANI: If the patient was bradycardic, they were excluded. So if the heart rate is already 50, you are not going to put those patients on the drug. You know, the drugs which don't lower the heart rate, they could be put on it. So I think we will have to absolutely make sure that if you've already got a bradycardia that you probably -- that would be an exclusion. So that would be a different issue to be considered on starting the therapy to start with.

CHAIRMAN PACKER: Okay. Tom?

DR. BIGGER: It has got less organ toxicity than some of the drugs that are used for conversion and delay of recurrence. For example, you don't see thrombocytopenia and you don't see glucocyte reaction and things of that sort. That is in its favor.

DR. LINDENFELD: Another advantage is no Dig --

CHAIRMAN PACKER: No Dig interaction.

DR. LINDENFELD: No cytochrome problems. You just have to really watch renal function here.

CHAIRMAN PACKER: Less drug interactions, more bradycardia. I think the Division gets the idea. Okay. Number 8, should sotalol be approved to reduce the frequency of relapse of atrial fibrillation in patients in normal sinus rhythm with a history of atrial fibrillation? I think that that is sort of the concept that we were discussing before. And, JoAnn, why don't we get your answer.

DR. LINDENFELD: Yes, I think given all of the data that we have seen, I feel reasonably comfortable lumping these two groups of patients together. But I would say that it should be approved to delay the onset of atrial fibrillation.

CHAIRMAN PACKER: Discussion?

DR. FENICHEL: Wait, you don't have to anguish about the distinction between chronic and paroxysmal. I just want to reassure members of the committee that if you think it should be approved for anything, say yes. Obviously if you say it should be approved for neither indication, assuming you think that they are two independent indications, then that takes care of it. But as long as you say yes for any,

there is a question down the way, 9B or something, that says do you want to make that distinction. So don't make it now. Carry on.

DR. LINDENFELD: Yes.

CHAIRMAN PACKER: Okay. Discussion? We always have a discussion for a critical issue of approval or non-approval. No one -- does anyone want to discuss? No one wants to --

DR. KONSTAM: Well, I will just say that here is -- I think we wind up being influenced by cost/benefit ratio as opposed to just the pure question of efficacy and the pure question of safety. Here is where we have got to put it all together. And I think to me -- I think that is why I just say that I am going to wind up being strongly influenced by my response to 7B and where does it really fall and what am I really comparing it to. So that is my discussion.

CHAIRMAN PACKER: Okay. Let me just emphasize the point we always emphasize at this type of question, which is you need not modify your answer or a restriction to a specific indication or a

subpopulation or a requirement for post-marketing or anything. All of that is in question 9. So the answer to 8 should be if you can think of any restricted or unrestricted, modified or unmodified reason for approval, the answer to 8 should be yes. And then you should clarify what your concerns and limitations should be in question 9. Okay? So you might think that sotalol could be approved for one person and 8 would be yes and 9 would be for one person. Okay? Let's start with JoAnn. I am sorry, JoAnn, you did say yes.

DR. LINDENFELD: Yes.

CHAIRMAN PACKER: Okay. Lem, we will start with -- we will go down with you.

DR. MOYÉ: I would say no. And just very briefly, I think we have to proceed very gingerly and certainly in the case of an antiarrhythmic therapy. These drugs have been shown to have such dangerous stingers in their tails. We need to really have a very solid data base from which to draw conclusions. They are often used in patients for whom they were not initially studied. They are used in very fragile

communities. We need to have some assurances that in fact this drug is going to be safe and effective in those communities. And with all the discussions today, I don't think we have that information. So my answer is no.

CHAIRMAN PACKER: Tom, we will ask you to vote, but your vote will not count here.

DR. BIGGER: Well, I am not voting. I am just making a comment. I think it should be approved. It is a little like getting married after your children are in college. It has been used for many years for this indication and much more broadly than the indication the sponsor is asking for. Considering what else is available and becoming available and how we are suggesting it should be used, I think it would be appropriate to approve it.

CHAIRMAN PACKER: Getting married after your children are in college, huh? Tom, I really have to think about that. Cindy?

DR. GRINES: I agree with Tom.

CHAIRMAN PACKER: About children in college?

DR. GRINES: No. I see it very commonly used for this indication and I believe it should be approved.

CHAIRMAN PACKER: Tom?

DR. GRABOYS: For all the reasons I have mentioned already, I don't think it should be approved.

CHAIRMAN PACKER: Okay. Could you just clarify those reasons again? Because this is the appropriate time to do it.

DR. GRABOYS: The concern is you are using a drug that is potentially proarrhythmic that is non-proarrhythmic for an indication that is not to prolong life or prevent sudden death. It is an indication for "quality of life" for a rhythm problem that inevitably is going to end up in atrial fibrillation anyway. So why risk one of our patients' potential lives for that soft an indication.

CHAIRMAN PACKER: Do you think -- Tom, I just want to clarify. Do you think that the drug -- that no drug should be approved for that indication or that the drug would have to be safer than this one?

DR. GRABOYS: Well, safety is the prime -- I think is the prime concern. But if I were going to review all of the membrane active antiarrhythmic drugs, I would like to hold them to the same criteria.

CHAIRMAN PACKER: Marv?

DR. KONSTAM: I am going to vote no and I just want to make a few points. One is I just -- Peter made the comment earlier about previous drugs approved and whether we would be holding this to a higher standard. And just in general terms, it is always sort of an agonizing problem. But in the end, I think you wind up having to say, okay, what about the drug before us today. So I think that is the take-home that I wind up making. And beyond that, I think it differs again with regard to the mechanistic questions that I will mention in a moment.

The other point I want to make is I am not sure how I really should be influenced by the fact that this is already an available drug with off-label use. The sponsor feels that approval is needed for the purpose of doing education. I understand that point, but I am also persuaded by the opposite that

taking the drug now and the FDA giving it the label to say yes but it is specifically safe and effective in a fib I think is going beyond what I would like to do, and I think the bottom line is people will be able to use this drug off-label if they feel they want to do it.

I think the thing that I wind up coming home on is the problem I am facing by the fact that we don't know what exactly this drug is doing. And it is on both the mechanistic level as well as on a clinical level. The drug is a beta blocker, and we think that on a mechanistic level the beta blockade has some significant contribution to its effect and it may be all of its effect. And I think likewise the corollary of that is on the clinical level, it may in fact be working predominantly by lowering heart rate in patients who go into atrial fibrillation. And I think from a pure efficacy perspective, that probably doesn't matter. But I think it does matter relative to the risk. I don't think the risk would be out of the acceptable range if I really knew that I was providing the medical community with a new mechanistic

agent. But I guess I am not convinced of that from the data set, and that is really why I wind up coming down negative on the cost/benefit ratio. Because I do think there is a risk and I don't think we know what it is and I don't think we know what it is particularly from studies like the Julian and other studies.

The only other point I wanted to add that was made earlier but we haven't focused in on is the absence of experience with this agent in the presence of dilthiazim or verapamil. I think there is going to be widespread use with these two drugs, and we know absolutely nothing about the safety and efficacy of the agent with those two agents. So I think that is another negative.

CHAIRMAN PACKER: Michael, your vote won't count, but we would like to here what you think.

DR. CAIN: In both drugs, I would approve it for the indication used, although when we get to number 9, it may be one patient.

CHAIRMAN PACKER: I understand. Ileana?

DR. PIÑA: I would vote to approve.

CHAIRMAN PACKER: Udho?

DR. THADANI: I would put the word symptomatic, because this one doesn't say it.

CHAIRMAN PACKER: You can -- we will talk about modification -- and I think everyone on the committee has very specific recommendations for limitation, restriction and modification. So let us postpone that until question 9. If you think it should be approved for anyone, the answer should be yes.

DR. THADANI: Yes, I think for one of the nine, I would vote yes. Because there are certain reservations I would like to make.

CHAIRMAN PACKER: Okay. My vote is also yes. Califf is yes. It is 6 to 3. Okay. Now, JoAnn, can you outline for us the specific restrictions that should apply? 9A is the approval should be limited to specific individuals. Who should it be limited to, if at all?

DR. LINDENFELD: Well, we have some specifics just by the exclusion criteria. It should not probably be given in overt heart failure. And we

know about patients with bradycardia or any contraindications to beta blockers. And probably not at least preliminarily in patients on rate-lowering calcium channel blockers.

CHAIRMAN PACKER: Anything else?

DR. LINDENFELD: Those are the main ones.

CHAIRMAN PACKER: Okay. The question also contains should it be restricted to those who have severe or disabling symptoms as part of their symptomatic atrial fibrillation?

DR. LINDENFELD: Well, I would like to see its use restricted to patients who have significant symptoms, but I don't know that I can recommend that on the basis of this data.

CHAIRMAN PACKER: You could recommend that based on an assessment of risk to benefit.

DR. LINDENFELD: Then I would probably recommend that at least patients with significant symptoms, yes.

CHAIRMAN PACKER: Okay. I think that everyone on the committee would agree that there should be specific mention of rate-lowering calcium

channel blockers. That there be mention of no use in overt heart failure. The sponsor has already proposed that. Other beta blockers -- let me also suggest that the patients who should not receive the drug includes the one that JoAnn mentioned earlier, which is elderly women because almost all of them have creatinine clearances less than the cut-off. I mean, when they have a certain creatinine. I don't know how you phrase that. My sense is that --

DR. FENICHEL: Well, Milton, do you think it is essential to phrase that as in addition to the restriction in terms of creatinine?

CHAIRMAN PACKER: I don't think that physicians translate a creatinine of 1.4 into a creatinine clearance of less than 50. I think that is what JoAnn's point was. But let me -- JoAnn, what do you think?

DR. LINDENFELD: No, I think so. I mean, this is not in keeping with current labeling practices, but it might even be reasonable to say that a 70 kg, 75-year-old woman with a creatinine of 1.4 or higher is not eligible for this drug by creatinine

clearance criteria. I just think that brings home to the doctor, if they read that box, that I think that is a patient that most people wouldn't be terribly worried about. But when you do the calculations, that creatinine clearance is below 40. And that is a lot of people with atrial fib.

CHAIRMAN PACKER: Bob, let me just get a sense of the committee and then find out how many in the committee would disagree with a restriction based on something more directed than -- I guess we are -- how many share the concern that it should be something more specific than a calculated creatinine clearance? Because the way the Division would normally do this would be creatinine clearance and JoAnn says, well gee, that is true but the creatinine clearance cut-off here isn't 20 or 30. The creatinine clearance cut-off is 40 and 50. And 40 and 50 cuts of a lot of people. Does the committee -- how does the committee feel about this? Cindy?

DR. GRINES: Well, I guess I agree that we don't really know how to calculate creatinine clearance. And I think if you are talking about

putting in restrictions, you probably should put a chart based on gender, age, and body size, and serum creatinine. Something that is more than just a specific patient. But I also wonder whether we have enough data to even make that suggestion since there is a lower dose available. And if anything, if one looks at the data on creatinine clearance of less than 60, those handful of patients actually had higher efficacy. So I am not as concerned and perhaps it should just be cautioned that a lower dose be given in patients with low creatinine clearance.

CHAIRMAN PACKER: Well, the sponsor is actually suggesting that such patients not receive the drug.

DR. LINDENFELD: And I think also there is some question about what the half-life is when you get the creatinine clearance down there. There was one suggestion that under 40 that the time interval of drug dosing might be 36 hours. So I think we don't have any way of telling what to do there when we get that low.

CHAIRMAN PACKER: Okay. Let me -- again,

how many of you would restrict the drug to patients whose symptoms were severe or disabling?

DR. THADANI: I think I would like to because if a patient is not symptomatic -- because the whole data base I have seen in symptomatic patients. So I think I would like to restrict it given the potential side effects to restrict it to that. So if you are going to use it asymptomatic or mildly symptomatic patients, I have not seen any overall benefit. And with the noise of some worry, I would probably restrict it to the patient who still remains symptomatic despite, you know, whatever. So I think I would go for the labeling that since, you know, severely or disabling fibs.

CHAIRMAN PACKER: All right, Tom? This is Tom Graboys. Tom, the assessment of risk to benefit here I think was very typical to your thinking process. How would you feel -- and this is to try to understand what you were saying earlier -- how would you feel if the labeling specifically said to patients with a history of severe and disabling symptoms when they were in atrial fib?

DR. GRABOYS: You mean as the prime indication?

CHAIRMAN PACKER: As the prime indication.

DR. GRABOYS: Well, I think that should be -- by definition, yes, I think that should be the sole prime indication. That still doesn't change my vote.

CHAIRMAN PACKER: No, I understand that. That is okay. Okay, how many would disagree with that?

DR. BIGGER: I think that is too restrictive. I think that language is too restrictive. I think someone with significant aggravating symptoms, not necessarily disabling or life-threatening. The wording sounds overly restrictive to me.

CHAIRMAN PACKER: Okay. What I would like to do is take two votes, because this is really important. I think everyone agrees about overt heart failure, rate lowering calcium channel blockers, concomitant beta blockers. There is agreement on the creatinine clearance or a renal function exclusion. I want two votes. Vote number one is on severe and

disabling symptoms. Vote number 2 is with or without structural heart disease. Those are specific issues asked for by the Division. So we will take severe and disabling symptoms first.

DR. FENICHEL: Milton, those were just examples.

CHAIRMAN PACKER: No, I know.

DR. FENICHEL: We just --

CHAIRMAN PACKER: But they are good examples.

DR. FENICHEL: Okay.

CHAIRMAN PACKER: So the first question is do you believe the drug -- the approval should be restricted to patients with severe or disabling symptoms at the time of their atrial fibrillation? The answer would be yes or no. JoAnn?

DR. LINDENFELD: Yes.

CHAIRMAN PACKER: Okay. Udho?

DR. THADANI: Yes.

CHAIRMAN PACKER: Ileana?

DR. PIÑA: Can you repeat that question again?

CHAIRMAN PACKER: Yes. Should the approval -- should the indication for the drug include a restriction or use only in patients with severe or disabling symptoms at the time of their atrial fibrillation. The wordsmithing will be worked out by the Division.

DR. PIÑA: Yes. I think that is too restrictive. These patients that -

CHAIRMAN PACKER: That is what we are asking.

DR. PIÑA: By the studies that we have used today to say, yes, the drug should be approved included patients with symptoms. It didn't say disabling and severe. So I think that that is too restrictive.

DR. LINDENFELD: I think we are partially basing that on the fact that we were concerned about the overall risk and that the drug -- that people feel that we wouldn't like to necessarily recommend this drug just for everyone to prevent atrial fibrillation, but rather those that have substantial symptoms with their atrial fibrillation. I think that is the --

DR. PIÑA: I agree. I mean, we have been going back and forth with this all day that the patients that dropped out were probably the patients who perhaps needed the drug more or the population we may see more often. I just don't think that we have any data to specifically say only severe or disabling.

CHAIRMAN PACKER: No, no, no. The severe/disabling can be imposed as a way of assessing the concept of risk to benefit. This is Tom's point.

DR. PIÑA: I would say -- and I certainly understand Tom's point and I agree with him that drugs are used not as they should. But I would say symptomatic a fib.

CHAIRMAN PACKER: Okay. So just to make sure I've got it correct, JoAnn, I think you voted yes for severe/disabling. Udho, you voted yes for severe disabling. Ileana, you are voting no for severe/disabling. I just want to keep it clean. Michael?

DR. CAIN: I would vote for severe and disabling.

CHAIRMAN PACKER: Okay. Marv Konstam

voted for severe and disabling. Tom?

DR. GRABOYS: Yes.

CHAIRMAN PACKER: Yes. Cindy?

DR. GRINES: I would vote yes if we could relabel all the existing drugs for the exact same indication. Because I don't think it is fair. This drug has no worse of a safety profile than anything else I have seen. And to -- I think it is unfair to label this one for severe and disabling and have a wide open indication for other drugs.

DR. FENICHEL: Well, let me remind you of what the labeling for quinidine says. The labeling for quinidine describes the meta-analysis showing that quinidine triples the mortality in those who receive it. And then it says this drug is for people whose symptoms are so frequent and severe that they in discussion with their physicians are willing to accept that increase in mortality in exchange for the symptomatic benefit which is presumed to come from the use of quinidine. So it is not an altogether unprecedented thing to describe the requirement in terms of severe and disabling symptoms. On the other

hand, I would hasten to point out, and I am sure the sponsor will point it out if I do not, that there is no allegation here that mortality is tripled by the d,l-sotalol.

DR. GRINES: Well, I guess the other drugs that are approved -- flecainide and other -- exactly. That if we are going to say severe and disabling symptoms for d,l-sotalol, I think that we have to be consistent with all drugs that maintain sinus rhythm.

CHAIRMAN PACKER: It is really two separate questions, and the question is what do you think should be done with d,l-sotalol. And you could say to the Division that they should seek a similar --

DR. GRINES: Right. Well, a phrase like that, I do believe that all antiarrhythmic drugs for atrial fibrillation should be used only for severe.

CHAIRMAN PACKER: Okay. I think that is fine. Tom? I think you have said it is too severe.

DR. BIGGER: Yes.

CHAIRMAN PACKER: I would agree with severe and disabling. So the vote on that, for people who count, is 6 to 1, Joan, for severe and disabling.

The next point is structural -- Moye didn't vote. I do have Marvin's vote and I don't have any comment from Rob Califf on this. So we can only use the votes we have. Structural heart disease? Who would favor restricting this drug to patients without structural heart disease? JoAnn, would you favor restricting the drug to patients without -- this would be a flecainide type labeling?

DR. LINDENFELD: No, I don't think I would restrict it.

CHAIRMAN PACKER: Would anyone restrict it to patients without structural heart disease?

DR. GRABOYS: Yes, I would. I just think again the data on proarrhythmia continues to be so impressive in terms of the dichotomy of proarrhythmia dependent upon the presence or absence of structural heart disease. Again, I am concerned with the whole concept of the trickle down. We are trying to come up with some indication for it that is going to incorporate physicians' practice. And if we open it up for across the board, you are going to have patients with ischemic disease, recent infarct. I

mean, there is going to be a whole panoply of problems.

CHAIRMAN PACKER: Okay. Does anyone want to vote along with Tom for a restriction to no structural heart disease? If not, then the vote is 6 to 1 in favor of phraseology with and without structural heart disease. The next consideration is, let's see, should the approval distinguish between chronic and paroxysmal fibrillation? We have discussed this already. JoAnn, what do you think?

DR. LINDENFELD: No, I don't think so.

CHAIRMAN PACKER: Does anyone think there should be a distinction? Okay. Bob?

DR. THADANI: Before you go further, I think one of the issues -- the strongest evidence was in patients with a chronic who were converted and then relapse rate was delayed. I have some concern with the paroxysmal because of the -- as we discussed in the study because intent to treat did not show a difference. I don't know. I have some of my reservations in that situation because unless you are doing repeated Holter monitoring. Plus, the patients

who were dropped from there. It is only on one study. So I feel more comfortable with patients who are in chronic a fib are converted and on this drug until the first relapse rather than paroxysmal. So I will have some concern there.

CHAIRMAN PACKER: But it sounds like everyone else -- Michael?

DR. CAIN: I just think it is important that if you use the word paroxysmal and chronic, I think you will increase the risk that people will misuse the drug, and I would recommend that you not get into that trap. And what you are really talking about is the treatment for people who had a recent history of atrial fibrillation who are now on a sinus rhythm. And leave paroxysmal and chronic out of it.

CHAIRMAN PACKER: Okay. If I get a sense -- I just want to make sure that what we are talking about resembles the following, which would be something like the reduction or a delay in the onset of or a reduction in the risk of recurrence of atrial fibrillation or atrial flutter in patients in normal sinus rhythm with a recent history of atrial fib or

flutter that produced severe or disabling symptoms.

DR. THADANI: And have been converted into sinus rhythm.

CHAIRMAN PACKER: No, no. We already said that. In sinus rhythm.

DR. THADANI: No, but recent -- in sinus rhythm at the time of start.

CHAIRMAN PACKER: No, it says in sinus rhythm. What I just said was in normal sinus rhythm with a recent history of atrial fib/atrial flutter that produced -- was associated with or produced severe disabling symptoms. Okay, Peter?

DR. KOWEY: Just a brief comment, Milton, as a point of order. When the sponsor came for the pre-meeting meeting with Ray, who is unfortunately not here today, the sponsor really didn't differentiate these two arrhythmias. It really was Ray who asked us to present the data to the specific subsets. And the reason was because of the recent dofetilide experience. I personally agree with what you are saying. The only thing I would ask, and I am sure this will happen with Bob, is that the words be

crafted carefully so that it is clear what the data in the data set showed, and I think that is what Michael was saying, rather than saying you can use it in an arbitrarily defined subgroup that we really have a hard time defining anyway. So I think we are all in agreement with that.

CHAIRMAN PACKER: Okay. I think we actually have consensus on this. And I think Michael's point that if you include paroxysmal -- the words paroxysmal or chronic -- you are going to increase the likelihood that the application of the drug would be misunderstood.

DR. CAIN: Electrophysiologists can't agree on how to pronounce the arrhythmia, let alone define it.

CHAIRMAN PACKER: Fibrillation, right? Nevermind. All right. Okay, a lot of the other issues are straightforward. But let me -- there is one -- there are two other very important issues here that need to be addressed. Should the data -- should the drug be started -- who should be hospitalized for initiation of the drug? This is a very important

nice to collect the data base on patients to give more comfort in Tom's question of patients who are elderly and patients with relatively poor LV function. So at least we will have a bit more objective data collection after the approval process.

CHAIRMAN PACKER: Okay. Let's go through the other issues very rapidly because most of them are fairly straightforward. I assume that everyone would agree that there should be adjustment based on renal function, and I think, JoAnn, you specifically indicated that specific clinical examples of what constitutes a patient who is not a candidate based on renal function, elderly women for example, be specifically mentioned.

DR. LINDENFELD: Right.

CHAIRMAN PACKER: Anyone disagree? Okay. Should any recommendation be made about anticoagulation with respect to the use of this drug?

DR. THADANI: Yes, I think -- oh, sorry.

CHAIRMAN PACKER: JoAnn?

DR. LINDENFELD: I don't think so. I think that just as when we discussed dofetilide, those