discrepancy that's consistent with what one might intuitively expect the discrepancy to be.

ACTING CHAIRMAN CALIFF: Dr. Armstrong.

DR. ARMSTRONG: Taken on its own, I mean, one would be inclined to stay silent, but because there's a comment in the label as it currently exists in hypertension and because of the biology that we've discussed earlier and because of the trends in Table 10 in our FDA document both for blacks and for Asians, it seems to me the right decision is not to stay silent on this issue.

So I'm just troubled with what the right thing to say is because something already has been said, and it seems to me it needs to extend to the disease of interest which we're discussing.

ACTING CHAIRMAN CALIFF: Well, I think there are two points of discussion here. One is what shall we do with the label, and then the second is I think it's important at this juncture to have some discussion and comment on how to proactively prevent this problem from continuing to occur.

I mean I've been involved in three panels

in different diseases in the last year where sponsors have brought in data that had no black people, and you're left sort of saying, "Well, we have no data. So what can we say?"

And yet, as I say, it's 14 percent of the U.S. population. So Ileana.

DR. PINA: (Inaudible.) I would suggest that the number of black patients were small and that something like (inaudible).

ACTING CHAIRMAN CALIFF: By the way, while we're on the general issue, the nomenclature for Hispanic outside of the United States is quite difficult, as you know, and for sponsors out there, I would urge that before you get into this field that you spend some time on how people are classified in South America, for example. It's different than in the United States.

But, Bob, what is the FDA doing to prevent this from happening. It's a pretty important national concern.

DR. TEMPLE: Well, the first thing is we're blaming Canada.

(Laughter.)

DR. TEMPLE: The second thing is it's not very clear about what to do. We've accepted large outcome studies from many parts of Europe. You know, the Wascop (phonetic) study doesn't have a lot of blacks, Hispanics, and others in it, nor does the SSSS because of where they were conducted, and there isn't really any easy answer to that.

I mean I suppose if we were thinking about it sooner, we'd urge Salim to try harder to be sure there's -- and maybe even set some recruitment goals and things like that, but it's very hard. It's a different country, and it doesn't have the same population.

So, I have to say historically the world worries tremendously about ethnic factors and how they affect outcomes mostly when the outcomes are unimportant.

There's frantic consideration all over the world about making sure you've got a good mix for all the things that don't matter that much, like whether the blood pressure falls a little and stuff like that.

When it comes to outcome studies, I think we've generally felt we had very little choice but to accept the one or two large outcome studies that existed, even if they were conducted in place that don't reflect our population.

That's obviously not entirely satisfactory, and I'm not sure what the answer is, but I hope you'll address my question of does everybody feel nervous enough about this to think that it would be ethically responsible to urge the conduct of a study in a black population similarly defined. Are we so skeptical about the results that we have so far that we think that is ethically acceptable?

We can certainly urge people to try to do that.

ACTING CHAIRMAN CALIFF: Let me turn the tables on you just for a second. We've heard from Salim that aggregating all the ACE inhibitor studies and heart failure is not even though data to make a statement. The FDA has a very large database of data that we haven't seen for the most part from which one --

DR. TEMPLE: That may or may not be true, Rob. Many of those studies are done outside. Many of the large outcome studies with ACE inhibitors are done outside the U.S. We can tell you with considerable assurance that blood pressure effects are small, much smaller in blacks with ACE inhibitors. That's not in doubt.

What we don't have, and it's not clear. You'd have to ask which studies are relevant. I don't think we've looked at the SAFE study with respect to that question, and that surely will have a reasonable black population, but many of the other outcome trials aren't U.S. So I don't know, except for SOLVD, of course.

So I don't know what we'll find, but we should look. We have some reason to look actually.

ACTING CHAIRMAN CALIFF: Dr. Pina.

DR. PINA: I would have, you know, a better sense of comfort of samples in heart data population (inaudible). And there were a very large number there.

DR. TEMPLE: I mean, we could go back and

look at rehab., for example. I mean, it depends on what you count. I you're counting beta blockers, ACE inhibitors, and thinking together about all of them, that gives you a larger database to look at.

I gather Salim couldn't replicate this, but we've been told that the favorable outcome in SOLVD is not present at all in blacks, that there is no adverse effect, but no favorable effect.

ACTING CHAIRMAN CALIFF: Okay.

DR. TEMPLE: It was like four percent versus 24 percent. Okay? That's just what we've been told. I'm not --

ACTING CHAIRMAN CALIFF: Well, I think it's become a pressing national issue with regard to beta blockers and ACE inhibitors, now two of our most effective treatments, and at least we can publicize it at this meeting, and I'm sure people in the audience will report on this.

DR. TEMPLE: We can certainly try to assemble all of the available data that has both populations in it.

DR. THADANI: I think you have to go

beyond that because this trial with the HOPE, if I treat 100 black patients and I see no benefit, I might even harm. So I think I've got major concern. I think you have to put in labeling we do not have enough patient population. We have no data that it does benefit or harm, if at all.

I could argue with you if you look at the numbers, there were 81 and 75 in blacks on the drug, 66 the other way. I realize the sample size is small. We can't make much issue.

We need a study in blacks to address this issue, and I think this should go in the labeling.

ACTING CHAIRMAN CALIFF: I'm going to ask for a vote actually of opinion on three questions, but, Bob, I do want to make the point again that the FDA has probably the largest set of data in the world, much of which has not been published from studies of ACE inhibitors and beta blockers, and it would be helpful if that data could be made available.

DR. LIPICKY: I'm sorry. I had my hand up.

ACTING CHAIRMAN CALIFF: Yes, sir.

DR. LIPICKY: I don't want to be talked into something that I don't want to do.

ACTING CHAIRMAN CALIFF: Okay.

DR. LIPICKY: Salim has looked at the ACE inhibitor heart failure trials. I don't think we can do a better job because we don't have the data. We'd have to ask somebody to supply us with the data.

We could look at articles and stuff like that and do a lousier job than Salim did. so I don't want to do that again. That apparently again will come out soon. So that part is done.

ACTING CHAIRMAN CALIFF: Well, no, Ray. Actually I'm writing the editorial on Salim's paper. So I can tell you he does not have that data in his paper.

DR. LIPICKY: Oh, well, --

ACTING CHAIRMAN CALIFF: So it won't be coming out soon.

DR. LIPICKY: -- so where are we going to get the data then? If he didn't have it, he has all of the results. How are we going to do it better?

DR. TEMPLE: Rob, it may depend on what

data you consider relevant. I think what I'm hearing is that we shouldn't consider only heart failure trials relevant, that we should look at SAVE, which is a different kind of trouble. We should look at --

DR. LIPICKY: You have SAVE.

DR. TEMPLE: You have SAVE?

DR. LIPICKY: Yes.

DR. TEMPLE: Oh, okay. But we could also conceivably look at --

DR. LIPICKY: And SAVE is a heart failure trial. It just happens to be around MI.

DR. TEMPLE: Sort of. Yeah, okay.

ACTING CHAIRMAN CALIFF: I would argue that you should look at all of the data you have on all kinds of patients treated with ACE inhibitors for morbid events.

DR. LIPICKY: We don't have the data.

DR. TEMPLE: Yeah, but these are trials that are all published. Everybody has the existence of the trial. They aren't private outcome trials.

DR. LIPICKY: They have the variances in there?

DR. TEMPLE: No, I don't know that. I don't even know --

ACTING CHAIRMAN CALIFF: I've registered my point of view. I think we ought to move on. I think I'm getting it from both ends here.

DR. TEMPLE: Rob, can I just mention one other thing? There isn't any question that the lack of information about the black population will be somewhere in this labeling. The question you need to help us with is how strong, you know, should it be right in the indications. We don't know, and things like that.

ACTING CHAIRMAN CALIFF: Well, I heard Joann basically say that the labeling should reflect the fact that there was not an adequate population to draw inferences.

DR. TEMPLE: Labeling or indications specifically? Which do you mean? There's a difference.

DR. LINDENFELD: Well, I'm not sure it has to be in the indications. I think somewhere in there is adequate.

DR. THADANI: Why not in the indications? We don't have any data.

DR. LINDENFELD: Well, we don't have any data to the other side either, I think.

DR. THADANI: Yeah, but it could go in the wrong direction. You said the study was done mostly in Caucasians. There's no data on either Asians or blacks. I feel more comfortable with that. I don't know.

ACTING CHAIRMAN CALIFF: Any other opinions on that before we vote?

DR. TEMPLE: There were things of both omission and commission, and you've got to decide which one you want here.

So what do you want to vote on, Rob?

ACTING CHAIRMAN CALIFF: What I'd like to ask for, I don't feel we need to vote on 2.1 and 2.2 because no one disagreed with Joann's assessment.

On the race question, should the label reflect the differences? I would like to change that to should the label state with regard -- we could ask it either way.

Well, I guess the question is whether it's in the indications or just in the label. Let's say just in the label and not in the indications to start with.

DR. LINDENFELD: Or in the clinical trials section, describing the trial.

ACTING CHAIRMAN CALIFF: Right. Should it state just in the clinical trial sections, but not in the indications section that there was not adequate data about race? I think that's a question we can vote yes or no on. If we could start on the right-hand side here.

DR. FLEMING: The direct implications of that are that basically if you do that, that blacks would be in the indication, but then later there would be a clarification of the strength of evidence.

ACTING CHAIRMAN CALIFF: Right.

DR. FLEMING: Well, the indication would be silent about race if you did it that way, and you'd find it in the indications.

I just have to add there was more than one way to write it in the indications. You can just say

there is little information about blacks. You could say there is no good basis for treating blacks. I mean, there's stages of what one could say.

ACTING CHAIRMAN CALIFF: All right. Let me change the question then to the indications should specifically state that we don't have adequate information about blacks. Yes or no?

DR. MOLITCH: Is this what you've done in the past, Bob?

DR. TEMPLE: I think if we were really skeptical about something we would. I don't have an accounting to give you. Just all of those are possible outcomes depending on what you thought was best, but we did do it once. I mentioned this before.

We specifically said that aspirin -- this, of course, wasn't a prescription drug, but in the professional labeling we said that aspirin was for preventing stroke in men because we didn't have enough data in women. I think we now believe that was probably in error, but it was what the data seemed to show at the time.

ACTING CHAIRMAN CALIFF: Dr. Pina.

DR. PINA: If the purpose of this is to get the clinicians to agree (inaudible), most of them will read the indication, and very few (inaudible). So I think it should be somewhere in the indications about the paucity of data in other than white populations.

ACTING CHAIRMAN CALIFF: Before we vote, I would like to clarify whether the other ACE inhibitors have the same. What is in --

DR. LIPICKY: Of course. They have less data than this one.

ACTING CHAIRMAN CALIFF: But is it stated in the indications section?

DR. LIPICKY: No, it's not.

DR. TEMPLE: About the outcome studies, no.

DR. LIPICKY: But the same problem is there with every one.

ACTING CHAIRMAN CALIFF: So one issue in voting yes on this would be that we would potentially penalize this particular drug when it's a generic issue.

DR. LINDENFELD: It's in there for hypertension for any of the ACE inhibitors.

DR. TEMPLE: Is it in the indication section in hypertension?

DR. LINDENFELD: For hypertension, yeah.

DR. TEMPLE: One thing, Rob, you have to appreciate is we are getting increasingly canny about asking analyses of racial, ethnic, and other subsets. It only became a requirement for submissions last year, maybe the year before. Older ones are less likely to have it because we weren't as aware.

DR. FLEMING: Rob.

ACTING CHAIRMAN CALIFF: Yes.

DR. FLEMING: It seems to me there are two issues though that might make this unlike other examples. One of them is unfortunately not unlike those, and that is there is a striking under representation of blacks, and strongly impressive as this study was, no study was perfect, and it may not have been designed specifically to address issues specific to the U.S.

But in a population here where 15 percent

of the population is blacks and they undoubtedly account for more than 15 percent of the events, to have had one and a half percent or something on that order representation is unacceptable, and strong statements have to be made to that effect.

Secondly, there is some data, and that data is of the order of 141 events. I've been involved in many trials that in totality don't have 141 events. So whereas I am very cautious to acknowledge that these data do not establish lack of benefit, at the same time there is a suggestion in these numbers here that there ought to be more insight about whether the effects that we see in the global group apply to blacks.

So I think it's the two issues together that I think must be -- that lead to the need to acknowledge what we're seeing in blacks or what we're not seeing.

ACTING CHAIRMAN CALIFF: Jeff?

DR. BORER: I agree with Ileana that if we bury this information somewhere in the clinical trial section, it's unlikely to be widely disseminated, and

that's not a good thing if we think it's important for people to know about it.

I do think that, therefore, it would be appropriate for a statement to be made in the indication section, but I think the statement should be that we don't have information, not a statement with a pejorative sense to it, and then in the clinical trial section one could show the data.

I'm not concerned with regard to your point, Rob, about penalizing a sponsor or something like that because, you know, if we made an error for one reason or another, or if we now perceive that maybe we made an error in not requiring things in the past, that's not a reason to be bound by that error for all time, if we agree that it's not right to have done that or to do it anymore.

And the second point is that we're dealing with a drug that has an indication that's very broad, with widespread public health implications, and that indication is far broader with far greater implications than this group of drugs has been approved for in the past.

So I don't have a real problem putting some statement in the indications, despite the fact that that's a new thing to do.

ACTING CHAIRMAN CALIFF: Ray.

DR. LIPICKY: Well, the thing that bothers me about the discussion is I must admit if it were up to me to write, I wouldn't know what to write. I'm not sure that there has been harm shown by this data, and in fact, in some portions of the data, it looks like it leans in the right direction.

What we're complaining about is we don't know enough, and you know, it on its face doesn't allow for a subgroup analysis to be meaningful, and we recognize that.

So it does not say to me, this data does not say to me -- and I'll just put it out as a statement -- that blacks respond differently. It says, what this data says is there weren't enough people for a need to be able to conclude that they respond the same.

And I don't know how to communicate that to a doctor because I don't think it should be part of

the doctor's decision making process. It is our dilemma as regulators and researchers and as influencing studies, and so on, to encourage better definition of that stuff, but I don't think it belongs in clinical decision making.

So I would object to putting it in labeling.

ACTING CHAIRMAN CALIFF: Well, your objection is duly noted. I think we need to move to a vote, and I'd like to just vote on this approach, which was Jeff's approach, which is to put in the indication section that there's not enough information to make a statement about blacks, and then in the clinical trial section to give the specific subgroup data so that people who want to look further can do that.

So if we could vote on that, yes or no.

DR. MOLITCH: In the interest of time, with 31 more questions to ask and answer, I vote that we leave it in the clinical trial session for the additional explanation, not in the indications, and I would not comment. I would leave out geographic

information.

ACTING CHAIRMAN CALIFF: So you vote no.

DR. MOLITCH: On both questions.

ACTING CHAIRMAN CALIFF: Okay.

DR. MOLITCH: And you can add another one and move it along.

DR. GRABOYS: Yes.

DR. LINDENFELD: Yes, I would agree.

DR. Di MARCO: I agree with the indications.

ACTING CHAIRMAN CALIFF: Yes.

DR. BORER: Yes.

DR. LINDENFELD: No.

DR. ARMSTRONG: Your question had two parts. Yes to the first part; no to the second part.

ACTING CHAIRMAN CALIFF: Okay. The second part was including the specific subgroup data in the clinical trial section.

DR. ARMSTRONG: And, again, the first part was?

ACTING CHAIRMAN CALIFF: Including the statement that there's not enough data about blacks in

the indications.

DR. ARMSTRONG: Yes to the first and no to the second.

DR. THADANI: Yes to the first, no to the second.

ACTING CHAIRMAN CALIFF: All right. You got John all confused here. Who do you need to hear from again here?

DR. THADANI: Why don't we go separately?

MS. STANDAERT: Well, somebody voted on two, and other people did and voted on one.

ACTING CHAIRMAN CALIFF: Well, those who voted yes in general voted yes on both.

MS. STANDAERT: What about Tom?

ACTING CHAIRMAN CALIFF: Tom verified that he voted yes on the first and no on the second.

All right. 2.3.B. Okay. All right. We're going to have to vote again here on both questions. Let's just go through one more time so Joan can get it right.

DR. TEMPLE: Well, Rob, we can assume that there's going to be discussion of the results in the

clinical trial section. I mean, you don't particularly need to vote on that.

DR. THADANI: Just vote on the indication.

ACTING CHAIRMAN CALIFF: Okay.

DR. TEMPLE: It's really only the indications and then some sense of what in the indications.

ACTING CHAIRMAN CALIFF: All right. So should it be in the indications? So let's just go through it one more time to make sure Joan has it.

DR. MOLITCH: No.

DR. GRABOYS: Yes.

DR. LINDENFELD: Yes.

DR. Di MARCO: Yes.

ACTING CHAIRMAN CALIFF: Yes.

DR. BORER: Yes.

DR. LINDENFELD: No.

DR. ARMSTRONG: Yes.

DR. FLEMING: Yes.

DR. THADANI: Yes.

ACTING CHAIRMAN CALIFF: Okay. So over Ray's objection, we voted yes on that.

Now we move to geographic region, and hopefully we can pick up the pace now. No?

DR. TEMPLE: No.

ACTING CHAIRMAN CALIFF: Bob said we needed to vote on that. So geographic region, Joann?

DR. LINDENFELD: I don't think there are any differences here. I don't have a plausible reason to expect one, and I just wouldn't make any point about this at all.

ACTING CHAIRMAN CALIFF: Any disagreement about that?

DR. THADANI: I think geographic distribution, there are some issues because the race issue, geographic, could be an issue as well. I think the population is mostly driven from Canada. It applies to practice issues. I'm not saying to put in the labeling, but I mean there are some concerns.

The benefit might be lower in States, although the patient population is not large enough, and so there are some -- I have some concerns. I think you have to say something where the patient population was driven from.

ACTING CHAIRMAN CALIFF: Paul?

DR. ARMSTRONG: Surely Dr. Thadani would accept no difference amongst Caucasians.

DR. THADANI: I think we accept that. We accept that.

DR. ARMSTRONG: In which case the geography becomes irrelevant?

DR. THADANI: Well, no. I think the problem is the practice pattern might have some influence, and that's the denominator you're going to run into because if you look at the United States, the small number is 1.5 benefit as opposed to 5.4 in Canada.

ACTING CHAIRMAN CALIFF: Okay. Well, since we --

DR. THADANI: And the number of risk ratio reduction was far smaller at least from that to have any relevance, but very small

ACTING CHAIRMAN CALIFF: Okay. So would anyone else vote yes for geographic region being mentioned?

All right. I would also vote no about it

being mentioned, but would agree that this is an issue that needs a lot more work because there are geographic patterns emerging in a number of international clinical trials that need better understanding.

All right. Let's move on to Question 3. Were the effects of ramipril on the primary endpoint of the diabetic subpopulation a new finding warranting explicit mention in the indication section?

Joann.

DR. LINDENFELD: Well, I think they are, yes, and I think it is stated explicitly in the indication.

ACTING CHAIRMAN CALIFF: Does anyone disagree with that?

DR. LINDENFELD: So it sounds like we have a unanimous vote that it should warrant explicit mention in the indication section.

Joann, what about 3.2, a new finding warranting explicit mention in the clinical trial section?

DR. LINDENFELD: Well, once it's in the

indications --

ACTING CHAIRMAN CALIFF: Show the data, huh?

DR. LINDENFELD: Right.

ACTING CHAIRMAN CALIFF: Okay. And then --

DR. TEMPLE: That's the answer.

ACTING CHAIRMAN CALIFF: All right. That's answered.

Question 4, were the effects of ramipril on the incidence of new diabetes a new finding warranting explicit mention in the indication section?

DR. LINDENFELD: I don't believe so, no.

ACTING CHAIRMAN CALIFF: All right. This is one we need to discuss.

DR. LINDENFELD: I think that the data -- it was an interesting finding. It was unexpected. It wasn't prespecified. I think that I wouldn't put it in the indications, and maybe at the clinical trials at the very end, but perhaps not even there.

DR. TEMPLE: No, we're trying not to put new claims into clinical trials without putting them

into the indication section.

DR. LINDENFELD: Right. Then just no.

DR. TEMPLE: It takes work to assure that, but --

DR. LINDENFELD: No.

DR. THADANI: I think it's important probably to have the implications. As Salim said, this was a finding. They should they should do another large trial to prove it. I would not even mention the indications at all.

ACTING CHAIRMAN CALIFF: Any other comment?

Well, I think this is one we should take a vote on.

DR. TEMPLE: Could you also while you're at it discuss who might do such a trial? This would be presumably people without risk factors; is that right?

ACTING CHAIRMAN CALIFF: this might merit just an additional comment from our diabetologist expert. I mean, my understanding is in the diabetes world, it's being recommended that everyone at least

with nephropathy go on an ACE inhibitor.

DR. MOLITCH: That's correct, but the question here is on the incidence of new diabetes, and I think it is not warranted for that. I think the data is too soft, and I would not encourage any mention of it.

ACTING CHAIRMAN CALIFF: Okay. Well, let's then go ahead and vote.

DR. MOLITCH: I vote no for all of that.

ACTING CHAIRMAN CALIFF: No for all three questions. Okay.

DR. GRABOYS: No.

DR. PINA: No.

DR. Di MARCO: No.

ACTING CHAIRMAN CALIFF: No.

DR. BORER: No.

DR. LINDENFELD: No.

DR. ARMSTRONG: No.

DR. FLEMING: No.

DR. THADANI: No.

ACTING CHAIRMAN CALIFF: Okay. So I think the summary is people are impressed, but would like to

see confirmation. It's a good, interesting finding.

All right. Were the effects of ramipril on glycemic control? The same three questions.

DR. LINDENFELD: These were -- I don't believe the data was enough to make any mention at all. So I would say no, no, and no.

DR. MOLITCH: Agreed.

ACTING CHAIRMAN CALIFF: Any other comments?

Okay. We should take a vote for a formal measure.

DR. MOLITCH: No, no, no.

DR. GRABOYS: No.

DR. PINA: No.

DR. Di MARCO: No.

ACTING CHAIRMAN CALIFF: No.

DR. BORER: No, three times no.

(Laughter.)

DR. LINDENFELD: No, again.

DR. ARMSTRONG: No.

DR. FLEMING: No.

DR. THADANI: No, whatsoever. There's no

adequate data. How often do --

(Laughter.)

ACTING CHAIRMAN CALIFF: So I guess the consensus of the panel then is that with regard to diabetes and glycemic control in general this is a hypothesis generating very interesting finding that's opening up potentially a field for further work.

And we move on to what are the effects of ramipril on diabetic nephropathy. The same three questions.

DR. LINDENFELD: Now, I think we've looked at this a lot. I think there's enough data to say, yes, there is a new finding warning explicit mention in the indications section for diabetic nephropathy.

DR. BAKRIS: I want to be the first before anybody says anything to congratulate a largely cardiovascularly oriented panel for appreciating the kidney, just to get it out.

(Laughter.)

DR. BAKRIS: Ray and I have been talking about this for centuries, and it's important just in case anybody is even dreaming about saying no so I can

sway you a different direction. It's important to know that you're changing the natural history of disease. This is a continuous variable. This is not you either had it or you didn't. This is something that you're changing natural history disease. You're changing albuminuria. It's a reflection, and if you look, if you actually took the time to read the papers that you have in your packet, those are all double blind placebo controlled trial, including stuff that Dr. Brenner was talking about with ACE inhibitors actually affecting renal morphology and arresting disease.

There's no question you're having an impact here, period, end of discussion.

DR. THADANI: Are you trying to influence the vote or what?

DR. BAKRIS: I'm not trying to influence your vote at all.

(Laughter.)

DR. BAKRIS: But there are people waiting outside that have vowels in their last name. So just be careful.

DR. THADANI: I realize that.

(Laughter.)

ACTING CHAIRMAN CALIFF: I think the key observation was that the kidney is attached to the heart.

DR. THADANI: You know, the trial which are, you know, backing are mostly in patients with established renal disease. I think here we are given a different point. The patients have their insulin dependent diabetes. They're already at a gross proteinuria. This is a very different population.

So I think rather than suggesting that we all have the world cares because you believe in it --

DR. BAKRIS: Well, I think you have to be careful here because, in fact, if you look at the data that are there in the trial, there is data also in non-diabetic disease and there's data in patients, biopsy proven data in diabetic patients, and the data is actually very consistent, and I think you have to keep the point that, as Barry said this morning, the data that we have so far is in way established renal disease, if you want to look at time to dialysis.

This is altering the course of the disease, and if it's one thing we do know about, it's the natural history of diabetic nephropathy, which may not represent all nephropathy.

DR. THADANI: But a sample size which is so small in most of the studies, I'm not sure that I buy your point.

DR. BAKRIS: Well, that's fine, but I'd like to see you do a trial with 1,000 biopsies.

ACTING CHAIRMAN CALIFF: Well, I don't want you to interpret this as not appreciating the kidney, but I have a different concern which when we talk about altering the natural course of a disease, we have many examples with a heart where altering an intermediate endpoint turns out not necessarily to be good.

And even in a field that we took for granted, HIV, early treatment now when it leads to prolonged treatment is coming under question as being the right strategy.

So I'm concerned about I'm sure that we've demonstrated that you can reduce the -- the

demonstration has been made that the albumen and the urine is reduced. I don't necessarily believe that we can mean that that means that this is going to benefit people in the long run.

DR. BAKRIS: Well, if you look at the long term trials, namely, one that is not too different from this, a normal tensive Type 2 diabetic, albeit a smaller number of patients who have now been followed up in seven years, the data you have is at seven years, but they're actually continuing to be followed.

There is a huge difference in the people that are on ACE inhibitor not just with regard to albuminuria, but also with regard to change in serum creatinine and, for that matter, creatinine clearance. And so, in fact, what you're doing is arresting or stopping disease.

I mean, the data are very clear. If you -- one trial that isn't in here because it just got published is the renal data from the ABCD trial, and basically at that very early stage of disease, if you aggressively intervene with the ACE inhibitor, you were able to stop disease progression.

In all of the advance trials, in the Lewis trial or whatever trial that's out there, the best you're able to do is markedly slow disease. You couldn't stop it, but you could markedly slow it, which may not be a bad thing, but let me remind you the number one cause of death in everybody with renal disease is cardiovascular disease, and there is a brilliant paper, stay tuned, coming out in Circulation looking at the relationship between micro albuminuria and vascular reactivity, showing a clear association with endothelial dysfunction, and it is double blind, placebo controlled. It's a very important study that draws the link there.

So I would argue that by reducing albuminuria, not only does that translate into altering the natural history of renal disease, diabetic renal disease and maybe even non-diabetic renal disease in specific circumstances, but you're also reducing cardiovascular events which you've already seen.

ACTING CHAIRMAN CALIFF: This is a very important issue, I think. We need to hear from some

other panelists.

Tom, maybe you first.

DR. FLEMING: Well, there are so many things to say. Let me just hit one issue and then let others speak and then come back with further later.

Micro albuminuria is certainly -- from what you're saying there is evidence that it's correlated. There are many really important issues that need to be addressed in terms of the magnitude of effect, the duration of effect that you're going to have to have for this to translate into long term clinical benefits.

The fact that we see associations gives some plausibility that this could be the causal mechanism, but it's also entirely possible that this is a marker for many other factors that are also influencing overall rates of progression, and the data that are here are certainly at best discussing what are the shorter term effects, and to state that they have conclusively established long term clinical benefits in terms of renal disease or renal failure, renal events is not established.

ACTING CHAIRMAN CALIFF: Ray?

DR. LIPICKY: Can I just -- can everybody look at Table 23(r) in the addendum that was in that blue book and just name the line on that table that you think really establishes that something is happening?

Before you get on to other trials, would you just look at the table on the back page and tell me what makes you say that the trial found something. I don't see anything too convincing on that table. We agree that the numbers are the same numbers, except for the 1.07. Everybody calculated the same numbers from the same data. What is it that we're talking about?

DR. FLEMING: The micro albuminuria result is a relative risk of .94. So what's your point, Ray?

DR. TEMPLE: Only overt nephropathy has a chance at this because that's the only one that has even nominal P value.

DR. LIPICKY: Which role are you citing as having established that something was found?

ACTING CHAIRMAN CALIFF: Jeff?

DR. BORER: Without detracting even one iota from the importance of the kidney --

(Laughter.)

DR. BORER: -- when I was in medical school, I was told by an instructor in physiology who had a grant from the American Heart Association that clearly his grant referred to research on the kidney because the only purpose of the heart was to pump blood to the kidney. So, you know, I'm with you.

But nonetheless, the data from the diabetic substudy, as I understand them, show really overwhelmingly that the primary endpoint is beneficially affected in diabetics if the diabetics are treated with ramipril, and I agree with that, and you've all agreed with it, and that's great.

Now we're talking about the effect of ramipril on another problem in diabetics, which is the progression of kidney dysfunction, and you know, I found the discussion by Dr. Brenner to be very attractive and very persuasive, but nonetheless, I'm concerned by several points when I look at these data.

One of them is the one that Ray is

alluding to. That is, the strength of evidence doesn't seem as great as what we generally would expect if we were going to approve a drug for a specific indication. So that's number one. You know, one would like to see these data either be stronger or be replicated somehow if we're going to look specifically at the use of ramipril for a beneficial effect on the kidneys in diabetics. That's one point.

The next point is one that's already been alluded to. I'd like to see, you know, Dr. Brenner's very compelling discussion notwithstanding, I'd like to see some data linking the pharmacological effect that we think we're seeing here with the clinical benefit.

So, you know, for those two reasons, first of all, the lack of the strength of evidence and, number two, the issue of the relation between pharmacological effect and clinical benefit. I'm concerned about drawing strong conclusions about indication here because the implication would be not that we should be giving this drug to people with vascular disease because, in addition to reducing all

the other things that it will reduce, it makes the kidneys better, but rather that people with diabetes with one risk factor ought to be treated with this drug, in part, because it's going to prevent their kidneys from deteriorating.

And that may well be true and the data are certainly consistent with that, but I don't think the strength of evidence is what we would usually expect. So I'm a little concerned about this.

ACTING CHAIRMAN CALIFF: Yes.

DR. MOLITCH: I think that the way the question is worded here, it is not a new finding. We're taking a set of data that's been presented here, which taken into context with many, many other studies now fits with the other studies, we've got a whole series of studies of both Type 1 and Type 2 diabetes that look at patients who already have micro albuminuria that this class of drugs is able to retard the progression to overt nephropathy, and when you have overt nephropathy, that you have an effect on decreasing the rate of fall of GFR, and then ultimately you have a decrease in the number of

patients who end up in end stage renal disease requiring dialysis and transplantation.

This is one of a number of studies that fits into that data set, and it fits exactly into that data set. There's no incongruity here. There is no -- I don't think that there was evidence that would support the prevention of the development of micro albuminuria, although there's some suggestion that perhaps that may be true with other studies, but that's certainly not true here.

And I think that once you have micro albuminuria that you can predict that a large majority of those patients go on and that this class of drugs is able to retard that rate of progression, and that this beta set is entirely compatible with many, many other data sets.

DR. LIPICKY: Would you point to the row in Table 23(r)?

DR. MOLITCH: Yes, Row 3.

DR. LIPICKY: That supports the statement that you made?

DR. MOLITCH: Overt nephropathy with the

sign of "at," that says .045 P value.

DR. LIPICKY: -- .075?

DR. MOLITCH: Pardon me? Twenty-three (r), with a .045 nominal P value.

ACTING CHAIRMAN CALIFF: I mean I think the problem a lot of us are having is we have one, two, three, four, five, six, seven different definitions, and we only have one which is less than .05, although I would --

DR. MOLITCH: There is insufficient data here for renal dialysis. We certainly don't want to approve micro albuminuria. We're not talking about laser therapies and sufficient data for doubling your fattening.

The sponsor has looked at a definition that looks at the development of overt proteinuria as defined by 24 hour urine collection, and then in the circumstances where there weren't sufficient 24 hour urines, they added the albumen-creatinine ratio. So that's that one.

DR. TEMPLE: Rob, can I ask? Do we know that that endpoint was established prospectively and

blindly?

I've heard there was a lot of discussion of that. It definitely didn't have an amendment to the protocol, but unequivocally written down somewhere that was the endpoint that you were going -- so there really is only one endpoint that we should be even thinking about paying any attention to, and lucky them, it's the one that comes closest.

(Laughter.)

DR. BAKRIS: Let me just -- not to cut you off, I'll give it back to you -- but just to make a point, if any of you are looking at time to dialysis, as Dr. Brenner very nicely said this morning, that's fine. When you collect your Social Security, which at the rate things are going you'll be about 85, is about the time you'd see time to dialysis in these people because that's how long it's going to take to get there.

That's not a meaningful endpoint in this stage of the disease, in this population, and correct me so as was pointed out earlier over here on a side bar that some of the data that I've included, the

double blind studies that are back here are on people with far more advanced disease, and the reason that was done to a certain extent was really to make the point that you're altering the natural history and the time to dialysis.

So I think we at least in the renal community in this country, and I would day say the endocrine community, are to a point where we need to look at it at a much earlier point because prevention is really where it needs to be going there, and the feasibility, as Barry say very appropriately this morning, is impossible because even all of the money in the NIH-Canada and five pharmaceutical companies wouldn't be able to fund a trial meaningful enough to actually get that kind of endpoint.

ACTING CHAIRMAN CALIFF: But let me try to express the counter view to that as best I can. I'm still undecided myself about how to look at this.

It is possible to imagine that there might be a drug that would reduce the time to development of albumen in the urine that also might turn out to be bad for the body or the kidney in some other way, and

so we've recently -- I don't want to divert the discussion to hypertension, but we've learned, I think, some of us think we've learned in the last few months, that it's possible to have several drugs that lower the blood pressure the same amount that have very different effects on overt clinical outcomes.

And so if we set a standard that says lowering the albumen is good no matter what, to me that's like saying lower the blood pressure is good no matter what.

DR. BAKRIS: Well, Rob, let me issue a caveat there. You're absolutely right, and I think the important point there is if you look at I would say 100 percent -- I haven't seen a meta analysis that doesn't support this -- 100 percent of all of the meta analyses that are out there, they all consistently show that agents that significantly reduce albuminuria and control blood pressure will slow renal disease progression. I can't think of one study anywhere that doesn't say that, and moreover, there's a nice correlation with reduction of cardiovascular disease.

Now, you could give me the argument, well,

that's all blood pressure, and what you need, the ACE inhibitors about that, and that we can be here until tomorrow arguing that point, but I think the issue is in terms of what you say you're absolutely right, and we won't go to that discussion, but let me just say that I think if you know of data that suggests that reducing albuminuria has adverse effects, I'd love to be educated because I'm unaware.

DR. TEMPLE: Rob, there's several different things being mixed together. One is the question of the surrogate. The second is the question of whether there's a finding there at all, and the third is what we know from other places and how that should influence our decision.

The first point is this is a secondary endpoint. It was the one that they were looking at. So that's helpful, but a P value of around .05 would be an unusual basis for reaching a conclusion on something like that.

Counter to that argument would be we already know a lot from other sources about ACE inhibitors. Therefore, we have a lot of priors, and

we should accept a somewhat less robust finding than we would insist on if it was out of the blue, and you know, I can't contribute to that discussion, but other people could.

The next question is the only drug we've actually -- first of all, if we take these one by one, there may be a widespread belief that ACE inhibitors are good for renal disease, but only one of them has the claim, and that's because we're waiting for data on that particular one.

So the question is pertinent to what data there are here. In all previous cases, we have actually had outcome data. We've probably been kicked slightly screaming and yelling over into thinking that deterioration of creatinine is something that you can base approval on, but at least so far there hasn't been approval based on small changes in albumen status.

That's not to say we should take that position forever, but it's a fairly big deal. It will change the shape of all the trials that are done in this area. You can show changes in albumen in very

short order, whereas changing in creatinine clearance is much, much slower. So it's a sort of a big deal.

Those are my contributions.

ACTING CHAIRMAN CALIFF: Ray?

DR. LIPICKY: I just want to add to that. It's like there aren't lots of times that this has happened. There is one trial, placebo controlled, that in diabetes, that basically establishes that, an ACE inhibitor, in fact, improves clinically relevant endpoint.

All of the trials that are being cited by George, I believe, are three, and they are non -- two of the others are in non-diabetics. So it isn't like there's a wealth of data here.

There are a lot of studies that show that indeed proteinuria is affected, and it is sort of striking to me that in this trial proteinuria was affected in the right direction in people who were non-diabetic and had no micro albuminuria to start with.

DR. THADANI: Also, Rob, there are a lot of concerns, patients who went into heart failure, but

if you look at the outcome, creatinine is going in the wrong direction. Renal dialysis numbers are small. So I'm not convinced like my colleague from the right-hand party convinced me that there's adequate data. I might be comfortable in the wrong direction, but to say that it does something to renal function, I'm not convinced.

DR. TEMPLE: Rob, I think Salim wants to say something that's relevant.

ACTING CHAIRMAN CALIFF: Okay.

DR. YUSUF: I'm here, Rob.

DR. TEMPLE: We'll see after he says it.

DR. YUSUF: Rob, I think today we are discussing HOPE, and to be fair to the FDA, although they have the whole database, the only part of the database they've analyzed is the diabetics, and then Hertzel showed more data on the non-diabetics which supports it, and to be fair to the FDA and to RAY, you guys need to check whether the analyses we showed you are replicated.

So it may be permitted even on HOPE to make a decision today.

The second thing is there are two other studies with ramipril that has been done in Europe that the company could provide to you that is at a later stage of the disease, and it's closer in concept to the Lewis study, and it may be best to defer this discussion till all of these data are brought to the FDA and you've had a chance to look at it.

ACTING CHAIRMAN CALIFF: Okay. Well, that would certainly make our job easier.

DR. TEMPLE: Very attractive, don't you think?

ACTING CHAIRMAN CALIFF: But I do want to express the same concern that Bob did. I think he was expressing a concern that if we make reducing albumen in the urine the measure, it may dissuade people from really finding out what the long term effects of future therapies are because you can show this, get a claim, get on the market, and then we may not know how to distinguish the effects on ultimate outcomes.

I guess I need guidance, Ray or Bob. Shall we take a vote, given Salim's last statement?

DR. LIPICKY: No, I think Salim told you

what to do.

ACTING CHAIRMAN CALIFF: Okay.

DR. LIPICKY: Forget it.

ACTING CHAIRMAN CALIFF: Good. We're moving right along then.

Let's see. The next one is -- yeah, we can skip seven, I guess, based on the same issue because there will be a lot more data forthcoming.

And number eight, were the effects for ramipril and the need for coronary revascularization, the same three questions.

Joann?

DR. LINDENFELD: Well, there were significant effects that were trended along with all of the other effects. So I guess the question is not so much whether or not they were convincing, but whether or not it's enough of an indication to be in the indication section.

I would probably say no. I think there's enough in the indications already that would go along with this.

ACTING CHAIRMAN CALIFF: Any other

comments?

DR. TEMPLE: Can you say that again? That was no because why?

DR. LINDENFELD: Well, now I have to think about it. This is a tough one. It was definitely positive. So I suppose -- in other words, I think when you tell everyone what this drug does that they will assume that it decreases revascularization, but --

ACTING CHAIRMAN CALIFF: Well, it would seem to me that --

DR. LINDENFELD: -- I suppose it's reasonable to put it in there. It's definitely positive. It's positive along with everyone else. It was a much smaller effect than the others.

DR. GRABOYS: If I were the pharmaceutical company folks, I'd be biting at the bit for this because I could see a series of about 100 ads coming out saying, "Here, we've got the magic pill right here. It decreases your need for bypass."

ACTING CHAIRMAN CALIFF: But what do you think about it?

DR. GRABOYS: I don't think it should be stated.

DR. THADANI: No, I think you would have problems, too, though, wouldn't you, Bob? Who decides who needs a bypass? If a patient comes to me and I've got an exercise test, as to depression, I know he is diseased. He gets bypass. Other patient comes in another center. My colleague doesn't do it. So I think there's a softer endpoint. Why it has to go in the labeling I'm not sure. You could describe it in probably the adult section, but not in the legay (phonetic).

ACTING CHAIRMAN CALIFF: But isn't that protected by the fact it's a blinded study? So seeing a difference --

DR. THADANI: But it's not in the primary endpoint we already worded. It does everything. It's somewhere driven by the numbers' need for -- I don't think they even showed us why if they can need a bypass -- suppose you go in and find a triple vessel disease, and then because of your creatinine function and (unintelligible) function is below 40 percent, he

goes for surgery, and it could have been just curious. I have no idea.

So I think all of the data is positive. I don't think you have to label the indication. It's probably described in the trial section.

DR. ARMSTRONG: My concern about this, Rob, is that there's lack of concordance with the unstable angina and the unstable angina validated with the ST segment shift. So this is a soft indication for which we have little collaborative information, and I don't think it's concordant.

So I would be against including this indication.

DR. BORER: Just to add to that, I really agree with Udho. I don't think it's appropriate to state as an indication a reduction in a therapy that's based on a physician's judgment. The reduction in the event that might lead to that judgment, that's fair game, but the therapy itself, it's true we have a lot of guidelines now and, you know, people tend to do things in more similar fashion around the country than might have been the case in the past, but nonetheless,

there is a judgment that's involved in selecting a therapy, and I don't think that we should be providing an indication for a reduction in an event that's based on that judgment.

DR. TEMPLE: Jeff, we have a bunch of labels that include that as a component of a combined endpoint, urgent intervention I had, in which that's the driving force behind the indication. Do you think we've been making a mistake here?

DR. BORER: Yeah, well, maybe, Bob, but I don't know that that's a discussion that we can have today, but in this case, there's a difference. These are not --

DR. TEMPLE: But the implication is that it decreases whatever it was that was making clinicians think they needed to do it.

DR. BORER: Right.

DR. TEMPLE: It's not that it's trying to control what makes them make the decision.

DR. BORER: Well, but we've already stated or it is already stated here that many of those things that might drive a decision have been reduced. I mean

there's an indication for giving the drug to reduce the processes that might lead to the judgment.

DR. TEMPLE: No. Which besides heart attacks?

DR. BORER: Well, heart attack is a pretty good one. Mortality?

DR. TEMPLE: No, it's too late.

DR. THADANI: Bob, also, you know what you're alluding to, a lot of the times we've allowed revascularization, and the previous trials have been refractory angina. Here is not that question. I mean, as Paul said and I said before, unstable angina hospitalization is not allowed. The patient -- you could be just influenced because --

DR. TEMPLE: Actually we thought that urgent revascularization is better than refractory angina because it was --

DR. THADANI: But this is not urgent revascularize.

DR. TEMPLE: Yeah, I realize that.

DR. THADANI: So I would not add that. I think it's a moot point.

DR. TEMPLE: So you wouldn't add it even if you thought it was true, even if there was no disparity between this finding and closely related findings?

ACTING CHAIRMAN CALIFF: Well, I'm obviously in the minority here, but to me having a bypass operation is something you'd like to avoid if you possibly could. I don't know many people that want it, and for example, in heart failure, hospitalization for heart failure is considered a strong part of the endpoint. That's very dependent on physician discretion.

DR. TEMPLE: Absolutely.

ACTING CHAIRMAN CALIFF: So I find this to be persuasive.

DR. TEMPLE: What do you think about the lack of concordance?

ACTING CHAIRMAN CALIFF: What's that?

DR. TEMPLE: The lack of concordance that was mentioned, that is, you do not have the same thing on other closely related --

ACTING CHAIRMAN CALIFF: I think when a

trial is almost dominantly going in one direction, you have a few things that are counter, like admission for unstable angina. I tend to side with everything else and not try to pick because there's some small things that go the other direction, but --

DR. THADANI: You know, also you could argue if you're going to put this, why don't you put in there was no reduction in hospitalization for heart failure. You always put the positive. You don't put the negative.

DR. TEMPLE: Well, you can put the negative in, too.

DR. THADANI: No, I'm just saying how far do you want to carry it.

DR. TEMPLE: There's nothing that stops us and we often do put in the secondary endpoints that didn't show anything.

ACTING CHAIRMAN CALIFF: Well, I think everyone had expressed their point of view, and we should go ahead and take a vote.

DR. YUSUF: Rob, can I just make a clarification? Is that possible? I know it's not

normal.

ACTING CHAIRMAN CALIFF: Quickly.

DR. YUSUF: Okay. The first thing is revascularization was a prestated secondary endpoint. It was not data dredged.

The second thing is the P value is quite impressive.

The third thing is in the meta analysis of all other trials of ACE inhibitors, there is the reduction, revascularization.

The fourth thing is worsening angina was significantly reduced showing internal concordance.

The fifth thing is MI is reduced showing internal concordance. The only thing that is the outlier is the unstable angina. So I think I'm going to put the framework --

DR. THADANI: Which is a very important outlier.

DR. YUSUF: Yeah, sure.

ACTING CHAIRMAN CALIFF: Okay. Salim, you've clearly stated your point of view. I think we ought to go ahead and vote.

Okay. Dr. Graboys.

DR. GRABOYS: What is --

ACTING CHAIRMAN CALIFF: We need you to vote on the question of whether the need for coronary revascularization is a new finding warranting explicit mention in the indication section.

DR. GRABOYS: No.

DR. PINA: I think it is (inaudible).

ACTING CHAIRMAN CALIFF: Let's see. You vote yes.

DR. Di MARCO: I'd put it in the clinical trial section.

ACTING CHAIRMAN CALIFF: So you vote no?

DR. Di MARCO: No on --

ACTING CHAIRMAN CALIFF: Okay. We're going to vote on the --

DR. Di MARCO: Okay.

DR. TEMPLE: I have to tell you we're not supposed to do that. If it's an indication, it's supposed to be an indication. If it's not, it's not. Sticking it in a different place doesn't get us -- doesn't remove the legal responsibility to be able to

say there's well controlled -- there's substantial evidence that it works. We haven't always followed that as well as we should have.

ACTING CHAIRMAN CALIFF: All right. So we just need to -- you have to make a decision. Is it in or out?

DR. Di MARCO: In

ACTING CHAIRMAN CALIFF: Okay. I vote yes.

DR. BORER: No.

DR. LINDENFELD: Yes.

DR. ARMSTRONG: No.

DR. FLEMING: No.

DR. THADANI: No.

ACTING CHAIRMAN CALIFF: Okay. The noes have it by a nose, that's right.

All right. We now move to the last question.

Five to three was the vote on that. We now move to the last question.

Were there effects of ramipril on congestive heart failure?

DR. LINDENFELD: I would say that this is not a new finding. Hospitalizations were the prespecified endpoint and were not affected. I know overall heart failure was, but it wasn't a prespecified endpoint and I don't think I'd put this in the indications.

ACTING CHAIRMAN CALIFF: Ileana, you had raised this before.

DR. PINA: (Inaudible.)

ACTING CHAIRMAN CALIFF: Any other --

DR. THADANI: I think there's more than a problem because nobody defines what heart failure was. One day a patient comes in with a little swelling. The other days -- so I think given that even the heart failure trend is in the right direction. Hospitalization is not, and what one is more concerned with a hospitalization. So I think we should not include that at all.

ACTING CHAIRMAN CALIFF: Is there a standard definition of heart failure that's used in clinical trials?

DR. THADANI: Well, when you're recruiting

patients in a clinical trial usually, well, just leaving aside systolic or diastolic dysfunction, the patient either has to have shortness of breath or they have some other clinical signs like edema; you're sure it's not due to (unintelligible) or JVD or other issues, and I think not giving -- all that does is allows the patient -- the physician to take yes or no. It's possible the physician wanted to put the patient on open label. It's just a guess. I don't know.

I know they collected the data for the reasoning either to -- a lot of patients with heart failure have rate increase or some other issues, and I think I'd be more comfortable if the hospitalization had gone in the right direction, and since they were not, I've got a major problem with this indication.

ACTING CHAIRMAN CALIFF: I guess I'm in the minority here, too, but you know, to me if you do a blinded study and you ask doctors is the patient in heart failure or not, at least I think that's a pretty good way to do things, and the more stringent you make the definition, the more money you spend on fewer patients.

DR. THADANI: Wouldn't you see some trend in the hospitalization?

ACTING CHAIRMAN CALIFF: What's that?

DR. THADANI: Wouldn't you see the right trend in the hospitalization at least?

ACTING CHAIRMAN CALIFF: Well, I think you'd like to, but things don't always happen the way you'd like them to happen.

Paul, you've spent a lot of time in heart failure. Are you going to -- is it inappropriate to do a trial where you don't have a prespecified definition that you ask clinicians to adhere to?

DR. ARMSTRONG: Well, not necessarily if you want to influence the behavior of those physicians, but if you're asking me whether -- how I'm going to vote on a label or an indication, that's a separate question. So I feel a responsibility relative to the defined secondary endpoint to vote one way, but I believe this probably makes a difference.

DR. TEMPLE: Rob, the trend was in the usual direction. There just weren't enough events.

DR. ARMSTRONG: Yes.

DR. TEMPLE: The hazard ratio is .86.

DR. THADANI: Rob, the definition is more complicated. When I'm doing wrong with the residents, you know, they can't even -- you know, they say JVD is negative, and you go and see that JVD is positive.

So I think it's very complicated just going on definition unless you have got some concrete other evidence.

DR. PINA: (Inaudible.)

DR. THADANI: We're not given the definition.

DR. PINA: Well, that's what I'm saying.

DR. LINDENFELD: But this says heart failure was not reviewed as an endpoint because it wasn't an endpoint; is that correct?

DR. THADANI: But here is the prevention part of this.

ACTING CHAIRMAN CALIFF: Okay. Well, so I think we've had a good discussion on this. I guess the vote would be would you include it or not include it in the indications?

DR. MOLITCH: No.

DR. GRABOYS: No.

DR. PINA: No.

DR. Di MARCO: No.

ACTING CHAIRMAN CALIFF: Yes.

DR. BORER: No.

DR. LINDENFELD: No.

DR. ARMSTRONG: No.

DR. FLEMING: No.

DR. THADANI: No.

ACTING CHAIRMAN CALIFF: Okay. That concludes our session. I want to thank the panelists for a lot of attention over a long period of time, and we'll reconvene tomorrow morning.

(Whereupon, at 5:11 p.m., the meeting was adjourned, to reconvene on Tuesday, May 2, 2000.)

C E R T I F I C A T E

This is to certify that the foregoing transcript in the matter of: 90TH Meeting of the Cardiovascular and Renal Drugs Advisory Committee

Before: DHHS/FDA/CDER

Date: May 1, 2000

Place: Rockville, MD

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.