set?

So, we had no problems with the ethics of that because before we started the study, we had no idea. The angiotensin receptor blocker, even if it was -- and I think it proved to be -- as effective in treating the glomerular disease of type 2 diabetes, as captopril was in type 1, if that effect was going to be offset by these adverse effects of severe hyperkalemia and acute renal failure, then you had an entirely different clinical decision to make. For that reason, there was not an ethical problem in doing our study, but that does not mean that patients with microalbuminuria shouldn't have been treated with ACE inhibitor in the clinic at least because there was data to say that that was the case.

DR. BORER: Again, thank you for a very illuminating presentation. Maybe we can go on to the risk/benefit summary and get to our questions.

DR. PARVING: It is my great pleasure to introduce Dr. Edmund Lewis who will give the summary with the risk/benefit.

DR. EDMUND LEWIS: Thank you. It's a pleasure to be back here.

(Laughter.)

DR. EDMUND LEWIS: We propose that therapy with the receptor blocker irbesartan alters the continuum of

diabetic nephropathy throughout its course, that the IRMA 2 study showed that, in fact, going from microalbuminuria to overt proteinuria was significantly affected and that phenomenon diminished by the drug, and that in the IDNT, the events associated with decreasing glomerular filtration rate and end-stage renal disease were significantly diminished.

Now, I want to emphasize that the endpoints that we chose were not arbitrary endpoints. The disease is a continuum. I think there's nothing in the literature or anywhere else that would suggest otherwise. However, in designing a clinical trial, you have to identify points in the course where you can try to tell a difference. Therefore, doubling of serum creatinine or a creatinine of more than 6 is not arbitrary. We chose those, I hope that you can see, and we'll present more evidence I guess, to show why that was the case.

Now, I don't think that one can underestimate the importance of trying to prevent end-stage renal disease, and I hope that ultimately in the presentation of the data what you saw as cardiologists -- today I'm becoming much more sensitive toward the cardiologists -- is that what we were doing, in terms of the renal system, was not putting the cardiovascular system at greater risk, that the same drugs that one uses to treat cardiovascular

disease in these patients would be used, that blood pressure would be managed, and that overall the mortality rate, the endpoints that you saw were not significantly altered. So, we're not saying treat these patients' kidneys at the risk of allowing harm to their heart. That is not the message, and I don't think anything about the data indicate that.

Can you put up 1.2? There you go.

Now, the reason why we nephrologists are so concerned about that renal endpoint -- we treat the whole patient, which includes the patient's heart actually. The reason we are so concerned about this -- and this is published annually in the U.S. Renal Data Survey. This happens to be a publication which shows exactly the same as the USRDS. In fact, it's showing you USRDS data I guess.

Here this orange curve is the survival rate of patients with type 2 diabetes on renal replacement therapy, on dialysis. As I've said, here at 12 months the survival rate is a little under 60 percent. At 24 months, the survival rate is 40 percent, which is very close to pancreatic cancer over that period of time, and it's almost identical to your consensus class IV heart failure. End-stage renal disease is a dreadful thing to happen to a type 2 diabetic, and that's why we are trying so hard to prevent it.

Up to now, there is no proven therapy. There is no data. I've told many, many doctors to treat with ACE inhibitors until the data become available, but going back 8 years, there was no question about captopril being approved for type 2 diabetic nephropathy on the basis of type 1 diabetic nephropathy data. This was the best you could offer. But there is no study that ever said in the overt nephropathy patient that ACE inhibitors were as effective, to this day.

So, what we're talking about here is not only the diagnosis that causes the most patients to go on dialysis, 45 percent, but actually the proportion of patients in end-stage renal disease programs in this country with the diagnosis of diabetic nephropathy is increasing every year more than any other diagnosis. So, it's an increasing problem, and certainly in countries where they can't afford $65,000 a year to try to keep these patients alive on dialysis, it is death. It is death.

The IDNT, in terms of benefit, allows us to look at two active comparators. It's not two trials, but it's more than one trial, and we keep seeing irbesartan versus placebo, irbesartan versus amlodipine. And at this stage of the disease where we can measure the functional capacity, the filtration capacity of the kidney, you can see that of course the primary composite endpoint is very

positive, but the all-cause mortality part, the cardiac part of the primary composite, does not reveal efficacy for irbesartan. And I don't think we would have expected that in this study. I think we've discussed that at length. It's the renal endpoints of the composite that are the important issue: the doubling of serum creatinine and end-stage renal disease.

I think it is clear from our data, both our renal data and our cardiac data, that the calcium channel blocker did not have an adverse effect in this patient population. Amlodipine appears to be a perfectly good drug to control blood pressure in this patient population, and according to our data, you would not get excess either cardiac events or renal events above that using other antihypertensive agents.

The doubling of serum creatinine, then, we are putting forward as the event that is early enough in the course of the disease where we could say that this is a very important endpoint. But actually it has still allowed doctors to treat patients afterwards, to try to prevent end-stage renal disease, so that there was an ethical issue there.

However, when one looks at the doubling of serum creatinine, you see that the median time to end-stage renal disease was 9. something months, and these patients

go on to your hard endpoint of end-stage renal disease. Now, some of them don't because they doubled so late in the study that they don't have time to go on to end-stage renal disease. But it is inexorable. They are going to go on to end-stage renal disease.

You can talk about doubling of serum creatinine as a surrogate for that. It is not a surrogate for renal function. It is a measure of renal function. And it's the renal function that is continuously going down.

So then, what we show is, relative to placebo, a 33 percent risk reduction -- the pink is placebo -- with a p value of .002, and a 37 percent risk reduction versus amlodipine, .003, and amlodipine versus placebo, there's no difference.

Now, I know that members of the panel -- in general people look at these Kaplan-Meier curves in a vertical way. But this is a time-to-event analysis, and from the point of view of the physician and the patient, it's actually the horizontal way that counts because what we can tell our patients, on the basis of this study, is that if they take the irbesartan -- here's the average follow-up of 31 months and here is your point of your event rate for doubling of serum creatinine, for those who have doubled, with either placebo or amlodipine, and here's the shift to the right -- you will not have your doubling event

for 11 months.

This isn't just a point chosen nonrandomly to show you this phenomenon. If you look at other points along the end of this curve, you see the same, more or less, 11-month delay.

And 11 months doesn't sound like much perhaps, but believe me, when you're on dialysis, it's a lot. And if your mortality rate is going to be 25 percent during that 11 months on dialysis, then being off dialysis sounds like a very good thing. So, I think that it is not only the relative risk reductions, it is also this delay in the important event that is very, very important.

And this is a very conservative issue because, remember, we're starting with patients who have already lost half their renal function. I don't think that it is overstating the case to say if they had only lost a quarter of their renal function when they started, that delay might be longer. That was certainly the case with the ACE inhibitors, that our most conservative result was in the captopril trial. Once we really started to use these drugs and test more potent ones and higher doses and better blood pressure control and so forth, we got much, much more dramatic results.

When you adjust for blood pressure, of course, irbesartan versus amlodipine, there is no difference in

terms of your renal endpoints because blood pressure control was identical in those two groups. So, you cannot imagine antihypertensive effect of irbesartan being the reason why we got these risk reductions. We had to adjust against placebo because -- not surprisingly, the hypertension of type 2 diabetic nephropathy is very hard to treat. Anyone who has tried knows that, and when you have to treat their blood pressure without ACE inhibitors, without ARBs, without calcium channel blockers, you have something on your hands. So, the fact that we had a few millimeters difference is not surprising, but it's really heroic that that was all that we had as a difference. Nevertheless, the difference between adjusted and unadjusted for blood pressure is not significantly different.

So, in terms of the face of the enemy, please remember that patients entering the IDNT had advanced renal disease when they started, and so our result is in patients who are very far along.

In terms of the IRMA 2 study, you have seen this, and our evidence is in these patients they do not enter the definition of overt proteinuria when they're on the irbesartan. You've had the entire discussion of microalbuminuria, but what I want to remind you of is that in type 2 diabetic nephropathy, you do not get to the stage

that we saw them in the IDNT without going through a long stage of increasing proteinuria. So, that is a clinical phenomenon. There are no clinical signs and symptoms, but it's a clinical phenomenon that is significant. And when you adjust for blood pressure differences for the two treatment groups, there is no difference in the relative risk reduction of actually going onward to a positive dip stick, which is an important clinical event. And please note with this 300 milligram group, the relative risk is reduced by 70 percent. 7-0 percent.

So, in terms of benefit, our conclusion is that irbesartan retards the progression of both early and overt nephropathy in type 2 diabetes mellitus with nephropathy by a mechanism which is independent of blood pressure control.

Treating 15 patients with advanced diabetic nephropathy entered into the IDNT trial for 3 years, you save one clinical event. That's in terms of renal outcome. Treating 10 patients in the IRMA 2 trial for 2 years, you save one event which is microalbuminuria going on to the positive dip stick overt nephropathy.

I think that it is important to state -- and I'm not presenting this as part of the BMS irbesartan application -- that there are not two clinical trials in the literature to which the medical profession has been exposed to. There are three trials in the medical

literature with that exposure, and in the very least what you have to say is that on the basis of that, there will never be an ethical trial looking at ARBs versus placebo in the future or ARBs versus non-renin-angiotensin inhibitor in the future because we've got all of this information.

The last trial published by Dr. Brenner one page after mine in the New England Journal --

(Laughter.)

DR. EDMUND LEWIS: The RENAAL trial was 1,500 patients. The design varied very, very little from our trial. The outcome events were identical. The patient population was basically identical. The baseline characteristics of the populations were identical.

So, I just want to point out to you, just in terms of the totality of information available as far as the prevention of progression of this horrible disease is concerned, that if you look at the risk reductions of that trial using losartan versus our trial using irbesartan, you see they used the same primary composite endpoint. They got essentially the same reduction with the same variance. If you look at the renal endpoints, basically the same reduction. If you look at doubling of serum creatinine, hardly any difference. If you look at the occurrence of end-stage renal disease, about the same. If you look at all-cause mortality, the same. So, I believe that that

trial supports what we are saying with our application, although it's not part of our application.

Collectively these results demonstrate that the renoprotective effects and the benefits of irbesartan across the continuum of diabetic renal disease, we hope you agree, has been demonstrated.

In terms of risks, you've heard Dr. Cooper address the side effects and the risks. I won't go on about that. Certainly the overall risks of this drug are very well known to you. I don't think it was a problem for your primary reviewer, and the specific risk, in terms of hyperkalemia and so forth, is no different than that which the medical community has a concern about and has to treat with ACE inhibitors. So, the risk/benefit assessment we believe favors the use of irbesartan across the continuum of renal disease.

Collectively the data are what they are. We hope you agree, we hope you concur with our statement that this drug should be approved for the treatment of type 2 diabetic nephropathy throughout its continuum. Thank you.

And with that, I'll stay here for questions.

DR. BORER: Actually, I don't think we'll have many questions at this point because we have questions that we have to go through. But I want to thank you very much for, again, a wonderful presentation. To orient everybody,

I want to thank the sponsor for the presentation in its totality. I certainly and I think everyone on the committee found it very informative and enlightening.

However, at this point, we're going to move on to the questions put to us by the FDA, so there's not going to be any more discussion and no more comments from the sponsor unless we specifically ask for them. So, I'd appreciate it if you keep that in mind.

There are a number of questions here. Some of them we may be able to go through quickly, some not. To try to be most efficient about it, what we'll do, after quickly going through the preamble here, is present the questions to our primary committee reviewer and then see if anybody disagrees with the answers that she gives.

DR. KOPP: One question.

DR. BORER: Yes.

DR. KOPP: Dr. Pelayo described the second study IRMA as a non-IND study. What does that mean and does that have any bearing on how we view that data?

DR. LIPICKY: No. It has no meaning.

DR. BORER: Yes. It is important because this needs to be part of the public record, that as we take a vote, even if we're all agreeing with everything JoAnn says, we have to do that by name verbally into the microphone, and I'll ask everybody to do that as we go

along.

With that having been said, we're asked to give an opinion about the benefits and risks of irbesartan for the treatment of nephropathy in patients with type 2 diabetes. I assume, Ray, you may have meant patients with hypertension and type 2 diabetes, or did you not mean that?

DR. LIPICKY: We did not mean that. I may as well start it out. I fail to see the distinction between having hypertension or not having hypertension if they have diabetic nephropathy, but of course there is an empirical difference.

DR. BORER: Okay.

Reviews of chemistry, pharmacology, toxicology, biopharmaceutics, biometrics, and clinical safety present no apparent barriers to its approval.

And we're asked to determine if the strength of evidence for a treatment benefit, relative to the risk, supports approval.

The direct evidence comes from the studies listed.

Question number 1. There were 411 total endpoint events in the placebo and irbesartan groups, 33 fewer in the irbesartan group than on placebo. One of the characteristics of a none-too-small p value is that the result is sensitive to the handling of subjects with

incomplete data.

So, 1.1. 16 subjects, 8 on placebo or irbesartan, never received any treatment. How were they handled? How should they have been handled?

JoAnn?

DR. LINDENFELD: Well, these as I understand it, were handled as intention-to-treat, and I believe that's proper.

DR. BORER: Is there anybody who disagrees with that?

(No response.)

DR. BORER: Nobody disagreed.

We'll vote on the question at the end, I guess, with a verbal statement.

408 subjects, 275 on placebo or irbesartan, discontinued study drug. These were the people predominantly who reached an endpoint and came off coded drug. How were they handled, and how should they have been handled?

DR. LINDENFELD: These were also handled as intention-to-treat, which I think is proper. I believe the cardiovascular endpoints were followed only until they reached the point of end-stage renal disease.

DR. BORER: Any disagreement? Yes, Steve.

DR. NISSEN: Again, we talked about this

earlier, but I'm quite disappointed that the other events were not collected after they reached those endpoints. So, I think that that to me is actually an important issue, and my feeling is that they were not handled as well as they should have been handled.

DR. FLEMING: And just a brief added comment. I agree with both my colleagues. I agree with JoAnn that ITT is the proper way to handle the discontinuations, and I agree with Steve that technically speaking, ITT doesn't mean including all randomized people. It also means including the follow-up of all randomized people. So, it does compromise the ability to at least more clearly understand the impact on those endpoints that were censored in follow-up after end-stage renal disease diagnosis.

DR. BORER: We'll put a bookmark there.

Bob?

DR. TEMPLE: Some of them were followed, though, because they have mortality data on all of those people, and there's that slide that shows which people who had an endpoint of doubling went on to end-stage renal disease. So, I was a little foggy on what they did and what they didn't follow. I guess strokes and things like that were not followed.

DR. BORER: Maybe we can have a clarification, very quick. Dr. Cooper perhaps can tell us. You followed

everyone except the ones who were lost to a mortality endpoint. We know about ESRD because everybody was followed to that event. We just don't know who had a stroke, who had a heart attack after ESRD. Is that correct?

DR. COOPER: That's exactly correct. The company made every effort to follow every patient with respect to ESRD and mortality. We have all of the data with respect to mortality for all patients except for 8, and we have all of the data with respect to ESRD in all patients with the exception of 37. So, we have to go back, as indicated earlier in the discussion, to ascertain the dialysis and transplantation status of those patients. But that's correct. The only data we did not systematically collect after ESRD were cardiovascular events that were nonfatal.

DR. LIPICKY: Can I ask a question? Because it's my impression it was after doubling of creatinine.

DR. BORER: No.

DR. COOPER: No.

DR. LIPICKY: It was ESRD. So, everyone was followed to ESRD?

DR. COOPER: Yes.

DR. LIPICKY: Even if they met the doubling of creatinine.

DR. COOPER: Yes.

DR. LIPICKY: Okay.

DR. BORER: 19 subjects, 13 on placebo or irbesartan, were lost to follow-up. Mortal status is known for 11 of 19, 7 of 13 on placebo or irbesartan. How were they handled and how should they have been handled? JoAnn?

DR. LINDENFELD: Well, these were included when the outcome was known, and as I understand the analysis, there was a specific sensitivity analysis done to be sure that if one attributed all bad outcomes to the irbesartan group, that this still remained, that the difference was very, very small. So, I'm not too worried about this small number of patients.

DR. BORER: Any disagreement here?

(No response.)

DR. BORER: No, okay.

2 placebo group subjects were credited with endpoint events for near doubling of serum creatinine. How were they handled? How should they have been handled? How many other near-doubling events were not counted as events?

DR. LINDENFELD: This is an area we didn't cover, and we can see if people think we should. There were 2 placebo patients that actually were credited with a doubling of creatinine who, when they went back and looked at the initial, by strict criteria the first study

creatinine did not actually double. The adjudication committee, as I understand from the briefing booklet, decided to include them in the doubling. I don't believe we know how this was handled otherwise.

I guess one other question would be of the endpoint events, how many were changed in the endpoints committee? I don't think we've seen that data, and perhaps you could just give us a brief answer to that.

DR. EDMUND LEWIS: Yes. With respect to those 2 patients, our protocol design was that the central laboratory had to confirm a doubling of serum creatinine event, which then went to our outcome committee for adjudication.

And in the 2 patients that you're referring to, what had happened was the geographic lab for that part of the world had not declared a doubling. However, duplicate samples were sent to our central lab and we confirmed a doubling. Now, we're talking about tenths of a milligram. But we confirmed the doubling. We sent that information, along with the information from the local labs, on to the outcomes committee and the adjudication was that those 2 patients indeed had doubled according to our predefined protocol determination.

DR. LINDENFELD: Maybe you can give us a quick answer to how many times did this happen in the other

groups, the irbesartan group and the amlodipine group.

DR. EDMUND LEWIS: It didn't. Those were the only two cases.

DR. LINDENFELD: They were the only two cases in the entire study.

DR. EDMUND LEWIS: Yes.

DR. FLEMING: Just one refinement of JoAnn's answer to question number 1.3. If I'm recollecting correctly, Jeff, you had asked this morning a series of questions that related to these issues, and if I'm recollecting correctly, in the 1.3, the 19 subjects lost to follow-up, if one did take a worst case analysis, I think the significance technically, if you believe .05 is a magic number, was crossed. It's hard to know what to make of that because a worst case analysis is incredibly conservative.

DR. BORER: Yes. It was .055 something, as I recall.

In summary, what effect have the sponsor's rules for handling these situations on the credibility of the principal finding? JoAnn?

DR. LINDENFELD: I think they've been handled well, and I don't think it should influence the credibility of the studies.

DR. BORER: Steve?

DR. NISSEN: Well, I sill am very troubled by the lack of cardiovascular event data after those patients reached the end-stage renal disease time point. And I'm particularly troubled because prior to that point in time, we saw point estimates for MI, cardiovascular death, and stroke that were going rather strongly in the wrong direction. And if those trends were to continue, they were pretty close, as individual endpoints, to statistical significance. So, those additional events that may have occurred later that were censored could well have led to a statistically significant result with respect to having a worse outcome than the amlodipine treated arm. So, I really do think it undermines my comfort level significantly.

DR. BORER: Ray?

DR. LIPICKY: I think I feel compelled to say, because the question was oriented so that you would, but you didn't, that since there was only a delta of 33 in the two groups, that a difference makes that indeed, depending on what you do with things and one of the conditions did make it happen where you lost the conventional significance, and that that was simply meant to heighten your awareness to where you were.

DR. BORER: Our awareness has been heightened.

Number 2. Of the 411 primary endpoint events

on placebo or irbesartan, 58 percent were creatinine elevation and 42 percent were death or need for dialysis. All of the apparent treatment benefit was the effect on creatinine. And now we need to determine what we think about this.

2.1, was this a statistical anomaly, and 2.2, was this because there were just so few clinical outcome events? Was this because effects on clinical outcome would not be expected over 57 months of follow-up? Was this because an effect on serum creatinine is a poor predictor of clinical outcome?

Subjects who experienced doubling of serum creatinine could later have end-stage renal disease and die. When these events are counted, the relative risk of death on irbesartan was .92 and the risk of needing dialysis was .80. Are these data supportive of an effect on clinical outcome?

Why don't you try and take the whole question as one, JoAnn?

DR. LINDENFELD: I don't think this is a statistical anomaly.

It's important to say I don't think the study was a 57-month study. The mean duration of study here was closer to 2. something years. So, it wasn't a 57-month study. If it had been, I'd be far more concerned about the

lack of cardiovascular events here.

I can't explain why there was not an increase in cardiovascular mortality. I think when we relate this to the captopril trial, there are several things that come up. One is that was a different population. Those patients had much less well-controlled diabetes. These patients are likely to have been on far better therapy at this point in time. So, I don't believe it's just a statistical anomaly. I think the follow-up may just have been a little bit too short to see substantial differences in cardiovascular outcome.

I think it helps that the relative risk of death is less, but it would be nice if it were significant. So, not strongly supportive.

DR. BORER: Can I just ask for an opinion? I think one of the key elements here that one can infer from this question is that we're being asked whether we believe that there's a clear relationship between doubling of serum creatinine and a progression to ESRD within 9.8 months. And we were shown data about this. Can you comment on that, JoAnn?

DR. LINDENFELD: I believe that there is a clear correlation between doubling of serum creatinine and end-stage renal disease, based on this data, yes.

DR. LIPICKY: Based on this data?

DR. LINDENFELD: I think so.

DR. LIPICKY: What do you see? What makes you say that?

DR. LINDENFELD: Well, we see a substantial difference in end-stage renal disease, if you believe a creatinine greater than 6 as part of end-stage renal disease. We talked about that earlier.

DR. BORER: So, the incidence of end-stage renal disease, 22 to 23, doesn't mean anything.

DR. LINDENFELD: Well, that's if you only use dialysis or transplant. If you use the creatinine of 6 -- and I think what I've heard makes me think that that -- and the other discussion that we heard just about the creatinine of 6 makes me feel that that was probably a reasonable addition.

DR. LIPICKY: But that has to be, right, because if you use creatinine as the one thing and you also use creatinine for the other, it's got to be the same? Isn't it? I mean, does that really convince you?

DR. LINDENFELD: No, it does not convince me, but I think it's supportive data. Does it absolutely convince me? There are two questions. Does the data absolutely convince me? No, the data doesn't. Do I believe the doubling of creatinine is an important precursor for end-stage renal disease which is important in

clinical outcomes? All of this data persuades me that that is true, in addition to other data, yes.

DR. BORER: Any disagreement? Dr. Kopp?

DR. KOPP: No. I would say not so much disagreement. I think I agree with what you said.

But I've puzzled during the day about why the rate of dialysis and transplant was so much higher in the captopril study, given that both were about 3 years and the captopril study involved younger patients. But I realized you mentioned one factor that would favor less renal disease in this group, which is glucose control was worse in the captopril study. Another is that blood pressure I think was not as well controlled. And a third I realized is that some people who doubled creatinine and therefore came off study could have then received an ACE inhibitor and postponed the onset of their ESRD. So, I think that might tend to unlink some of this, particularly over a 2.6-year study.

DR. LORELL: Yes, I agree very much with that comment. I would support that.

DR. BORER: Let's move on to question number 3 then.

DR. FLEMING: Another comment, Jeff, on 2 if we could.

DR. BORER: Oh, I'm sorry. I didn't see you.

DR. FLEMING: It might be worth getting into just a little more depth in 2, if I could.

When I think of effect -- and it may be a simplification, but in addition to the marker here which is looking at changes of a certain magnitude in creatinine -- there are at least maybe three fundamental domains of what's clinically important. One that I might say is a direct obvious renal, which is dialysis/transplantation. Then there's the domain of mortality, which includes renal to an extent, of course renal-related deaths. And then there's the third domain which would be the cardiovascular events. That would include the stroke and the MI, cardiovascular death, heart failure.

My sense is what's happening here is when you analyze these data in different ways, you're getting different weightings of these three domains. With the first of those three domains, there's a signal for benefit. The second and third domains, there's essentially an indication of lack of difference or, to put it another way, to obtain evidence that is convincing of small differences that would take a much larger trial.

So, if I could just briefly refer to a series of five analyses that become more inclusive as you go through them, when you look at the primary analysis, you see the 411 events that we were asked to look at here. If

you look at a breakdown of that, when you look at the first occurrence, what you find is there are 64 deaths in control and irbesartan. So, there's no difference in first occurrence of deaths. There's actually no difference in first occurrence of dialysis. There's no difference in first occurrence of transplant. The entire difference is in first occurrence of the doubling. But it's misleading to look at it that way in the sense that, for example, for dialysis you're truncating the follow-up there at the first occurrence of the primary endpoint. So, we want to follow on beyond that.

And that leads to the second analysis which is looking at end-stage renal disease. The first analysis we've seen, there's an excess of 33. There are 33 events prevented. And this is a relative risk of .8 and this has the p value of .023. When you look at the end-stage renal disease, you're getting almost the same relative risk reduction of .77 as the relative risk. You have 19 fewer events, and yet not quite significant. So, if one takes the approach that end-stage renal disease is so proximal to dialysis that it's a reliable surrogate, that there isn't an issue about surrogacy, then for this particular endpoint, we're seeing an estimate of a 23 percent reduction with not quite statistical significance and 19 fewer events.

It's interesting if you look at dialysis. What we were shown is that translates into 15 fewer events. So, in fact, it's sort of a confirmation, I might say, that end-stage renal disease is close enough to dialysis to basically refer to it as a reliable measure. But dialysis, like end-stage renal disease, showing 15 to 19 fewer events, is around that area that we would consider convincing. It's about a p value of .07 to .1, something in that neighborhood.

When you add death, the deaths are essentially comparable. In fact, I think most of the deaths that occur -- there were 87 versus 93 deaths. So, there were 180 deaths. Only 36 of those were people who had had a prior dialysis. So, a large fraction of these deaths are occurring to people who had not had a prior dialysis.

So, basically it would be called competing risks, which points out that at least for the duration of follow-up that we had in this population, there is a significant myriad of health challenges these patients are facing and the renal complications are obviously one important part, but there are major complications outside of the renal. And it would appear from these data -- and it may be what people would say we would expect -- is that there's no reduction in those particular deaths.

So, when you go to the next level of analysis,

which is dialysis/death, what you're seeing then is still a numerical 13 fewer events, but now relative risk is .89. So, you're only reducing the relative risk by 11 percent. Obviously, very nonsignificant.

And it's interesting that if we compare that, that's the endpoint in captopril that showed a 50 percent reduction. This particular endpoint, we're showing an 11 to 13 percent reduction.

And personally I find it very acceptable to focus on the renal-related phenomena here, death, transplantation, dialysis. But if you then go one step further and you add in what was at least documented for the cardiovascular events in the secondary endpoints, now you're looking at 209 versus 229 or 20 fewer events, corresponding to a proportion of patients who have events, 36 versus 40, so a 4 percent absolute reduction or about a 9 percent relative reduction.

So, my sense is when you look at this to answer this question, one really needs to break apart these domains. And what, at least my interpretation, these data are telling us is if you focus on end-stage renal disease or, correspondingly, dialysis as the only measures you're looking at, you're seeing something on the order of a 20-23 percent reduction, but it's p values of .07. So, it's very close to whether you would say that's convincing evidence.

When you then add in death -- so, you're looking at dialysis-free survival -- because you're adding in almost as many additional events that were not impacted at all in terms of their reduction -- that 23 percent reduction is cut in half to an 11 percent relative reduction, very nonsignificant, although I don't worry about it being nonsignificant. I'm looking more at the magnitude. And then it's reduced to 9 percent relative reduction when you bring in the other cardiovascular events.

So, it seems as though there is -- this is an issue that we have to decide, is there adequately convincing evidence that you're affecting the clinical renal events because there's clearly a signal toward that. But the other events, even if you just go to death, aren't being influenced nor are the cardiovascular events being influenced.

DR. BORER: Well, we'll have to keep all that in mind as we move along here.

May I ask you, Tom, just one thing? I think you've really covered the waterfront. The point is made in the questions that we don't see the curves begin to separate until 18 months. And that's true. Of course, we've heard about the natural history of these diseases, and it's not terribly surprising that we might not see an

impact for a while. But I'm impressed with the fact that at least until you get out to 42 months, by which time the numbers become so small that the statistical stability of point estimates would have to be of concern, the curves seem to continue to diverge. It appears that we're having an increasing effect over time. Do you accept that or can you comment on that?

DR. FLEMING: I think what you're referring to is this is what the primary analysis does show when you look at --

DR. BORER: Also the end-stage renal disease analysis.

DR. FLEMING: If I go through my hierarchy of five analyses, those are a tier 1 and tier 2. They're fairly close.

It's certainly an interesting issue. It's relevant. It's going to mean that statistics such as the log rank test will be pretty sensitive to those kinds of emerging effects. It means that it's possible, plausible that if one had continued this for a number of additional years, then the magnitude of the signal may have been more apparent. It comes back to a comment just before the break I think that Dr. Temple had asked about what ability would there be to follow up these patients in this study to see whether there is more data than what we've had presented to

us for effects of the signal on dialysis. It's entirely possible that it would show more signal.

DR. BORER: Let's go on to question number 3. Irbesartan reduced the composite event rate compared with amlodipine by 23 percent. Considering the low nominal p value, is this as good as a second study? This p value is smaller than for the comparison between irbesartan and placebo because amlodipine did worse than placebo. How does that confirm a benefit of irbesartan?

JoAnn?

DR. LINDENFELD: I don't believe that this is as good as a second study. First, when you look at those curves, they were different. Amlodipine was just slightly worse, not statistically significantly so from placebo, so it's not a surprise that this p value is lower than when compared to irbesartan. So, no, I don't think it's as good as a second study.

Does it help a little bit? It helps me a little bit in that in the amlodipine group, the blood pressure was well controlled, and I think that's a helpful finding, but certainly not as good as a second study.

DR. BORER: I want to ask Tom for a clarification here again. I'm not sure what we can infer from the nominal p values here. The way I would look at it, it's unlikely that the difference between irbesartan

and placebo was due to chance alone for the primary analysis, and unlikely that a difference between irbesartan and amlodipine was due to chance alone in the primary analysis. I'm not sure what you can infer about placebo and amlodipine and about the difference in the p values between those two. That seems beyond what we can really draw conclusions about. Am I right about that or am I misinterpreting here?

DR. FLEMING: Actually my sense about this is similar I believe to what I understand JoAnn is saying. When I look at this, there is some level of reassurance about the irbesartan effect against placebo when you look at it against amlodipine and you track that same effect. Of course, the extent to which I can draw that reassurance is based on the assumption that amlodipine can really be viewed as a placebo.

Where I worry is that I don't know whether we can say that amlodipine is a placebo, at least as it relates to the measures on the primary endpoint. Certainly when we get to the cardiovascular measures, if we're going to pool amlodipine with placebo, then I almost feel like, gee, is that really fair not to pool it where it's going to make irbesartan look worse, which are the cardiovascular endpoints. If we do that pooling relative to other measures such as cerebrovascular events, MIs, neurologic

abnormalities, if you pool amlodipine and placebo and compare it to irbesartan, it looks like irbesartan is 30 percent worse. Well, I don't believe that either. I think what's happening is amlodipine is better than placebo. So, to then pool amlodipine with placebo in those measures that will make the statistical strength of evidence look better seems to be a little bit, at best, arbitrary. So, there is this clinical issue, can you pool this when you're really having to essentially say, to strengthen your evidence, I'm willing to say amlodipine is a placebo. So, there is that clinical complication.

There's also a statistical complication. If I allowed myself to generate a p value by essentially comparing to the placebo and comparing to the placebo with another arm in the trial and view that whichever one of those p values look more impressive and report that p value as being meaningful, you're going to have an inflated risk of false positive conclusions. You can't conditionally pool something from another arm with my control arm if it's going to strengthen my evidence. It would be interesting.

Would it have been pooled had it weakened the evidence?

Would we still have done the same pooling analysis of amlodipine against control if it would have weakened the strength of evidence because amlodipine itself

would have carried some benefit on this endpoint?

So, bottom line is I strongly object to anybody sprinkling p values on such ad hoc suspect analyses to, in a sense, strengthen the interpretation of those.

On the other hand, coming back to what JoAnn said, I think there is some level of reassurance. It's not remotely what I'd call a second trial reassurance, but there is some level of reassurance by saying that the amlodipine arm was similar to the placebo arm and the irbesartan was better than each of the two.

DR. BORER: Steve?

DR. NISSEN: I think I'm agreeing with you, Tom. We can't have it both ways. We can't say amlodipine is placebo-like for one set of endpoints, but then ignore the others. The minute we start to do that, we're creating an anomaly. It seems to me that if we look at amlodipine as placebo, then we're forced to compare what happened with irbesartan and amlodipine with all those other endpoints. Clearly, there are several of them that go disturbingly in the wrong direction.

So, I think you have to look at the totality of the data here, and in that sense, I don't find it reassuring at all because, for a patient, you really have to ask the question. The patient enters a clinic and you have to decide which drug you're going to give them, and I

think if some endpoints go in one direction and some go in the other, the net clinical benefit is very hard to establish and certainly doesn't strengthen the evidence against placebo to lump amlodipine in the same category.

DR. BORER: Let's go on to number 4. Comment on other secondary endpoints in IDNT.

4.1. There was a prespecified analysis of time to first cardiovascular death, nonfatal MI, CHF hospitalization, disabling stroke, or amputation. There were 416 such events with no significant difference in the distribution among groups. Is this further evidence of a lack of clinical benefit? Is it comforting that there's a lack of apparent harm? Were there simply too few events, et cetera?

4.2. We discussed part of that here. There was a prespecified analysis of time to first cardiovascular death, nonfatal MI, coronary revascularization, CHF hospitalization, need for ACE inhibitor or ARB for heart failure, disabling stroke, amputation, or peripheral revascularization. There were 518 such events with no significant difference in the distribution among groups. Is this further evidence of a lack of clinical benefit? Is it comforting that there is a lack of apparent harm? Were there simply too few events to show a meaningful effect?

JoAnn?

DR. LINDENFELD: Once again, we have to come back. Lack of clinical benefit. I think the primary endpoint here was renal disease and that's where we really want to show the clinical benefit, and we've discussed that data. So, in this study, in this trial, I think we have a lack of a clear-cut clinical benefit in these cardiovascular endpoints, but certainly this doesn't imply a lack of clinical benefit on end-stage renal disease.

Now, again, the point has come up over and over again. If we see this doubling of creatinine, why is it not reflected in these other events? But again, we've discussed that, and these are two different things. This lack of clinical benefit for cardiovascular outcomes doesn't dissuade me that there's a clinical benefit in renal disease, which is real.

I don't believe there were too few events to show a meaningful event. Perhaps the study needed to go longer. Maybe that says that, yes, there were too few events. But I don't believe there were too few events. I can't explain the lack of cardiovascular outcomes here.

DR. BORER: Any other comments here? Tom?

DR. FLEMING: A very brief addition to that. The sense in which I might argue there could have been too few events is we're estimating something like an 8 percent reduction, and that's not significant. It's informative in

that it's suggestive that the actual effect, if it's real, is very modest. I'm not willing to say that these data prove that there isn't an effect on cardiovascular events, and in that sense it's too small a trial. We probably would have needed a much bigger study. If we would have viewed, for example, that conclusively establishing that the 8 percent is real, that would have taken a huge study.

So, this is the third domain that I had referred to in my answer to question 2, and my sense of that is consistent with you, JoAnn, that the first domain is what the intention and the focus was. It's still relevant to know what the third domain showed because these are very clinically relevant endpoints. And what the data show is they suggest that if there is an effect, it's very modest and it would take a much bigger trial to sort out whether there is in fact a very modest effect on cardiovascular events versus no effect.

DR. BORER: Now, the next question we actually have to -- I'm sorry. Go ahead.

DR. LORELL: I appreciate your insights on that. I think they're very helpful. I think it's also very much worth emphasizing that the treatment design in this appears to have had at least two potent cardioprotective interventions that were seen in all three groups. One was aggressive blood pressure control. A

second was that a relatively high number of patients were on profoundly cardioprotective beta blockade. We weren't told about aspirin, but I'll assume, unless I'm corrected otherwise, that aspirin use was comparably distributed. So, I would look at the way these patients were treated as having a very powerful cardioprotective intervention that was done in all three groups, and I think that may have partially blunted the ability to see any difference because of the low event rate.

DR. BORER: Bob?

DR. TEMPLE: Yes, I think I had much the same comment. We keep saying there was no difference, but there really isn't any hypothesized difference. They're all on appropriate regimens with all kinds of stuff. There's a hypothesized difference in renal events, but there isn't any hypothesized difference in any of the others. I mean, there is some disturbance about the fact that amlodipine looks a little better on some of those. That's certainly something to think about. But you wouldn't really have predicted an advantage in those events in this setting unless somehow the renal events led to fewer of the other events, and it probably wasn't followed long enough to see that.

DR. BORER: Steve?

DR. NISSEN: Just in response, part of the

reason why you might have hypothesized that is if progressing to doubling your creatinine and getting renal failure is a very bad thing, leading to myocardial infarction -- we've all heard that once you get to end-stage renal disease, you've got this terrible cardiovascular morbidity and mortality, and therefore preventing that might be expected to prevent those secondary consequences. So, I guess I think you could hypothesize that. Even though the sponsor didn't necessarily power it for that, I think we wouldn't have been shocked if we saw that.

DR. BORER: The next question we have to stand up and be counted on.

Are the results of IDNT alone an adequate basis for approval of irbesartan for the treatment of patients with type 2 diabetic nephropathy?

JoAnn, why don't we start with you and then we'll go to that side of the table and move around?

DR. LINDENFELD: I would say no to this question. I think that the study shows an improvement in the doubling of creatinine, but we've generally required two studies at .05 or one study at a much lower p value than this. In addition, there's a small number of endpoints. So, just as a standalone study with no other data, I would say no.

DR. BORER: Dr. Brem?

DR. BREM: I would make one comment and it comes to the point you made very early in the discussion and that is, is this for diabetic nephropathy or hypertensive patients with diabetic nephropathy?

DR. BORER: I think we can define how we want to interpret that. Why don't you carry through the thought?

DR. BREM: I think the way it's written here -- Dr. Lipicky, if I'm misquoting you, please interrupt -- I think he's trying to get at an indication for diabetic nephropathy, yes or no, independent of the hypertension. And I'm not sure on one study of this nature that we have enough information to make a blanket approval.

DR. LIPICKY: Then to make it easy, make it with hypertension. So, I'll call your bluff.

(Laughter.)

DR. BREM: I think even with hypertension, I'm not sure this study alone, in the absence of everything else --

DR. LIPICKY: You've answered my question.

DR. BORER: Dr. Kopp?

DR. KOPP: I had a question about those standards. It's two trials each at .05 or one trial at .00125. Where does that second number come from?

DR. LIPICKY: Both Tom and Dr. Temple are here to amplify on what I'll say. But basically if you just take the common sense view, that if somebody finds something, well, one has arbitrarily by history defined finding something as a p of .05. Usually you say, well, Tom found that. I'd like to know Harry found that too. Almost everybody says maybe Tom is right, but I want to know someone else found it. So, that's another .05.

So, if you now require for your standard of evidence -- and I'm not sure you should; in fact, I am advocating you should, but I'm not sure you should -- two trials of .05, statistically that's .05 squared. So, then you have to divide by 2 because you have to end up in the same distribution of the tails. And that comes out to .00125.

So, you have this various grading then of strength of evidence from the convention, 1 chance in 20 of being wrong, to a really very small chance of being wrong. One has to make the decision where you think this strength of evidence is. And I would maintain that you ought to be closer to the two studies at p of .05 than to one study at a p of .05 because one study at a p of .05 is just too shaky.

DR. KOPP: Clearly then my answer is, according to those standards, this doesn't make it. I agree that I

don't think we can consider this two independent studies so we don't have that criteria met.

DR. BORER: Bob?

DR. TEMPLE: I just want to comment a little further. We have just been at a workshop on this discussion.

Historically the agency always said that you need independent substantiation of a finding, basically in the form of another controlled study. The Food, Drug and Cosmetic Act was altered in 1997 to allow us to reach a conclusion on the basis of a single study with what is "confirmatory evidence," whatever that means because that has never been properly defined.

We've written a lengthy document on what constitutes good enough evidence and have generally said a couple of things. First of all, other data from other studies, maybe with a different endpoint, can sometimes help you believe in one study. Obviously, that's a matter of judgment. And we've also said that when really all you have is a single study, it ought to be at a more extreme p value, confidence interval, whatever you care to do. Whether that translates to .00125 or .001 or whatever is again a matter of judgment.

But it is fairly clear that we're allowed to think about -- and the document says this -- data from

other sources. Now, this is anticipating later. But you're entitled to take into account such things as the other study showing a different endpoint that may or may not be relevant. How to do that is an intense matter of judgment. I wouldn't try to tell you what to do, but you're permitted to reach that sort of conclusion. You even can think about related drugs, if you want to. But how to do those things and what the precedents are is very iffy, and there aren't very many. So, you're in substantially uncharted territories, but you're allowed to think.

(Laughter.)

DR. LIPICKY: Just to add to the part of you're allowed to think and nobody knows what the right answer is, it isn't just the p value. Right? It's partly, well, yes, you made a p of .05, but if you change one patient, and now you're at a p of .1, well, geez, that's not really a p of .05, just as in this case, it's a p of .02, but if you lose a few patients, it's .07. Now, that's a big difference. So, part of the question is not prior knowledge or is it a p of .05, but how robust is the data. How likely is it that if you take the numbers you're looking at and act on them, you would be making a mistake? So, it's another part of the whole business, and it doesn't come down to p values only.

Nor is it really one study/two studies. I mean, you could have one study that has a p of .01, let's say, and is so robust that you wouldn't possibly think that it could turn out any other way. Or as Dr. Temple says, you know so much that you would have predicted that, and indeed this now turns out that way.

And so, there's all kinds of this. That's what's being talked about now. Where are you on this continuum of your confidence that what the trial found is real?

DR. BORER: So far, to summarize, we're at 3 to 0 against, in terms of question number 5, and we'll go to Beverly Lorell.

DR. LORELL: Well, picking up on Dr. Temple's comment and on your comment, Dr. Lipicky, I'd welcome some discussion among the committee about their interpretation of the supportive value of the RENAAL study. Admittedly, it's a bit on uncharted ground, but at least to my mind, those data in a very similar design --

DR. LIPICKY: You haven't seen it. I think our proceedings here should be related to data you have seen and where you have seen a whole review like you've just seen of this, and there may be things that you know about that haven't had that degree of stuff and I don't think you should count that. Dr. Temple may think differently.

DR. TEMPLE: Well, I think we've vetted and the committee has vetted captopril data, so you might think that was relevant.

It is hard to take the RENAAL study into account because you haven't had an opportunity to see it, although we have.

(Laughter.)

DR. LIPICKY: Well, but that is a difference.

DR. TEMPLE: Yes.

DR. LIPICKY: And we would represent to you that the captopril study is as it was. We couldn't make that representation for the RENAAL.

DR. TEMPLE: We tend to be nervous about -- no offense to anybody -- presentations in journals without an opportunity to see the data, even though everybody is trying his or her best.

DR. BORER: I think we'll get to the strength of supporting evidence in the subsequent questions, but maybe we can try and deal with this one first, which is specifically, if you look at IDNT alone, is that adequate for approval?

DR. LORELL: Well, but in response to that explicit question, I would say no.

DR. BORER: Do you want to state a reason?

DR. LORELL: For the same reasons that have

been discussed, that it is a single study with a modest p value.

DR. BORER: Dr. Cunningham?

DR. CUNNINGHAM: I would also say no for the same reasons.

DR. BORER: Mike?

DR. ARTMAN: I would say no. I think there are a lot of confounding issues. We really haven't delved into some of the issues related to polypharmacy and whether that was all controlled for, et cetera. I think that the issues related to gender and ethnicity -- there was some hand-waving.

We've talked about the issues related to the black population and we're told that that couldn't account for differences. Then we looked at North American versus European and they said, oh, well, that's because all the black people were on the North American side and that accounts for the difference.

You know, I just am underwhelmed. And the mantra that Ray has instilled into us has been does the intervention make you live longer or feel better, and I don't see compelling evidence for either one of those. So, I would say no.

DR. BORER: Tom?

DR. LIPICKY: You cannot blame it on me.

DR. ARTMAN: Oh, I blame everything on you.

(Laughter.)

DR. BORER: He wasn't blaming it on you. He was giving an explanation.

DR. ARTMAN: I'm giving you credit. I'm attributing it to you.

DR. BORER: Tom?

DR. FLEMING: Well, issues have been discussed, but essentially when I look at data from a single trial and I'm confronted with the question should this study, at least in my own recommendation to the FDA, be viewed as adequately convincing. We lose a little bit with the single study of the replication concept. That is important. It's not just a p of .025 squared times 2, which is what .001 is. There is that merit to being able to see an independent set of investigators maybe in a somewhat related setting being able to show that the results of positivity could be confirmed.

Having said that, though, I do accept that a single trial in settings could be adequate, and I certainly am influenced a bit by what the strength of evidence is when you say .001, i.e., the .025 squared. There are settings that would move me away from even saying I would need to see that from a single trial, if I'm looking at a mortality endpoint, if I'm looking at secondary measures

that are strongly reinforcing primary.

So, in this setting, I completely concur with the sponsor's perspective that the first focus of this is the renal components and dialysis. And when I look at that, I see some p values that are in the neighborhood of .025 to .075, something lurking around .05. When I look at the secondary measures, I don't see that they have to be positive in order to make me view this as a single positive trial, but I do think that when the primary is about .05, I do need to see those secondary measures showing positive reinforcement for this study to be judged in its own right as a single convincing trial. And for mortality and for the cardiovascular endpoints, there's not evidence of benefit.

My view of that is I think this is just on the edge of what I would consider adequate strength of evidence for this to be called, just barely, a single positive trial, but I don't see it as meeting any of those other factors that would bring me to a much more convincing perspective that this study conclusively establishes benefit at the level that I would wish to have as a standard for strength of evidence from two independent studies.

I guess the last point is -- and I don't know what FDA's view about this is -- I would also be persuaded

if this was a setting that was a rare setting that would be incredibly difficult to enter patients. This is a setting where this is going to be very widely used, and I think having a standard of being adequately convinced it's effective is particularly compelling in a setting where you've got an intervention that's going to be so widely used.

So, I look at it as a study that just does get into the realm of strength of evidence for being called a single positive study, but I couldn't see an approval being justified based on this study alone.

DR. BORER: Blase?

DR. CARABELLO: I would vote also no. I think it was a single study. I found the amlodipine data helpful in helping me believe that this was not simply an effect of blood pressure lowering, but I was mostly disturbed, despite discussion to the contrary, about its lack of effect in women in North America. I just am bothered by the fact that that subset analysis seemed to be so weak.

DR. BORER: Steve?

DR. NISSEN: Well, one of the questions I ask is, although it is off-label use, almost all these patients now are getting treated with ACE inhibitors. A recommendation to approve will cause a shift in prescribing practices. So, what level of evidence do we want to have

to actually cause that to take place?

The p value here is really .035 for the primary endpoint, and if you'll recall, the sponsor's analysis of the blood pressure differences suggested that at least some of the positivity was due to that. So, now we're getting perilously close to even the standard for a single study.

You add to that the confounders, as in race, gender, and location, North America versus not, and now there are just too many confounders that could take this on the wrong side of even being adequate as a single study. So, I just think there's just not compelling evidence from IDNT to approve. So, my vote is no.

DR. BORER: Alan?

DR. HIRSCH: The first time I think I've ever gotten to speak last, and yet I've learned how to use the word opine.

(Laughter.)

DR. HIRSCH: First, I have to say to my previous instructors, Dr. Brenner and Dr. Lewis, I also heard you and I have absolutely no doubt that ARBs alter the structure and hemodynamics of end-stage renal disease or the kidney proceeding to end-stage renal disease. In other words, the paradigm I understand is important and affects a great number of patients who will ultimately in this country and the world die of their disease. But I

opine no as well, and I should justify why.

The same issues. I'll repeat a few of them. Single trial, I think, whose statistical significance is borderline. For me the supporting data and the secondary endpoints and the use of IRMA 2, though they support the pathophysiology, in general don't yet convince me that the single has adequate power.

Like Dr. Lorell, I certainly am aware of published data from losartan and RENAAL, and that helps me but we're not there yet. So, I can't include that in my analysis.

A little bit like you were saying, Dr. Temple, whereas if I were a manuscript reviewer, this is clearly an important trial and significant, our role as advisors to the agency is different. There's a higher standard of evidence because it will change practice. So, I say no now.

I'll go a step further to set up the discussion later I think that you wanted, Dr. Lorell. We do change precedent by how we interpret trials, and I fear that when we take a single trial, as you might imply, and permit the global data to change our analysis, that we permit use of surrogates that we're not all quite comfortable with, number one, that we might permit a somewhat low sample size to be used not to understand why there's no efficacy in

North America when, in fact, we're regulating North American use -- or I should say American use. And I worry that then we'll also promulgate incomplete follow-up regarding those cardiac events in future trials.

So, overall, looking at a large potential use with a very, very important disease, it doesn't quite reach that level of significance. So, I opine no.

DR. BORER: Opine is Ray's usage.

Just with regard to the strictly stated question number 5, I'm going to vote no as well, but I want to give some explanatory statements.

First of all, although I agree with the thrust of Ray's suggestion earlier that diabetic nephropathy is diabetic nephropathy, and the presence or absence of hypertension probably -- probably -- doesn't alter the fundamental nature of the disease. Nonetheless, when we're talking about approval of a drug, we have to consider the efficacy and the safety for its intended use and the balance between the two. And I really have no information at all that would allow me to give an opinion about that with this drug in patients with diabetic nephropathy who don't have hypertension. So, just as Dr. Brem suggested, I would limit my consideration of this drug to patients with type 2 diabetic nephropathy with hypertension. Those are the patients we saw where the risk/benefit relationship may

be different than in the other populations.

Having said that, I agree that it's a single trial with a level of consistency, indicated by the p value that's relatively close to the margin that nominally we accept, and there are some other issues.

However, and perhaps to presage aspects of the discussion that we'll get into, I really don't have any trouble with a creatinine of 6.0. I'm not a nephrologist, but my understanding of the literature and my clinical experience is that when patients have dramatically subnormal creatinine clearance, as people with a creatinine of 6.0 do, they progress, and they progress relatively rapidly. And if they're not dialyzed, then they will die, and before they die, they'll be very uncomfortable people. I don't need a set of data collected by the sponsor about the effects of pericarditis, the effects of anemia, the number of episodes of nausea and vomiting to believe that because I think it's been well documented in the literature, and I think that nephrologists probably know that and people in other subspecialties may not have the same feeling for it. But I do see this patients with some frequency because of my focus on patients with valve disease who have cardiac surgery. So, I have no problem at all with the endpoint of 6.0 or dialysis or transplant. I think the one is a short step from the other.

And I have really no particular problem with the doubling of creatinine as a pretty solid predictor of the progression to these bad endpoints that we don't want people to get to.

Having said that, I think that I to a lesser extent and the entire committee perhaps to a greater extent would feel more secure. We would have a more secure view of the data and the interpretation of the data if in fact we did have that additional information that Tom had asked for earlier about the progression to dialysis and the progression to transplant beyond the first event ESRD. So, I'd like to see those.

I think if at the end of the day we don't come out voting in favor of suggesting to the FDA that they approve this drug for the requested indication, that those data should be obtained and given for review because they might change the opinion of some of the people who are looking at these data, specifically the kinds of things that Tom was asking for.

I'm really not terribly concerned about the gender and ethnicity issues. I don't want to get into mechanisms. I'm already on record as telling Tom at an earlier discussion at another meeting that I have no idea how any drug causes its clinical benefits, but I can talk a little bit about pharmacologic effects.

I think that there's an analogy here. The gender issue, the ethnicity issue, all the other substudies are indeed substudies. If we're concerned about them, then we could suggest that the FDA say something about that in the label and note the lack of information or the lack of security in certain subpopulations. But they are substudies. They're post hoc assessments. There was no hypothesis being tested there. So, I'm not terribly concerned about that.

And I'm also a little sorry that we got into such a detailed -- I'm not sorry that we got into the discussion, but that the issue of the nonfatal cardiac endpoints seems to assume such great importance because I am convinced that when you look at the totality of major events, that there are fewer major events on drug than without, although there does seem to be a different distribution of some of those cardiovascular events than the renal events which causes you to lose a little bit of confidence in the strength of the overall conclusion.

So, again, in summary, I believe that IDNT alone isn't an adequate basis for approval of irbesartan for treatment of patients who are hypertensive with type 2 diabetic nephropathy, but I'm not as concerned about some of the other issues that have been raised as you've heard from some of the other committee members.

DR. TEMPLE: Jeffrey, I think not everybody who voted clearly referred to this study alone. You just did. The question was designed to not have you consider IRMA yet and just go on this study, but it wasn't clear to me everybody was treating it that way.

DR. BORER: I think Alan didn't and one or two others didn't, but I think most everybody focused on this alone.

DR. TEMPLE: The second observation I want to make is we've been severely criticized for putting a mention of a subset in the labeling, referring to the MERIT trial, where we thought we had better than usual cause. It's just worth observing that here the subsets are extremely small and it would be a miracle if they all went in the same direction. So, we're having some trouble for doing that at all. Just so you know, people are threatening not to include U.S. patients in their trials because we pay so much attention to it, but don't worry about that.

(Laughter.)

DR. BORER: Well, just for the record, nominally they did go in the same direction. The magnitude of the effect was small, but as you've said, small numbers, post hoc. I don't know what you make of that.

DR. FLEMING: Jeff, one other quick

clarification. I think there may be more concurrence in what you were saying than you might have suggested in handling the primary analysis. You were saying you were persuaded that end-stage renal disease, which includes in its definition a creatinine at level 6, would be an adequate clinical endpoint, as would dialysis. I didn't hear anybody disagreeing with that.

And when you referred to my interest in seeing more data, if one accepts that these end-stage renal disease endpoints are clinical endpoints, one gets a p value of .07. If one uses end-stage renal disease as the primary endpoint, and if you look at dialysis, you get a significance level along that line as well. If you use the primary endpoint, as they had defined it, which is a twofold increase in creatinine, then you slip just on the other side of .05 to .023. So, when you said you would accept that, basically, at least in my own comments, when I say you're on the edge of .05, it's accepting end-stage renal disease as clinical endpoints.

DR. BORER: Let's move on then to 6, 7, and 8. IRMA 2 randomized 611 subjects with type 2 diabetes and microalbuminuria to placebo or irbesartan, two doses, for 2 years. The primary endpoint was time to progression to overt proteinuria, and the analysis plan compared each active arm to placebo. The results ordered by dose, but

only the 300 milligram dose group was statistically significantly different from placebo.

Number 6. Comment on the handling and implications of premature withdrawal of 166 patients, 27 percent.

JoAnn?

DR. LINDENFELD: Well, patients who reached the endpoint of overt nephropathy were withdrawn. The implication, of course, is that that makes it difficult for us to see ultimately effects on GFR.

DR. BORER: What does that do to your level of --

DR. LINDENFELD: That's coming up, I think, in another question. But it makes it difficult on the basis of the data to presume that a reduction in proteinuria reflects a change in creatinine clearance.

DR. BORER: Any other comments on that point?

(No response.)

DR. BORER: No? Then let's go on to number 7.

There was a trend toward a greater increase in the rate of change in serum creatinine on irbesartan than on placebo. Comment on the hypothesized relationship between proteinuria and renal function as evidenced by creatinine clearance.

DR. LINDENFELD: I think I would make the same

comment again. This data just doesn't allow us to make a relationship between proteinuria and creatinine clearance.

DR. BORER: That answer certainly stands.

I think -- and perhaps you don't think it's worth doing this, but I think the issue that Ray may be getting to us about is that the 300 milligram dose caused a greater fall in creatinine clearance than the 150 milligram dose or than placebo. And we heard that that may be a good thing. What do you think about that?

DR. LINDENFELD: Well, as I understand the explanation, that was an early effect and then stabilized after that early effect. I'm not concerned about that effect.

DR. BORER: Number 8. A 133-subject subgroup was randomized to have GFR measured at 3 months, at the end of active treatments, and then 4 weeks after the last dose. At 3 months and at the end of active treatment, there were no statistically significant differences in GFR between placebo and either dose of irbesartan. 4 weeks after the last dose, GFR increased in all three treatment groups. Differences from placebo were again statistically non-significant, or perhaps not statistically significant. Comment on the hypothesized relationship between proteinuria and renal function as evidenced by GFR.

I think it might be fair, unless Ray doesn't

think it's fair, for us to include in that discussion not just the GFR substudy, but the other data that we saw for the entire group.

DR. LINDENFELD: I would comment here that we've seen a lot of information suggesting that the changes we would see with angiotensin receptor blockers are likely to be permanent changes, or at least if not reversal of the underlying disease, prevention of advancement of the underlying disease. And when one removes the irbesartan, at least the 150 milligram dose, and sees a return right back up to placebo levels, that makes us think that this was a hemodynamic effect of some sort rather than perhaps a clear-cut change which we would expect to see longer. It can't just be a blood pressure change, the fact that the blood pressure was allowed to go up, because we didn't see that same thing happen in the 300 milligram group. So, on the other hand, the 300 milligram irbesartan group did have a persistent lowering.

So, it doesn't help me. It certainly doesn't add to this relationship between proteinuria and GFR, but I don't know that it subtracts from it either.

DR. BORER: How about the relationship between irbesartan and ARB and proteinuria? I think one of the thrusts of the question here may be does the delay in any loss of apparent stabilization of proteinuria with a 300

milligram dose, after you stop the 300 milligram dose, give you any sense of the action of irbesartan compared to placebo, for example.

DR. LINDENFELD: Maybe I'm not quite understanding this question. Why don't you repeat it or rephrase it for me.

DR. BORER: My understanding of these data are that they were shown to us to suggest that because proteinuria didn't return even really towards baseline 4 weeks after stopping the 300 milligram dose, that in fact there was some protective effect that was maintained after stopping the drug, as compared with placebo or the lower dose where things moved back towards baseline. And should we draw any inferences from that finding about the activity or presence of beneficial activity of irbesartan?

DR. LINDENFELD: Well, I think it's marginally helpful. I'm concerned. I would have liked to have not seen the 150 milligram group go right back up to the placebo level. So, the 300 alone -- you know, if we had a 250, what would that have done? It's helpful but it's not enormously persuasive.

DR. BORER: Dr. Kopp?

DR. KOPP: Well, I think the sponsor was careful not to speculate, but I won't be so careful. So, one possibility is that the low dose is operating purely

hemodynamically and the higher dose has some additional structural effect, even an antifibrotic, not just a stabilization effect. So, one possibility is that during this time of suppression of angiotensin II activity, TGF-beta, and so forth, there's the possibility for some remodeling to have occurred so that structurally you're better off at 24 months, even without the drug, that you were at the beginning. Obviously, without biopsies, who knows? But it does suggest there's some structural benefit, not just stabilization.

Either that, or 4 weeks wasn't long enough and there's some residual effect that is clearly -- in that situation, I'm not saying there are drug levels around but some change in cellular phenotype has been maintained that doesn't reverse. Of course, it would be nice to see the same thing at 3 months. That wasn't done.

But I think it is favorable that 300 milligrams had a long-term effect even in the absence of the drug for 1 month.

DR. LIPICKY: But you have answered the question I think unless you want to discuss it some more.

DR. BORER: We do. Bev?

DR. LORELL: I think that at first, in hearing the discussion today, there did seem to be some disconnect between the behavior of microalbuminuria and creatinine

clearance. But I think, on the other hand, the point was made in the discussion as an hypothesis for which there is support, that the somewhat disparate behavior of creatinine clearance may have been related to hyperfiltration associated with hypertension in removing that component of hyperfiltration.

But I actually did find it both interesting and supportive that, in terms of looking at the primary endpoint of microalbuminuria, that that benefit was not only persistent but appeared to even go in the improvement direction with stopping the drug for 4 weeks.

DR. BORER: Well, let's go on to number 9 and here's another one where we have to make a statement into the microphone.

Are the results of IDNT plus IRMA 2 an adequate basis for approval of irbesartan for the treatment of -- however you want to say it -- hypertensive patients, or if you don't want to be hypertensive, then any patients, who have type 2 diabetic nephropathy?

JoAnn, why don't you start and we'll go around the table again.

DR. LINDENFELD: This is obviously a difficult question. I would answer no to this. I think that the IRMA data is supportive, but it's not quite enough additional data, given the things we discussed in the IDNT

study. It's not yet quite enough additional data to make me feel comfortable that all the data we have is convincing.

DR. BORER: Why don't we start on the other side this time. Mike?

DR. ARTMAN: I actually liked the IRMA 2 trial a lot better. I thought the rationale, I thought the data were compelling. And, yes, there is this disconnect between the early direction of the creatinine clearance. That was at the same time that there was the greatest reduction in microalbuminuria. So, I think those data are compelling. However, I don't believe that they're robust enough for me to support the approval. So, I would agree with JoAnn and say no on this one.

DR. BORER: Tom?

DR. ARTMAN: One more comment. I do think that if we are going to approve an indication, it has to be for the population from which the data were gathered. So, I agree strongly that it would have to include the word hypertensive patients, and I'm surprised that Ray, who has taught us again not to stray from the study population, would try to sneak that in.

DR. BORER: Tom?

DR. FLEMING: I think the IRMA 2 trial provides us evidence that there is an effect on progression for

microalbuminuria to proteinuria, and there is a lot of evidence. Dr. Lewis gave a very informative presentation about natural history and that this is an important step in the cascade of events that lead to very significant and important clinical consequences.

However, we have a myriad of examples and experiences to know that a correlate does not necessarily make a surrogate, that in fact now having a treatment-induced effect on that marker is reliable evidence of a treatment-induced effect on the clinical events that are down the cascade that we're really trying to prevent. We weren't even able to directly assess the next step, which is GFR rates.

My sense is IRMA 2 is informative. It establishes an effect on an important early phase marker that I believe does provide enhanced plausibility of efficacy. That type of data, though, typically in my view requires confirmation then in studies that would, in fact, more reliably demonstrate the effect.

We have one study which, in my own view, is on the edge of what would be strength of evidence for a single positive study. Now we're talking about a study on a marker. If the first study had been much closer to being convincing, I would have found the two together to be adequate, but a second study that establishes an effect on

a marker that does, in fact, provide enhanced plausibility of efficacy, but falls far short of what we would consider as strength of evidence for a single study for establishing benefit, that doesn't add in adequate strength of evidence to the first study to make it a convincing package from my perspective. So, the two studies I believe together wouldn't provide an adequate basis for approval. My vote would be no.

DR. BORER: Blase?

DR. CARABELLO: Essentially we've been told that this disease is a continuum, a trip from New York to San Francisco. And I think we clearly have the piece from New York to Cincinnati, and I believe IRMA 2. We have the trip from Chicago to Denver. I believe that the drug helps to prevent the doubling in creatinine. It's the Cincinnati to Chicago and Denver to San Francisco pieces that aren't there that I wish we had to complete the whole story that would make this a more convincing argument. So, I also would have to say no.

DR. BORER: Steve?

DR. NISSEN: We've got lots of examples where a drug may be effective at one phase of a disease process and not so effective in another phase, and that's why it's hard to put the two together because they don't support each other as much as they might if they were looking at a

similar population. So, that's the problem I have, is both studies taken separately are useful, but I find that I can't combine them in making any kind of reasonable decision because I'm not convinced that the process is the same early in the disease and late in the disease without more evidence that that's the case. So, my vote is no.

DR. BORER: Alan?

DR. HIRSCH: It's not often when we all sort of come to similar conclusions.

I think the two studies have great beauty and actually do provide great help in advancing future care for patients with renal disease. I'm impressed. And the goal, of course, is to change outcomes, so I will summarize again.

One, I do think we have a signal of efficacy in two separate trials. Yes, I think that IRMA 2 is supportive of IDNT in the sense that we've shown a signal that's positive. But again, I find these are different signals in different populations, and therefore I really have a hard time combining them.

Again, I would emphasize the natural history continuum. There's been vision in place in these things along the natural history, but I find each of the signals along the continuum to be just weak enough that I can't connect them, making the metaphor to crossing the country

by airplane. So, therefore, with two surrogates, an improvement in proteinuria and an improvement in doubling of creatinine, they would need to be linked yet again in my mind to a stronger clinical outcome to achieve approvability on their basis alone.

DR. BORER: Dr. Brem?

DR. BREM: It's difficult to top the community summation, and I certainly agree with it. Again, what's missing is the difference, the leap between advancement of microalbuminuria and change in renal function, which is what we all believe probably occurs, but hasn't been convincingly shown.

Based on just these two studies alone, in the absence of any other information, I would have to agree with my colleagues and vote no.

DR. KOPP: I would vote to approve. I think a couple of a points I'd like to make. One is that this is a continuous process histologically so that if you do a kidney biopsy of somebody in the microalbuminuric phase, it looks exactly like that of somebody in the later phase. So, there's no reason to think that the histology is different. In fact, there's reason to think that it's the same. It simply becomes progressively more severe, as you saw this morning, wider glomerular basement membranes, more mesangial matrix expansion. So, I think it is a continuum

of one disease.

Earlier I spoke against the first study, but I think I focused on the glass being half empty. I take it that the glass for the first study is half full. Admittedly, the p value is only .023. Although I found all elements of the primary composite endpoint to be convincing -- I'll go in the reverse order -- death, dialysis, and a creatinine of 6 I have no problem being very hard clinical endpoints as I think most of us did.

For me a doubling in serum creatinine is very worrisome and is, as I think Dr. Lewis was trying to make the case, more than just a surrogate but actually a measure of renal function such that in this disease, in particular, but really in most nephrotic conditions a certain sign that this patient is destined to progress absent further therapy.

So, I took the composite endpoint to be quite convincing, and my only limitation was that the p value was .023 with the caveats that if you argue about particular situations, it might drift to a .05.

The second study with the higher dose of irbesartan had a p value of less than .001. And I am convinced, as I say, that this is the same disease treated at two different points. I do take the comment over here that because we're studying two different points, they are

not exactly in support of one another, but I choose to focus on the other side that it's the same disease process we're treating, and so I vote to approve.

DR. BORER: Bev?

DR. LORELL: Thank you. I thought that the IRMA 2 study was really a very well-done and very beautifully presented study. I would view it as a supportive study and not as a second study of the same weight as the IDNT trial in terms of changing practice for a very large number of patients in the United States.

I would vote no. I think that that is very close. I would like to see additional supportive data for some of the harder endpoints that we discussed earlier around the table.

DR. CUNNINGHAM: Well, I think I see the glass as being maybe one-third full. I think it's also supportive and somewhat convincing.

But I have to say, as a person who's sitting in the consumer seat, that what I see as the real problem here is the drug that wasn't study, that being the ACE inhibitors. And I think from the consumer perspective, that's really what we'd like to see the data on. So, my vote is no.

DR. BORER: Just as a point of clarification, we all would like to see that I think, but we're really

being asked to judge this application not what --

DR. CUNNINGHAM: I realized that. That's why I said no. But I wanted to put on the record somewhere along the way that that was my view.

DR. BORER: Okay.

I'm right on the borderline, but not to presage any final comment here, as we go down the question, I'm at this point still on the minimally negative side. I agree with everything that Dr. Kopp said. I believe that IRMA 2 deals with the effects of this agent on the same disease at a different point and it's very positive. It would be lovely if we had the GFR data, and as a non-nephrologist, it's probably not appropriate for me to make the jump from proteinuria data to GFR data, although I'd be willing to do it.

I'm not concerned that we don't have biopsies because I don't think we could get them. I think Beverly said it before, and I'm convinced by the information we were shown that we have enough information to be reasonably certain what the biopsies would show if we had them.

So, I think this study is strongly supportive and I think that it gets me right, just about, to the point where I'd be willing to vote for approval, but not quite. I'd like to see just a little bit more. Maybe those data are available or maybe that little bit more will become

clarified as we go down through these questions. So, I'll reluctantly, still at this at point, vote no.

With that, let's go on to number 10. A drug with a related mechanism of action, captopril, has an indication for diabetic nephropathy in patients with type 1 diabetes. The primary basis of that approval was the demonstration in a 409-subject 2-year study of a 51 percent reduction, p equals .004, in risk of doubling serum creatinine, and a 50 percent reduction, p equals .006, in risk of mortality or end-stage renal disease. Both effects were manifest in the first few months of treatment. Captopril also reduces the progression for microalbuminuria to overt proteinuria.

10. Are the results with captopril germane to a discussion of irbesartan? In particular, is nephropathy in type 1 diabetes enough like nephropathy in type 2 diabetes? And 10.2, are the pharmacological effects of captopril and irbesartan adequately similar?

JoAnn?

DR. LINDENFELD: I believe that we've heard enough today and seen in our background booklets that, yes, the nephropathies in these two types of diabetes are quite similar and would be expected to respond similarly.

In terms of the second point, of course, the pharmacological effects are not exactly the same. But I

believe that we've heard some data today and there's some data that exists that the effect on renal function is at least in great part an angiotensin effect. So, I think there are enough similar mechanisms to make the data with captopril helpful.

DR. BORER: Dr. Brem?

DR. BREM: I agree. Although there are obvious differences in the first captopril study that have been well described already in terms of age and blood pressure normalization, I believe that the basic progression of disease is probably similar enough in both models or both types of diabetes that it would be expected that both should behave and respond to treatment in a similar fashion. So, I think they are germane.

DR. BORER: Okay, that's a yes.

Dr. Kopp?

DR. KOPP: Yes, I think they are germane.

DR. BORER: Beverly?

DR. LORELL: I agree.

DR. BORER: Dr. Cunningham?

DR. CUNNINGHAM: I don't know if I'm convinced that the pharmacological effects are the same, but I think they're certainly useful.

DR. BORER: Do we need a more specific yes or no there?

DR. CUNNINGHAM: I guess yes then.

DR. BORER: Mike?

DR. ARTMAN: Well, yes, I think the results with captopril are germane, but I take exception with the pharmacological issues. I do not think we can equate irbesartan with an ACE inhibitor. I think there are differences in the pharmacology. There are certainly differences in the stimulation of AT I versus AT II receptors. Whether or not sort of this unopposed action of AT II receptors is good, bad, or ugly, I don't think we know. So, I don't think we can generalize the pharmacology of ACE inhibitors to that of the AT I receptor blockers.

DR. BORER: Tom?

DR. FLEMING: I defer to my clinical colleagues in interpreting the biological parallels. The data are confusing when one looks at them head to head, but I think we'll get into that in future questions.

DR. BORER: Blase?

DR. CARABELLO: Certainly the two drugs have some similarities and also some substantial differences, but I think the similarities probably outweigh the differences, so I would vote yes.

DR. BORER: Steve?

DR. NISSEN: I'm actually a little surprised by this discussion. It's tough enough to look at effect of a

drug when you have other drugs in the class and say, well, an effect is a class effect. Now, we're talking about two different classes of drugs, and so I'd want to have pretty good evidence that the effects are very, very similar before I'd extend that across drug classes, let alone within a class. And we've already seen in many examples where drugs in the same class don't have the same biological effect. So, I think it's a potentially dangerous precedent to say that two drugs that happen work through kind of similar mechanisms would have the same effect from two different classes, and I think we ought to be very careful here. So, my vote is no.

DR. BORER: Alan?

DR. HIRSCH: You are a strict constructionist. The words are relevant and germane. So, I think they're not identical, but they're certainly kissing cousins and relevant. I would say yes.

DR. BORER: I'm going to vote yes too. I've been convinced by the discussion that the nephropathy in type 1 and type 2 diabetes is sufficiently similar so that one should be able to draw inferences from one and apply them to the other.

And with regard to the pharmacological effects, I agree with everything Mike and Blase say. Steve, there are a number of differences here between ACE inhibitors and

angiotensin receptor blockers. And I'm on record as saying I don't know how drugs cause their clinical benefits.

Nonetheless, I think the fact is that both of these types of agents and both of these agents act on the same general system, and I think that, as Alan says, they're germane and relevant, though not identical. And I vote yes.

Number 11. If the results with captopril are relevant to irbesartan, are the results on protein excretion similar with respect to direction and magnitude? 11.2, are the results on doubling of creatinine similar with respect to direction and magnitude? Are the results on death or ESRD similar with respect to direction and magnitude? And if you say no to any of those or if you say yes, probably we ought to have an explanation of why.

JoAnn?

DR. LINDENFELD: I guess the key word here is similar, and I would say yes, they're similar. The effects are greater in the captopril trial, at least they were certainly greater on the doubling of creatinine. I think it was a 48 percent reduction as opposed to 33 percent, and greater in proteinuria and end-stage renal disease, somewhat greater. But the direction is very similar in all of these.

DR. BORER: Mike?

DR. ARTMAN: Yes. I think the directions are similar, but the magnitudes seem to be much greater with captopril than with irbesartan.

DR. BORER: Do you draw any inferences from that observation that you'd like to share with us?

DR. ARTMAN: No.

DR. BORER: Tom?

DR. FLEMING: Well, we're comparing results from different studies. That's always hazardous. Yet, I'm not persuaded that they're similar enough that I would say similar. If I chose, as best I could, a comparable endpoint, which would be dialysis, transplantation, and death, we're looking at an 11 or 12 or 13 percent reduction against a 50 percent reduction. That's getting to be an important difference. And the mortality, small numbers, in the captopril setting, but there was a 40-odd percent reduction in mortality and there was more than a 50 percent or about a 50 percent reduction in dialysis, whereas here there's no effect discernible in mortality; dialysis reduction is 20 percent. The setting is different to an extent, but then again, to the extent that the setting is different, it makes me less comfortable to extrapolate results from the other trial.

So, I'm not as knowledgeable as my colleagues about whether the biological phenomenon and pathways and

mechanisms of action are truly sufficiently parallel that we can really rely on a different trial and a different agent, but at least looking statistically at the evidence, I see a substantive difference in the magnitude of effects that are being estimated.

DR. BORER: Blase?

DR. CARABELLO: Yes, well, certainly the ACE inhibitors appear more effective, but there's been no head-to-head comparison. It's sort of like saying, well, one team beat another team by 50 points and the other one beat the other team by 20 points, and therefore the difference ought to be 70 points. And that's just not the way it works. So, I don't think I can draw very much from those differences.

DR. BORER: Does that mean that you think that they're relevant or not relevant?

DR. CARABELLO: I think that they are relevant, but I can't draw any differences between them.

DR. NISSEN: Again, I think it's a slippery slope here. You're talking about a disease. One is a disease of insulin deficiency. Another is a disease of insulin resistance. And how that plays out in the vascular system leading to the kinds of events that lead to mortality and morbidity in these patients is probably somewhat different. I think again we've got to be very

careful about setting that kind of precedent. I would not want to go on record as saying, well, something that works in type 1 diabetics should be inferred to work in type 2 diabetics because I do think the pathophysiology of the disease, not necessarily the kidney, but the disease overall is very different. I think, again, we ought to be very careful about the kind of precedents we set in these discussions because I think it sends potentially the wrong message.

DR. BORER: Alan?

DR. HIRSCH: Well, let me reemphasize sort of what Steve just said. Whereas I've been stating that I certainly believe they're relevant, we around this table can't ignore the similarities in directional trends. Now I'll go the other direction and say although we've as a group said that the magnitude of benefit in the captopril trial might at that time of history been due to the care given at that time or because less cardioprotective drugs were used or glycemic control was less intense than nowadays, all those things may be true, but I hesitate to make too much of a comparison because it's also possible that the diseases are not identical, that we really do have different molecular entities, we have different potential pharmacodynamic effects. Bradykinin does exist. There are known differences between what ACE inhibitors do and A2

antagonists do in tissue and to mRNA expressions.

And finally, there's the dose question. It's really hard to know at the end of the day how this dose of captopril in this population compares to this dose of irbesartan in this population. It's very hard to bring these together other than to say, yes, they're similar.

Yes, that's a no.

DR. BORER: I'm going to vote yes. I think they are relevant. I think the results are directionally generally similar, and the magnitudes obviously are not. But these are different trials in different patients at different times with different protocols, et cetera, and it's very hard for me to get too excited about that. I think that these results have an influence on the way I think about the results of the irbesartan trials, and I'm not going to quantify that.

With regard to the fact that they're different diseases, the patients had different diseases, type 1 and type 2 diabetes, they did. But, of course, we've been shown data suggesting that the nephropathy in type 1 and type 2 diabetes seems to be pretty similar, and we also have in our books data from the enalapril study in patients with type 2 diabetic nephropathy, though not hypertensive, so I'm going to be drawing a parallel from a different group. But patients with type 2 diabetic nephropathy

improved in at least one measure of their renal performance when they were on enalapril which is also an ACE inhibitor.

So, when I put all those facts together, those observations together, I have to say that I am influenced by the captopril data. The question is how much and how much do I have to be, but my answer is yes to 11.

Number 12. Did I miss somebody? I'm so sorry. Go ahead.

DR. BREM: I guess this half of the table doesn't count. Once the cardiologists have spoken, I guess that's the word.

(Laughter.)

DR. BREM: Obviously, I'll restate what you said. We're not comparing the true efficacy of the two agents with one another. We're just asked a straight question, are they in the same direction and are they consistent with one another? I think the answer is yes, they are consistent with one another. And I would say, for that reason, they're germane and relevant.

DR. KOPP: Yes. Without belaboring it, I would say yes. I think they're relevant and we'll come in a minute to decide are they a quarter of a study, a half of a study, one study.

DR. LORELL: I also believe they're relevant, and I'd like to comment on the two reasons why I think they

are.

I think the data presented today and, in fact, the slides that we were shown this morning which described the effect of placebo in the captopril trial and doubling of serum creatinine and the similar slide that was presented for placebo in the irbesartan data are extremely striking in that the event rate is almost identical at 48 months. So, it suggests that although, as you pointed out, one is type 1, the other is type 2 diabetics, that what the kidney is doing and seeing may be remarkably similar.

I think the data are also relevant for the point that Steve Nissen brought up earlier and that is although this may be somewhat disturbing and not ideal, I think the reality in the United States in clinical practice across the country is that patients who already have type 2 diabetic nephropathy are in large part being treated with off-label use with an ACE inhibitor.

So, with those two arguments for relevance, I think it is worrisome that the magnitude of benefit seemed to be so much stronger and more robust in the captopril study, albeit it was type 1 diabetics and non-hypertensives. That influences me perhaps, rightly or wrongly, in wishing to see a more robust data set for irbesartan or any other AT I receptor blocker since I think the impact of approval would be to profoundly change a

current, very widespread practice of use of ACE inhibitors.

DR. BORER: Was that a yes or a no vote?

DR. LORELL: It's a yes for relevance. It's a no that I don't think the results are similar in magnitude.

DR. BORER: Dr. Cunningham.

DR. CUNNINGHAM: I would agree. I think they are the same in direction, but the magnitude is very troubling.

Actually since it's my first time on the committee, I'm going to go back and say I do not really think that they're pharmacology the same, that the angiotensin receptor inhibitors are the same as the blockers. I think we don't know that. That actually was two questions. So, I might say yes to one and no to the other for 10.

DR. BORER: Number 12. Now, the key question here. Are the results of IDNT, IRMA 2, and prior expectations derived from the captopril database an adequate basis for approval of irbesartan for the treatment of either hypertensive or not hypertensive patients with type 2 diabetic nephropathy?

JoAnn?

DR. LINDENFELD: I believe they are. I would vote yes for this. It's close, though. But I'll tell you what. The IDNT trial is not perfect and it's not terribly

robust, but the IRMA trial supports it. I'm helped a little bit by the amlodipine data which at least lowered blood pressure, so we know this wasn't only a blood pressure effect in the IDNT trial.

And I believe that, while I agree with everything that's been said, that the two drugs, captopril and irbesartan, do not have entirely the same mechanism of action, in fact, could be very different, one of the pertinent mechanisms of action here is through angiotensin, and so they do share an important mechanism of action.

So, I am concerned by what Bev said that by approving this drug, we could change the standard of care, and there's a big concern here about the magnitude of benefit. But I'm not sure that can be our concern. If the drug meets the standard of approving, I don't think I can let that change my vote of yes for this.

DR. LIPICKY: Can you clarify a little bit? So, what you're saying is that your priors from captopril are enough to say that when you said no-no to the previous questions, that now you mean yes-yes. Did I say that right?

DR. LINDENFELD: No, you didn't. I said I still would say no-no for the first two questions, but what you've asked here is whether or not the data from captopril, because of at least some shared mechanisms,

would be enough to tip me over and say the totality of the data suggests that this should be approved. Then I would say yes.

DR. LIPICKY: But that's because you're convinced from the captopril trial that, in fact, there is class effect on the disease because this is a different class --

DR. LINDENFELD: Right.

DR. LIPICKY: -- so it's not even the same class. And it's a different disease.

So, I'm just trying to make sure I understand what you're saying. So, what you're saying is that although it's a different class, you're willing to buy an ACE inhibitor class effect on the captopril trial. There the delta in clinical events was 18 people I believe. Here it's 0, but in captopril it was 18. So, on that basis, you're willing to buy this also. Is that really what you're saying?

DR. BORER: Ray, always does this.

(Laughter.)

DR. LINDENFELD: I think what I'm saying is I was very, very close. I think there's a lot of really good data here in two good studies, and we've seen a pathophysiologic sequence for which there's a lot of data which I believe, and the fact that we have an awful lot of

data with ACE inhibitors that share a common mechanism tips me over to say that that's just enough more to say that this data now becomes in my view enough to say yes.

DR. FLEMING: Could I just ask for further clarification of this, following up on Ray? Can you give us some insights, just in a precedent-setting manner, of how we have done this in the past? I find this intriguing. We're looking at two pivotal studies and coming to a conclusion, and then we're searching for other relevant data which is certainly relevant to do so, moving outside of the class, though. Essentially is this then saying any agent within these two classes? How much are we extrapolating? Any agent within these two classes then largely would rely on the studies that had been done here, together with some surrogate endpoint data to then be an approval? I'd just like to have a sense of how this is playing out.

DR. TEMPLE: Well, we don't keep good track. First, let's stay within a class. The division pulled together the basis for approval of the various ACE inhibitors in congestive heart failure, and quite consistently we've approved those claims with p values between .05 and .01. Pretty consistently, usually one study. Now, that's because those are all the same pharmacology. So, that's one precedent.

Another might be said to be the recent approvable for Valheft, for valsartan. The committee divided closely on it. We reached a somewhat different conclusion. I don't even want to blame anybody else for it. I reached the somewhat different conclusion based on a subset analysis, but clearly influenced, I would say, by the similar pharmacology and a particularly persuasive subset. So, I don't want to over-attribute it.

But I think the answer is you are allowed to let these things -- think of them as priors or think of them as mechanistic explanations -- influence you. The reason we bring hard questions like this to advisory committees is that it's very hard to pin down exactly what you're doing when you do it. They surely come into the category of what confirmatory evidence might be under the words that the law uses, although we've certainly never pinned down what that means exactly. What I heard JoAnn say was she was sort of here and she got pushed over by the amlodipine comparison and these data, and I think that's how people actually think. They put it all together. Obviously people can disagree on what the right conclusion is.

DR. LIPICKY: If I might contribute to that a little bit because this is really a very difficult issue. For a precedent, we have approved for congestive heart

failure captopril on the basis of a single trial for exercise tolerance, a p of .0048 or something like that. So, precedent -- that is, what have you approved things for in the past -- may or may not be useful. I don't think we would do that ever again at this point for that disease because, indeed, there have been things learned.

But indeed, nephrologists, as you have heard today in very elegant presentations, would pull all of this stuff together, including captopril, and have it influence their thinking process. Well, are we to say nephrologists are crazy and they don't think right? I'd be happy to say that --

DR. BORER: Remember that you were called a nephrologist earlier.

(Laughter.)

DR. LIPICKY: So, this is all a matter of judgment and I think it is not necessary to ask the question what are the precedents because I think the precedents only say what have you done and you may have done wrong things. So, there's the logic of it.

DR. FLEMING: One does struggle, though, to see if there is a logical consistency. Severe sepsis, a major FDA recent issue in December where this issue went in the other direction. A study that looked pretty good, but everything else had been negative, and FDA went ahead and

approved, more or less, saying it's this study even if everything else had been negative.

Now we're hearing -- well, we don't know what we're hearing yet, but I guess what we're being asked to discuss is if there is a study that's out there that's positive that shows a considerably different effect, actually more positive, which actually could pull us in the right direction, but it looks very different and it's a different class, that we should be persuaded by that. One would like to be scientifically consistent when one thinks through the strength of evidence you would have to see to approve an agent.

DR. TEMPLE: Sometimes a very strong result in a single study, even in the face of past failures, is convincing. And in the sepsis case you describe, I think that was the basis for it there and the others were not persuasively negative. They were persuasively --

DR. FLEMING: The committee was 10 to 10 in the vote on that one study.

DR. TEMPLE: Well, I mean, obviously they're going to be close. The p was .005. That's either strong or weak, depending on your attitude.

DR. LINDENFELD: One other thing here is we haven't seen any data, I don't think, that suggests to us that this doesn't work. It may not be strong in any single

study or any single area, but we haven't seen anything that suggests that it's unlikely to work. And that influences me a bit.

DR. BORER: Steve, a final comment and we'll go on.

DR. NISSEN: Yes. I guess, JoAnn, the problem with that is that if we make a decision to approve, it has consequences, and I think I know what those consequences are and I think we better face that. And that is, that some of the patients currently treated on ACE inhibitors are going to be switched over to irbesartan. Do we think that's a good thing or a bad thing? Do we think there's enough evidence here to tell physicians that we're now going to approve this agent, the first agent to be approved for this purpose, and the standard of care, whether it's right or wrong -- I know it's off-label. But this drug is going to get detailed and people are going to be told, listen, don't give your patient lisinopril. Give your patient irbesartan because we have FDA approval for this indication. Do we really want to do that? And if we do, let's vote for it, but I don't think I want to do that.

DR. LINDENFELD: That's a really important issue, but that issue wouldn't change if we had larger numbers with the same reduction in creatinine doubling and the p value were stronger.

DR. NISSEN: Right.

DR. LINDENFELD: That wouldn't change that. The fact that you think that an ACE inhibitor is better than this drug -- if we just had even stronger data for this drug but it still appeared that it was less effective than captopril, you'd still be in the same bind.

DR. NISSEN: No, but in the presence of weak evidence, then do we really want to change the standard of practice, which is one of the things -- that's one of the effects of what we do, fortunately or unfortunately.

DR. BORER: In fact, the FDA doesn't define standard of practice. Guidelines committees do. And my guess is that the impact will not be quite so great as that on patients who are being treated one way or another way because there are biases in the minds of every nephrologist I would guess. I think all we're being asked to say here is do we believe this stuff works or do we not, as JoAnn says.

Having said that unless, Dr. Temple, you had another comment --

DR. TEMPLE: Well, if there were mountains of evidence that all the other ACE inhibitors did what you want, you could wonder about that. But in fact, what you've got is captopril and everybody uses something else, I'll bet, because they want a once-a-day drug.

DR. BORER: Dr. Brem? We've had one vote yes for approval based on these three separate sources.

DR. BREM: Well, I've heard these three separate sources, but I've also heard references to outside sources, including the enalapril study. So, if one is going to be consistent and use outside sources like the enalapril study, then I suppose we can say we can use the outside source that was the losartan study which is the same class of agent as this, showing virtually the same findings as what was presented all through today. So, I would say if you're going to be fair, you're fair for everybody on both sides. And it would be supportive evidence, albeit it we haven't gone through the same detail as what was discussed today, but it's certainly consistent both in magnitude and direction. And it is further supportive data for approval in my opinion.

DR. BORER: So, is that a yes?

DR. BREM: Yes. It would be a vote for approval.

DR. KOPP: Well, not surprisingly, I say yes again, and I'll stop there.

DR. LORELL: I'm going to address question 12 very narrowly, exactly as stated, and I view that the prior expectations from the captopril database in fact are not an adequate basis for approval. And I'll restate briefly what

I said a few minutes earlier, that I think using the terminology that Dr. Pfeffer raised earlier that observations are hypothesis-generating, I think the remarkable difference in the magnitude of effect, as well as the time of appearance of effect, in the captopril studies, the benefit, the curves diverge much earlier. I think it's hypothesis-generating that in fact the two drugs may not be identical and may have quite different magnitude of effects. We don't know that because that study has not been done. So, strictly answering question number 12, the prior expectations derived from the captopril data for me do not push over toward an adequate basis for approval.

DR. CUNNINGHAM: My answer would be no too. I think from the consumer perspective, I really worry that if the standard of practice currently is using angiotensin inhibitors, approval of this could actually move people to use a drug which might be less effective for which we don't have enough data. Unfortunately again, the issue is we don't have the data we need really to help the people who have this. I think having renal failure is a dreadful problem and dialysis is obviously a terrible thing to have to endure. Just we don't have the information we need. But no.

DR. ARTMAN: I'm kind of surprised at this whole discussion, and I wouldn't say no. I'd say, hell,

no.

(Laughter.)

DR. ARTMAN: I think that we're talking now about a different study population with the captopril, we're talking about a different class of drug. It's hard for me to weigh that in, in any sense, to strengthen my decision about irbesartan.

So, if we follow this to its logical conclusion, I guess we could begin to argue that maybe we should be recommending approval of captopril for type 2 diabetic nephropathy. I don't know. It just seems over the top to me, so I would say no.

DR. BORER: Tom?

DR. FLEMING: No. And I share your sense exactly. I do believe that it's relevant, when you're making a judgment about the effect of an intervention, to be aware of and take into account what is available on efficacy of interventions that are studied in related settings. Though, to be giving that substantial weight here, I would have wanted to have had a much more careful discussion about the captopril data, what the studies were, what any other studies were that would be relevant to this decision.

Appropriately we gave a great amount of attention to these two studies, and I believe with that

tremendous information we've been provided and in an intensive day of discussion, we have absorbed an awful lot of understanding. And even at that, there are a lot of complexities that are still difficult to fully understand.

To now be reaching out and asking this committee -- boy, in 15 years of being on innumerable advisory committees I can never remember being asked to essentially say if it's no, but now look at external data from other agents studied in other trials with all the complexities of understanding differences that you see across studies, across specific disease areas and classes of agents, that you would actually, without having any direct presentation and discussion of those other data, be asked to revise or reassess your assessment. It's very troubling to me. But I do appreciate the need for FDA to think about this, but it's troubling to me the process, that we're being asked to think about it after having focused almost exclusively on these two trials.

Based on that, I'd say no.

DR. BORER: Blase?

DR. CARABELLO: We are going to get to question 13, I assume.

DR. BORER: Yes, we will.

DR. CARABELLO: Okay. Having said that, then I will vote no on 12. I don't think that ACE inhibitors --

although I think their results are germane, I think there are still enough differences between the two classes that they don't persuade me enough on top of my previous arguments about why I thought the data wasn't strong enough and compelling. So, I'll vote no.

DR. BORER: Steve?

DR. NISSEN: I also will say no. I want to bring up one more time the fact that it's not like all the endpoints are all going in the same direction here. I've got to remind this committee that many patients that come into this process of nephropathy have cardiovascular disease and they tend to die of cardiovascular disease. When I see point estimates for cardiovascular death, myocardial infarction, and stroke, in comparison to amlodipine, go substantially in the wrong direction, I'm troubled. So, that takes away.

We talked about this external study kind of adding to our confidence. Well, there are things that take away from my confidence, and that substantially undermines my confidence in the benefit of irbesartan here.

So, I want more data before I'm willing to stick my neck that far out and say that this is good for people when I know the cardiovascular endpoints are such a prominent problem in this patient population.

DR. BORER: Alan?

DR. HIRSCH: I'll start off with my no, but I'll try to add something new as we as a panel face these decisions in the future.

I think we're all feeling uncomfortable because there are three things we're weighing. We're weighing this intrinsic data set for this particular ARB. You've heard our opinions about that. We're obviously weighing this need to consider precedent-setting if we want or don't want to do that. And then the third thing is how we think it will affect the market.

So, I'll just add, though I care a lot about how standards are set for clinical practice, I very well trust the renal community to make its guidelines. I think guideline committees are where the market and the practice standards will be set. That's not our role, though I care a lot.

Vis-a-vis precedent, I actually do care very much. I think Tom was getting to this, that we think as a group how we look at data and how we set precedent. Ray, we can ignore some bad past ones and maybe make better current ones.

So, with those two things in mind, looking at the first thing we usually do, which is this data set, I'll stay with no.

DR. BORER: I'm going to vote yes. I want to

point out to everybody that there's nothing in the label of this drug as it now exists, because it's an approved drug, that would preclude anyone from using it in a patient with hypertension who happens to have diabetic nephropathy. It's a drug for people with high blood pressure.

The issue of whether it actually is beneficial for the kidney disease, over and above that, is what we're talking about here. I'm convinced that it probably is, and I'm sufficiently convinced both by the two trials that we saw, taken in tandem, plus what inferences I'm going to draw from drugs of a different class, it's true. So that I think that in total these data are sufficient to allow me to believe that it's reasonable to treat patients for prevention of progression of their diabetic nephropathy, as well as for their hypertension. So, I'm going to vote yes.

I think that if, at the end of the day, because we have a couple more votes here, we still have a net no, as we do right at this moment, perhaps it would be useful to cite what other kinds of information we might want to see so the FDA could think about that. Maybe some of those data can be drawn from the existing database.

Having said that, let's go on to number 13. It doesn't require a stated vote for everyone. Are there results from other development programs that impact on approval of irbesartan for the treatment of type 2 diabetic

nephropathy?

JoAnn?

DR. LINDENFELD: Well, the RENAAL study certainly, although we've said that it's difficult for us to talk about that too much because we have not actually seen the data and what's published sometimes, it's been brought up, is not always the data, once we see an FDA analysis.

But again, there are other enalapril trials, other ACE inhibitor trials. While, again, these are different mechanisms, I think that there's a weight of data from a number of other things that there are shared mechanisms of benefit here in other trials. So, this would push me a little bit more, but I'm probably not the one to say too much here because I said yes already.

DR. BORER: Does anyone else want to add to that? Blase?

DR. CARABELLO: Yes. I think the RENAAL trial is compelling. I remember reading it in the New England Journal and saying, gee, isn't this interesting. A sartan works in type 2 diabetes, and thinking, gee, if I saw a second study that said that sartans worked, that I would probably be convinced. I realize the depth of plumbing of the data is different, but I do think it has an impact here and it has an impact on me.

DR. BORER: Steve?

DR. NISSEN: I really have to take exception to that. Again, I'm worried about precedent, and I'm worried about the slippery slope. We don't have the RENAAL data in front of us. One of the things I've learned in the last year or so on this committee is the data isn't always what it seems to be, and until you get a real look up close and personal at the data, you ought to be very careful. I don't know if that trial will ever be presented to this committee, but when it is, we ought to look at it with the same scrutiny and the same microscope we looked at the IDNT and the IRMA 2 data. In the absence of that kind of scrutiny, we ought to be very, very careful about the precedent of making decisions regarding data that is not on the table.

DR. FLEMING: One more comment? One more question?

DR. BORER: Tom?

DR. FLEMING: A question for Bob and Ray. You have said you've seen this data. We haven't had the data presented to us. Do you really want to go around the table and get our vote? You're certainly at liberty, since you've seen the data, to factor it in however you choose. Do you really want to go around the table and get our views on data that you didn't share with us?