pharmacologically, then we won't need electricity.

MEMBER HARRINGTON: Although, but, then, you've got to make the case, Mike, that there is an advantage to the drug therapy, as you say. And then you have to enter into what are the risks of the pharmacologic strategy versus what are the risks of the electrical strategy.

And if ultimately 30-plus percent of the drug patients are going to get the electrical strategy anyway, that needs to be considered in the totality of, is it worth it.

MEMBER LINCOFF: But, again, the hypothesis here was, I mean, we have never directly evaluated that. Maybe we should evaluate that assumption or examine that assumption because there is no question the electrical Cardioversion is better than any drug therapy. No drug therapy has ever approached the conversion rate.

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So I think that is an intrinsic assumption of this whole development effort. It doesn't mean we can't examine it because one could question whether or not these reasons why electricity may be less than, less desirable than, pharmacologic therapy could be questioned.

CHAIR HIATT: Well, we could propose other strategies, but that wouldn't be fair. I mean, you could have thought about maybe Cardioversion is a standard of care and it should be employed immediately.

I think Dr. Granger would disagree and say that, "No. It's okay to wait." So placebo is ethical and an appropriate decision and an appropriate thing for us to contemplate. But it still isn't -- you can't just take the two-hour drug period in isolation because other things happen to both groups and, therefore, that is a strategy, too.

So because we are trying to weigh

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risks and benefits and we have got very clean signals of efficacy very early on, the thing that I think is sort of absent a little bit from the material we had and is sort of getting filled in now is, what do these patients look like at 24 hours and 7 days when other standard therapies were employed? You can't divorce yourself from the fact that they will be employed.

DR. MASSIE: I wanted to look back at slide 46. This is the one that gives for the vernakalant group the success of Cardioversion by day and recognizing the numbers are smaller and it's a little bit scattered.

It does appear that we recognize there wasn't much efficacy beyond day seven. But, as it turns out, beginning at day three, we're down into the 25 to 30 percent success rate.

So it's day one and two, the ones that I actually didn't think existed, day one

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and two from the onset, where there is the big difference. And that's a bit of a concern.

The other concern about the slide is I see that this is ACT I and ACT IV. What happened to ACT III?

DR. LIU: I can offer some explanation. The two studies -- by the way, my name is Jeen Liu. I am the statistician from Astellas.

We had two pivotal studies: ACT I and ACT III. Both were designed to study the conversion rate in the short duration, short minute to three-hour to a seven-day.

So in ACT III, we actually didn't collect a specific time or number of days patients were in AFib. So that study didn't provide useful data to facilitate this analysis.

DR. MASSIE: But, of course, ACT IV is an uncontrolled study. And the question is, how sure are you about the time

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in ACT IV? People came in. They got converted. We have already said we don't really know how long these people are in AFib because they're not always symptomatic or they go through in and out periods.

But do we have the data from ACT I separately?

MEMBER HARRINGTON: I just want to clarify something you said. Did you say that you don't know the time of AF duration in ACT III? Because I'm looking at slide 41. And it says that to get into the trial, you had to have AF for 3 hours for 45 days. How did you determine that if you didn't collect it?

DR. PRITCHETT: This is Ed Pritchett.

Patients were classified, stratified into one of two bins. The experiment was done with two bins. There was a 3-hour to 7-day bin and a 7-day to 45 bin. That was the experiment that was done. Okay? The data about how long were you in atrial

fibrillation was collected in two of the trials, ACT I and ACT IV, which is shown here without placebo data.

So there is no placebo data in this curve. This is simply looking at conversion rates. You know, the experimental bin is shown there in the three-hour to seven-day window. And, you know, that was the primary efficacy analysis.

So what you are looking at is an exploratory analysis. What it shows is the longer you have been in atrial fibrillation, the less likely you are to convert. That's not a surprise. I mean, that is true of eery modality that we have to convert people. And it has been known since the beginning of time.

I mean, there is a sense that we learned this from goats in Maastricht, but in point of fact, this is in clinical observation that has been around for years. The longer you have been in atrial

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fibrillation, the less likely you are to convert by any more modality. And the more likely you are to go back into it.

So, I mean, I personally am intrigued by this data because I think it is quantitative support for what intuitively clinicians have known for a long time. But in point of fact, the experimental design here was the three-hour to seven-day window.

MEMBER HARRINGTON: So if it was so well-known and you were trying to quantify better what the relationship was between the time of the duration of AFib and subsequently the ability to convert, why would you just put it into two bins and not actually collect the actual value?

DR. PRITCHETT: Well, the reason for using two bins is you can stratify pretty easily on two bins.

MEMBER HARRINGTON: You can do that if you collect the absolute vale and you just stratify based on some cut point.

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DR. PRITCHETT: Well, you could do that, but you wind up with an awful lot of bins at that point and it becomes quite a lot more difficult to manage.

MEMBER HARRINGTON: No, no, no, it doesn't, I mean, if you say that the bin is zero to seven and then when you're randomizing people, everybody less than seven gets stratified on one bin and everybody more than seven gets stratified in the other. But was there any other reason why you wouldn't have collected the specific data?

DR. PRITCHETT: It simply wasn't done.

DR. MASSIE: So do you have --

DR. PRITCHETT: It was done in these two trials but not in the others.

DR. MASSIE: So do you have ACT I as an individual trial?

DR. LIU: Yes, yes. Actually, it's a similar analysis using only ACT I study. It is in the briefing document, 55,

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page 55. It's a slightly different methodology. I think if you look at the figure, you can reach the same conclusion.

If you want, we can project this. Why don't we project it, please?

DR. MASSIE: It's not quite as nice as a daily barr. It fit curves, but --

CHAIR HIATT: While we are trying to just stay sort of broad stroke and fill out some data, again, Dr. Harrington asked and I had a list, a little separate list here, of trying to kind of add up the bad stuff.

So on the safety side, you know, at 24 hours and 7 days -- and I think we could cut this a variety of ways but deaths, torsades, new heart failure, embolic events, bleeding events, those kinds of things.

If there's some way to summarize that so as we kind of get to the safety side of this, if we could sort of look at a consolidated -- these are low event rate

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numbers, but the actual exposure is relatively limited as well. If you just look at the first 24 hours in this whole development program, there are three patient-years of exposure.

So as you think about as we try and deliberate the safety side and maybe that won't come up for a few minutes, but if there is some way to kind of consolidate the number of sort of what we would typically look at in terms of cardiovascular, bleeding events?

DR. KITT: We don't have that analysis. What we have is all adverse events, which is found on table 16, which is within the first 24 hours. But our incidence rates of hemorrhagic or strokes were very low. And so they don't meet the criteria we used for this table.

CHAIR HIATT: I understand that, but they're low by definition.

DR. KITT: Right.

CHAIR HIATT: And we are going to

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try to extrapolate this experience. Again, I'll just emphasize three patient-years of exposure if you count the 24-hour window --

DR. KITT: Right.

CHAIR HIATT: -- and lower 1,000 patients to tens of thousands of patients being exposed a lot across the states. And so you have to take these low-frequency events and try to ask whether they really would contribute.

Dr. Ruskin I would applaud for doing the 95 percent confidence interval around some of those events because, in fact, it's not the point estimate necessarily we are worried about but the extremes of the risk.

And so if numerically you could just count them up, that would really be helpful. Drug plus placebo 24 hours, number of people dead. I know the MIs and strokes were not really seen but serious bleeding events, you know, some of these are a step

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down from what we usually typically look at at cardiovascular trials but new ventricular fibrillation, pulmonary edema, sinus arrest.

There are a lot of things kind of occurring on drug in very low numbers. If you start to add them up, you start to develop a sense of a bit of a safety concern.

And we're just looking for kind of a simple tabulation of the numbers. We're not going to try to extrapolate. And we could do that. We could come back to that if you would like.

DR. KITT: Okay. Yes. Please give us a second.

CHAIR HIATT: Yes. You bet. So we'll go to other questions and then --

DR. KOWEY: Dr. Hiatt, can I comment? I'm Peter Kowey. I'm an electrophysiologist in Philadelphia.

I completely agree with you that in order to increase your confidence about the incidence of adverse events that are

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uncommon, it would be good to increase the experience.

If you just try to do that by extending your period of observation, which is what you are suggesting, I think --

CHAIR HIATT: No, not really.

DR. KOWEY: Well, you are asking for data out to seven days, when the drug is very, very long gone.

I agree with you that we need more confidence with regard to these infrequent adverse events, but I think the way to do that is to increase the number of patients that get the drug.

CHAIR HIATT: I agree.

DR. KOWEY: And that's the rationale for what you saw for the postmarketing studies and further observations of safety because it's unique patient experiences that will teach you about the confidence intervals for torsade and the confidence intervals for hypotension, the

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things that we really need to know about.

So we'll do, obviously, what you suggest and do the best we can with it, but you have to understand that attribution to the drug past 24 hours, for example, at 7 days, even at 24 hours is tough, but at 7 days, it's really difficult.

And I want to make just one other point, if I might, while I'm up here. There has been a lot of discussion about the spontaneous conversion rates that might occur with atrial fibrillation. I agree that if you take an unselected AF population that comes into the emergency department, there's a fairly high spontaneous conversion rate.

As you saw in the clinical trials, the spontaneous conversion rates in the placebo groups was very low. The placebo conversion rates in the trials were single digits. Why was that? Even though these patients had atrial fibrillation of relatively short duration, the answer is that

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the investigators who were seeing the patients as the doctors, the patients, had a very good idea of which patients were going to spontaneously convert and probably didn't put them into the trial because it would have been a self-defeating thing to get people all signed up and then have them convert spontaneously to sinus rhythm.

So there had to be an investigator-imposed selection bias to enroll patients that were really the relevant patients for pharmacologic conversion because I have no other way to explain why three hours or one day of atrial fibrillation would be associated with a single digit spontaneous conversion rate. It doesn't jibe with the data that you heard. It doesn't make any sense.

DR. MASSIE: There was only a two-hour observation period. We're not talking about the data that we have been shown from other sources.

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DR. KOWEY: Well, if you look at all of the pharmacologic conversion studies, including the ibutilide data, where patients didn't get other therapies for 24 hours, -- and you will see some more of that tomorrow, by the way, -- the spontaneous conversion rates are still very, very low within that 24-hour observation period.

So it isn't just two hours. It really is 24 hours. And the conversion rates, spontaneous conversion rates, are very low.

CHAIR HIATT: Well, the numbers are what they are. Certainly we're not going to dispute that. Your earlier point I generally agree with that since this is not chronic therapy, the only way we are going to learn more about safety is by exposing more patients and that it is generally true that the 24-hour time frame probably reflects most of the safety at risk but not necessarily.

I mean, there could be thrombotic

events that could be precipitated during that time that might manifest out at seven days, but certainly that is going to be more robust.

Now, back to that thing, though. We're going to have numerically more of these events on drug than placebo. And that's the issue we are going to have to wrestle with, that there will be a numeric difference.

And I just wanted to ask the sponsor at some point to just kind of add up those things and so we could just look at them.

MR. MANGAL: My name is Brian Mangal. I'm the statistician with Cardio.

Just to go back to one of your earlier points about the size of the database and the amount of exposure we have, based on the 773 patients that we have exposed, we did look to see what the upper bound of the confidence limit would be around a rate of infrequent events. And we're 95 percent

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confident from the size of our database that we would be able to detect an infrequent adverse event rate of .4 percent or more.

DR. MASSIE: As long as we're assigning homework, as I remember, a substantial proportion, and I think I remember like 85 percent or so, of these patients were not enrolled in North America for the pivotal trials.

And I'm not sure that's right because I was looking through the various analyses. But I think management of atrial fibrillation is probably very practice-dependent and I suspect might be very different from country to country, although we had some things from the Euro Heart Survey and others that showed similarities as well.

What do we know about background therapy, background clinical conditions, baseline diagnoses, and all the rest across countries? And how relevant do you think

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this data is to the American population?

CHAIR HIATT: That's an excellent question. And, actually, another way to look at that and one of my questions was, is there a treatment by country interaction?

DR. KITT: There is no treatment by country interaction.

MEMBER HARRINGTON: The sizes of the boxes, though, will be small. Could you show us the data of first the enrollment by country? I know it's in the briefing book, but if you could put a slide up and show us the enrollment by country and then show us the primary endpoint, point estimate, and confidence intervals by country visually so that we can see that?

DR. MASSIE: But also I think most relevant to I guess what we will find out in a postmarketing study if that is done, background therapies of interest, diagnoses of interest, age. You know, I think there could be a lot of potential. And it would

certainly be reassuring if we didn't see a lot of differences between, say, that 15 percent North America and the other countries.

DR. KITT: We do not have a slide of enrollment by country, but I can tell you that in our ACT I study, 48 percent of the patients came from Denmark, 29 percent of the patients came from Canada, 14 percent came from Sweden, and 10 percent came from the U.S.

In ACT III, 39 percent of the patients came from Denmark, 18 percent came from Canada, and 18 percent came from the United States.

DR. MASSIE: Thirty-five to 40 percent from Canada and the U.S. for the 2 studies?

DR. KITT: Correct. Most of the patients came from the Scandinavian countries.

DR. MASSIE: More of concern to me

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would be -- well, that's important because that's not a small size -- the differences in the patients in their background therapies.

DR. PRITCHETT: Dr. Massie, this is Ed Pritchett again speaking.

I am not sure that we actually can parse that out very quickly from the studies, but remember that the published guidelines from the Heart Association are developed now jointly between the American Heart Association, the American College of Cardiology, and the European Society of Cardiology.

So at least the people who write guidelines have to come to some kind of more or less consensus about what they think ought to be done. Now, whether that is filtered down and managed in the practice level, we can't be sure, but at least in terms of what the guidelines say, the guidelines for Europe and the U.S. are the same now.

CHAIR HIATT: You know, I mean, I

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inferred that there was no treatment by country interaction. And, Barry, I think it's a really fair question. It might affect the generalizability of the findings to different populations, but it didn't appear to be a treatment effect driven by Europe versus U.S. or something like that. So it's probably relatively robust across a variety of sort of Western populations.

DR. MASSIE: Actually, the broader implication of my question is not really efficacy. And, of course, for these types of numbers, interaction testing is not going to really exclude much. It's very hard to have a treatment by country interaction done.

But I am more interested in the safety issues. That's why I am interested in the concomitant medications and other different practice things across countries.

I mean, what drugs are being used differently in the two countries? You know, what types of patients are being enrolled in

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the two countries? Rather than the effect, I am interested in the safety.

MEMBER KASKEL: Is there any data on how many patients might be receiving potassium supplements or status of their potassium homeostasis?

DR. KITT: Potassium had to be corrected prior to enrollment into the study. I think it needed to be at least 3.5 before they could be enrolled in the study.

MEMBER KASKEL: And also in the nonresponders, do we have any reason or any evidence as to why they might not respond to treatment? Is there anything there, a trend in nonresponders, that might be useful?

DR. KITT: I think it could be the duration of their atrial fibrillation, that patients with longer duration didn't respond.

DR. CANNON: Dr. Kitt, could you tell us more about the ACT II results? So these were the patients who had had CABG or other heart procedures, post-op patients. In

slide 53, you show the efficacy of vernakalant Cardioversion similar to what you saw in the ACT I, ACT III, and ACT IV populations at 90 minutes.

So I have two questions. One is, can you tell us about the durability of that response in the vernakalant-treated patients at even 6 hours or 24 hours? Was it similar to what you saw in ACT I, ACT III, and ACT IV? That's the first question.

And the second is, were adverse events and serious adverse events more frequent in that post-op population than it was in the non-postsurgical populations, particularly with regard to hypotension, bradycardia?

DR. KITT: Yes. Dr. Dickinson will answer that question.

DR. DICKINSON: Hi. I'm Garth Dickinson. I'm a medical consultant with Cardio.

Slide up, please. This slide

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shows you the Kaplan-Meier curve for conversion in ACT II. And the big difference in this study compared to our other trials was the placebo spontaneous conversion rate.

So it's 14 percent here versus 4 percent in all of our other trials. And I think this reflects the population. The post-cardiac surgery population tends to be a bit more unstable, flip back and forth. And you will also see that with the durability.

Next slide. So the durability out to 24 hours was 60 percent, 60 percent in both the vernakalant-treated group and in the placebo-treated group, those that spontaneously converted, very similar.

Can I have that other comparison slide? I think that's 35.

DR. CANNON: So in the vernakalant-treated patients who successfully cardioverted within 90 minutes, about a third reverted to site 2 atrial fibrillation in 6 hours roughly?

DR. DICKINSON: Yes.

DR. CANNON: Okay. That's another way of looking. What about the adverse events and serious adverse events in the ACT II population?

DR. DICKINSON: Okay. Just one. Can I have this slide up, just to show you one other thing just comparing to the literature? This is the ibutilide study. Basically what it shows is really an identical kind of population. At 24 hours, 60 percent of the patients who were converted to sinus rhythm are still in sinus rhythm, very similar. So I think it's population.

Slide up. And as far as serious adverse events are concerned, we had very few in the ACT II study, essentially one case of AV block, complete heart block, and one case of hypotension.

These both occurred at the time of the infusion. And their duration was less than ten minutes each. And they were

completely respondent.

DR. CANNON: Thank you.

MEMBER HARRINGTON: Dr. Kitt, you have shown us the data for the symptom scale. Can you tell us the methodology of how that was done? In other words, at 90 minutes, when the primary analysis was done, was the person doing the symptom assessment blinded to whether or not the patient was in sinus rhythm?

And, secondly, was the patient still blinded to whether or not he or she was in sinus rhythm? Did people tell them, "Well, you've converted successfully" and then the symptom score was done or help me understand that?

DR. KITT: We did not assess whether or not -- our primary endpoint was assessed by a clinical endpoint committee. And so that was what we based our primary endpoint. I don't know whether or not the nurse coordinator made any comment to the

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patient about what their rhythm was at that time.

MEMBER HARRINGTON: So the effort wasn't made to try to reduce that bias? You didn't instruct your investigators, "Look, at 90 minutes, we want you to deliver this symptom checklist. We want this to be done by someone without knowledge of the rhythm status"? You didn't do that specifically?

DR. KITT: We did not do that specifically.

CHAIR HIATT: So, again, Rob, to kind of key off some of your questions, another global question I had is that there was clear symptomatic benefit associated with this therapy, particularly around the conversion back to sinus. There were also clear adverse events, which are relatively short-lived.

I think I know the answer to this question, but I am posing this a bit as a rhetorical question that it would seem to me

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that if symptomatic relief is important in this kind of therapy, that having a balance of adverse events versus favorable symptomatic outcomes should be done in a global sort of assessment, you know, like an SF-36 or something like that.

So that it doesn't appear to me that the short-term adverse events really somehow outweighed the overall clinical benefit of the patients feeling better in sinus rhythm.

I just want to pose that to you. Did you think about that? I mean, was there any kind of concern that that might diminish the overall symptomatic benefit? Do you see where I am going with that?

DR. KITT: Dr. Pritchett I guess wants to address that. Thank you.

DR. PRITCHETT: The SF-36, as you know, is supposed to integrate how the patient felt over the last 30 days. So administering it at the end of 90 minutes

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would sort of -- if it really does that. And I'm not sure it does in patients with atrial fibrillation. But if it really does integrate what took place over the last 30 days, I don't think it would be particularly helpful here.

You know, I have been interested in the issue of symptoms with atrial fibrillation, asymptomatic atrial fibrillation, for a long time now. I wish we knew more. The state of the art is not very good.

We don't understand why some patients are symptomatic on some occasions and sometimes they're not or why they have one symptom on one occasion and a different symptom on another occasion or why one patient has one constellation of symptoms and another has another.

You know, the symptom checklist that was used here was very long. It had 17 items in it. And it covered a broad range of

things. And the reduction that you saw here was very simple. Just let's just say how many patients had no symptoms at these time points. We looked just at asymptomatic.

You can also add up the number of symptoms that a patient had. And you can compare those between groups. You can try and grade the symptoms between mild, moderate, and severe. That has been tried. But we're really stretching what we know when we try and do that.

I am quite impressed with the sort of consistency of the symptom outcome with the objective ECG outcome in these patients. And it's about as good as you are going to get right now.

CHAIR HIATT: Let me just follow up on that. I really applaud you all for looking at this aspect because it seems to me that it's an extremely important endpoint in that it did seem to track really fairly closely conversion, though I can pull it out

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in a minute. There was one figure where there was a little bit of a dissociation. It was on placebo that the conversion rates and the symptomatic benefits were a little out of synch.

Nevertheless, I would also say that I think that the symptomatic benefit far outweighs the adverse events on the drug. I was posing the question to see what you all thought, but --

DR. PRITCHETT: I think we need to do better, but it's where we are. I mean, this is the state of the art.

CHAIR HIATT: Yes. But, to finish off, there's clearly symptomatic benefit when you convert. And if you convert quicker on this drug, you are free of symptoms quicker. I think that seems unequivocal, but it also seems pretty clear that at 24 hours, once everybody has converted, they have about the same symptoms for it.

DR. PRITCHETT: Certainly, as we

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would expect.

CHAIR HIATT: Yes.

DR. PRITCHETT: I mean, if symptoms are associated with being in sinus rhythm, it shouldn't make a whole lot of difference about how you got there.

CHAIR HIATT: Correct.

DR. PRITCHETT: Okay.

CHAIR HIATT: And you would agree, then, that your symptom score largely reflects sinus rhythm?

DR. PRITCHETT: Yes.

DR. MASSIE: I just would like to return to the second case of the VFib, which has been explained and considered, at least by the investigator, as unrelated, despite the fast that it occurred two hours after the drug was given.

Do we know? It was a non-synchronized Cardioversion, which happens now and then. I have actually not experienced one causing VFib, but it could.

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Do we know when the shock was given in relationship to the QRS cycle? Do you have those recordings?

DR. KITT: No. No, we don't. It was a loose monitor. One of the leads had come loose, and the shock was a non-synchronized shock. And then the patient was immediately defibrillated back into sinus rhythm. That's all we know.

DR. MASSIE: So that I would have to say the conservative approach is given within two hours of the drug that this might not have happened had they not been on this drug.

DR. RUSKIN: Jeremy Ruskin, Boston. I wouldn't argue with that. I think it is a conservative thing to do. But the case doesn't fit any of the sort of classic fingerprint criteria of a drug-induced pro-arrhythmia.

And I looked at the intervals immediately prior to Cardioversion. The ECG

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during the shock is not available. But there is a 12-Lead immediately afterwards. And the QRS is not prolonged, and the QT is not prolonged.

So if it was a pro-arrhythmic effect of the drug, it was by some as-yet-unknown mechanism. And I wouldn't argue that that is possible, but it wasn't a result of any of the classically known pro-arrhythmic mechanisms, which would have had some manifestation on the ECG. And there were no spontaneous atrial arrhythmias before or after the shock.

So you can't exclude the possibility, but it doesn't have the fingerprint, the classic fingerprint, of a drug-induced event.

CHAIR HIATT: Thank you for that explanation. I think that we are often confronted with drug relatedness in clinical trials. And you often ask investigators to make those assessments, which I think are

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kind of worthless. They usually don't read the investigational brochures anyway.

But you know there are two ways of looking at it. One is to try to do what you did and try to ascribe causality, which I think is very helpful because, you know, there are some clearly sort of other disease-related deaths. They just happen to occur on drug. The other simple way to do that is to say there are more people dead on drug than not. You just can't write that off.

We're going to go just a little bit longer and then have the FDA presentation after lunch. I want to ask the sponsor about off-label use. There is this one death where there's clearly you give the drug, the patient dies. In that, then, there's a lot of hand waving about, well, that patient shouldn't have gotten the drug anyway. Okay.

And I know you are going to have sort of a postmarketing surveillance system

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and try to maintain some kind of a safety in its use. But I still worry a lot about off-label use. You know, I could see where more and more patients who are kind of post-MI could get this drug, more and more patients that might have other contraindications. And there could be more deaths, no matter what you try to do to limit the drug to the population study.

Can you comment on that beyond what you are going to say to me anyway, which is we got all that hard-wired with our postmarketing surveillance thing? Are you worried?

DR. KITT: Yes. I'm always worried when patients die in our clinical studies or when any patient dies after receiving a drug. I spent six years doing pharmacovigilance. So I am very concerned about any drug-related event.

I think the best that we can do is to clearly put it in our label that patients

who have an acute MI or ongoing ischemia should not receive this drug as well as our educational plan with our sales reps and our scientific liaisons when we start to physicians about use of this drug to make it very clear that there are certain patient populations who should not receive vernakalant.

CHAIR HIATT: Okay. Despite those efforts, do you think that could still happen; i.e., patients with critical aortic stenosis, patients with Class IV heart failure, patients who are post-MI by 48 hours? Is there still a measure of risk here that you can't mitigate?

DR. KITT: That's true of any drug. No matter how well you educate physicians, there will be misuse of that drug.

CHAIR HIATT: And in my mind with some other relatively recent examples, it's the off-label use that I worry about a lot

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because you know what the risk is in the population study.

DR. KITT: Dr. Kowey?

DR. KOWEY: Peter Kowey from Philadelphia.

The most commonly used drug in this country for AF termination is IV amiodarone. So if you're worried about off-label or unlabeled use, then we need to talk a long time about, first of all, what is the efficacy, which I can't begin to tell you. And second is what is the safety, and what is the dose? And what kinds of things should you monitor? And what do you follow up with?

So I am very concerned, as you are, about using drugs off-label, but the reason why I think this is an important initiative is an attempt to be able to instruct doctors about the proper use of a drug and what they can expect from it. We're not going to know everything.

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And the answer to your question is, of course, somebody could use it in the wrong patient, absolutely. But it's up to the sponsor, I think, to educate, to observe, and to prove that they can do the right thing. And you have to obviously make that decision. But I am very concerned about off-label use, as you are.

CHAIR HIATT: And just to follow up that comment, there are clearly other therapies out there that are probably far more risky and maybe far less efficacious.

DR. KOWEY: Oh, yes.

CHAIR HIATT: Yes. So --

DR. KOWEY: Including a drug that is labeled for the indication already --

CHAIR HIATT: Yes.

DR. KOWEY: -- that I can promise you that most doctors in the United States don't want to give because they are very concerned about its safety.

CHAIR HIATT: It's too bad we

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can't pass judgment on those drugs, too, but we can't.

DR. KOWEY: Well, you did.

CHAIR HIATT: I didn't.

DR. KOWEY: And I was actually the person that presented the information. So I'll take some responsibility. But ibutilide, for all of its worths, is a drug that is well-described. I think doctors understand its efficacy and they understand its safety. Whether they choose to use it or not is another issue, but there is no question that what we wrote in the label and what the FDA wanted in the label back when it was approved was highly appropriate information.

I think it has led to very safe use of that drug, although it's somewhat limited.

MEMBER HARRINGTON: Peter, so help me understand, then. There was a question I wanted to bring up since you just brought it

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up, the unmet need issue here. If we're talking about what the current practice is in the United States, help me understand that for 100 of the patients that would be potentially eligible for this therapy, how are they being treated now? Are the majority of them getting electrical Cardioversion or are the majority getting amiodarone? What are they getting?

DR. KOWEY: We actually have two large registries that are in progress that are attempting to look at this global use of drug for atrial fibrillation in the United States. So some of the stuff is not published yet, but I can give you a broad idea.

The numbers look like somewhere around 75 to 80 percent of patients are electrically converted in the United States versus about 20 to 25 percent who are pharmacologically converted presently.

That, by the way, is almost

completely reversed in Europe, where it's about 80 percent pharmacologic, at least as the initial strategy, followed by electrical conversion. So it's much different, as Dr. Hiatt implied earlier. I guess it was you, Bill, that said earlier about differences in countries. Maybe it was Bob. So there is a big difference between the two.

If you look at what drugs are used for pharmacologic conversion in the United States, by far the overwhelming winner is intravenous amiodarone. Intravenous amiodarone is used 25 times more frequently than ibutilide in the United States. So every one ibutilide shot, it's 25 IV amio shots in the United States. And there's a smattering of other drugs that are used: IV procainamide is one, oral propafenone and oral flecainide.

In Europe, intravenous 1C drugs are used very frequently. Flecainide and propafenone are available as parenteral drugs

in Europe. And they are the leaders in the European market.

MEMBER HARRINGTON: Do you think that IV amio is used because people ultimately see themselves as transitioning this patient to oral amiodarone?

DR. KOWEY: It's a big hook. A very large hook in amiodarone parenteral use is that. First of all, it's not terribly expensive. It's available. People think they know how to use it. And then, in addition, they know that they can make a very complete transition in therapy very soon after they have given the IV drug.

So yes, absolutely, positively oral is a big hook.

MEMBER HARRINGTON: Thank you.

DR. MASSIE: I think, you know, collecting more postmarketing data is really critical. The question is how it's done. Often it's done in the context of really intensive educational campaigns just where

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you're collecting the data, which could perhaps make it not representative of general use outside as well.

I think that this can't be a really simply registry, which is very tempting because any other registry gives you incomplete data. But, nonetheless, I think there are a lot of things we need to know about concomitant medicines and concomitant diagnoses.

And I would think that the case report form, at least in terms of baseline information, should not be very different from that from a major clinical trial. What you collect afterwards might be simpler, but it would still be adverse events and efficacy in Cardioversion.

I am concerned that the numbers remain relatively small, 2,000 patients suggested. And obviously the FDA would have a chance to discuss and figure out what they would want in such a registry as well. They

remain relatively small.

And I am concerned that they will not be representative of practice either, both by choice of locations and by attentive education that goes along with enrolling people in such types of postmarketing surveillance studies.

CHAIR HIATT: If we come to the end of the day and recommend the drug should be approved, then we will need to discuss that specifically, I think maybe formal observational studies using propensity-adjusted kinds of analyses because there are, in fact, lots of treatment options that one could select from.

I wasn't clear why ACT IV was not placebo-controlled. I just never understood why people would do that. All the bad stuff is now just on the drug.

Anyway, other questions?

MEMBER HARRINGTON: Just one more quick. Could Dr. Kitt define for us heart

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failure? You have made a point that the heart failure patients fared differently? Is this systolic heart failure or is this just all symptomatic heart failure? And do you have data that would allow you to parse out the systolic heart failures from the diastolic or the systolic-preserved heart failure?

DR. KITT: Congestive heart failure was simply defined as somebody who the patient who would come in and say, "I had heart failure." That's how it was defined.

MEMBER HARRINGTON: Not defined by ejection fraction or --

DR. KITT: In ACT III, we did collection ejection fractions in those patients who had an echocardiogram within the previous three months, but it's very limited data.

MEMBER HARRINGTON: How limited? I mean, of the patients with heart failure, what was the median ejection fraction?

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DR. KITT: Just a minute if we look to see if we can get that data for you.

MEMBER HARRINGTON: Because I am just trying to tease out the issue. If it's people who have a history of symptomatic heart failure, that is one issue. And, as Dr. Cannon and others noted in the earlier remarks, this is a population that has a lot of systolic preservation heart failure.

DR. KITT: Right, yes. Just a minute. Okay. Slide up, please. I think this probably also includes ACT IV. So here are our baseline characteristics by ejection fraction. We cut it off at those with greater than or less than n-50 percent. So here are our baseline characteristics on that population.

So clearly there is more history of congestive heart failure in patients with ejection fraction of less than 50, about 11 percent gave a history of congestive heart failure that had an ejection fraction greater

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than or equal to 50 percent.

Slide down, please.

CHAIR HIATT: This may seem an awfully detailed question. On your table 18, page 61, incidence of ventricular arrhythmia events, you know, I couldn't get the numbers to add up. In most of these tables, they did add up.

But if you look at the bottom of this table, I think these integrals are mutually exclusive, right: zero to 2 hours, 2 to 24. Zero to 24 is cumulative, then. So if you just take the 9 events on placebo plus 38, it doesn't add up to 41.

The other parts of the tables did add up, but I thought the ventricular arrhythmia differences might be important to explore.

DR. KITT: Patients could be counted more than once on this table. What we did was we summarized the Holter and the 12-Lead ECG, which were read, and as well as

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adverse events, which were read by different cardiologists. So one particular cardiologist could have called something one thing --

CHAIR HIATT: Okay.

DR. KITT: -- and somebody else could have called it something else.

CHAIR HIATT: All right.

MR. SIMON: I've been electro-cardioverted twice: one in '96 and one in about '99, I believe it is. And I was never given the option of pharmacologically converted. Number one, I am assuming that is just the doctor's preference and says to you, "That's it, patient. This is what you need."

With your drug, how would you get it on the market? How would you get it to the doctors, in other words, for them to prescribe it versus Cardioversion or ibutilide? I just want to see how it goes from if you get approval to usage by patients.

DR. KITT: I would foresee that if the drug gets approved, it would get on the hospital formulary. And obviously this is a medication that would be given in a hospital, in a monitored setting by physicians who are trained to do Cardioversion, such as cardiologists or electrophysiologists or ER physicians. Our sales force and our scientific liaisons would then educate those specific target audiences on the correct usage of vernakalant.

And then it would be up to the physician to decide based upon discussion with the patient and the patients' background, comorbidities, whether or not they would be a candidate for treatment with vernakalant.

I think the way I would probably foresee it being used would be that this would be an option that you could get tentative infusion, be observed, and then if you didn't convert, the second infusion can

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be given.

But while that is going on, if they believe that you need to get back into sinus rhythm, that may give them time to set up for electrical Cardioversion, getting an anesthesiologist or whatever available. And if you convert, then you don't need to undergo that electrical Cardioversion.

Dr. Kowey, did you --

DR. KOWEY: Yes. Peter Kowey again.

It's a superb question because it really does get down to the crux of how you translate an innovation in medicine to patient-level care. Obviously education is extraordinarily important.

And I think the company understands that there is a massive burden that they are assuming to educate physicians about how to use this particular drug in the context of the kind of care that they are already giving.

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The other thing I think is very important to remember is that we're talking about electrical conversion, a pharmacologic conversion, somehow like they're competing techniques, when, in reality, they are complementary. In many kinds of clinical practice, we will do exactly as Therese just said, which is we'll try a drug. And if the drug doesn't work, we have the option of doing something else, which is electrically converting the patient.

So I think it's much better to think about this drug as part of -- and I think Bob said it earlier -- a strategy, rather than that as a separate innovation that is coming out of the blue somewhere.

The physicians that are going to be using this are used to using drugs, and they are used to doing Cardioversions. And they are going to take this and employ it and integrate it into their care.

Will they use a lot of it? I

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guess if it works well and it's safe, yes. And if it doesn't, they won't. It will find its level in care, but it will be people who know what they're doing and have been doing this for a long time who will be using the drug and benefitting hopefully patients like you.

CHAIR HIATT: I think we're getting a bit near the end of the question session. We will have certainly more time to debate this this afternoon. Are there any other questions the Committee wants to ask of anyone before we perhaps adjourn for lunch?

(No response.)

CHAIR HIATT: If so, then I guess we're adjourned until -- let's give us an hour -- 1:20.

(Whereupon, a luncheon recess was taken at 12:20 p.m.)

OPEN PUBLIC HEARING

CHAIR HIATT: We're going to start with the open public hearing, which may be

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quick depending upon who might or might not be here for that, and that will allow us to transition to the FDA presentation.

So as you're all getting seated, I have to read this script. Bear with me here.

Both the Food & Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it's important to understand the context of an individual's presentation.

For this reason the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship you may have with the sponsor's product and if known its direct competitors.

For example this financial information may include the sponsor's payment

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of your travel, lodging or expenses in connection with your attendance at the meeting.

Likewise FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationship at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance on the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said in many instances and for many topics there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, so every participant is

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listened to carefully, and treated with dignity, courtesy and respect.

Therefore, please speak only when recognized by the chair. Thank you for your cooperation.

Are there any speakers at the open public hearing?

If there are, please come forward.

(No response)

CHAIR HIATT: Anybody out there want to say anything? Anything at all?

(No response)

All right, the open public hearing portion of this meeting has now been concluded. We will no longer take comments from the audience.

The committee will now turn its attention to address the task at hand, the careful consideration of data before the committee as well as the public comments.

So our next agenda item is the FDA presentation.

FDA PRESENTATION
VERNAKALANT FOR CONVERSION OF ATRIAL FIBRILLATION

DR. UNGER: Well, good afternoon everyone. I'm Ellis Unger. I'm the deputy director of the division of cardiovascular and renal products. And I'm very pleased to present FDA's perspective on vernakalant for conversion of atrial fibrillation.

And the points I'll be touching on will be the determination of benefit. And I'll try to speak some to this quandary of quantifying benefit in a setting where you have spontaneous conversion from atrial fib to sinus rhythm.

I'll speak some to the limitations of the data that we received, then I'll talk a bit about some special risks.

So if there is an elephant in the room, I guess this is the element. And basically here you are looking at the probability of converting from AF to sinus

rhythm versus time.

With the X axis only going out to a day, and the company did an excellent job of characterizing this part of the curve, basically from zero to two hours, and these data are made up, but they are pretty representative of what we found in the phase III trial.

So after two hours, 90 minutes, you have roughly 50 percent of patients converted. Placebo was 4 percent. But we've heard that over 24 hours that maybe half to two-thirds of patients in fact will convert spontaneously from atrial fibrillation to sinus rhythm.

However in this study, or in the vernakalant development program, after two hours other modalities were used to convert patients to atrial fibrillation.

If we had maybe more foresight we might have said, keep your hands off the patient for 24 hours. Nobody will be harmed

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by staying in atrial fibrillation for 24 hours. Let's see what happens. And in fact this may be what we would have observed, and the fact of the - in this case what actually happened was, at this point in time, many of these patients, because they received other modalities, they jumped up near in the 90 percent range, and so did these people.

But if we'd kept our hands off these patients, in fact these lines may have converged. So that is very problematic.

I can tell you that I performed the secondary review on these data and explored the efficacy data quite extensively. And I would say the data were in fact very robust to exploration. No question about this. I looked at various subgroups. I didn't prepare slides on it. But the efficacy was robust across multiple subgroups. It's in the document that you received in the briefing package. It's all in there, U.S., non-U.S.

It was very robust except for congestive heart failure, which sponsors explained earlier there are fewer data and the efficacy in fact is less striking.

So that's the situation that we have unfortunately.

In terms of congestive heart failure, my understanding of the data is that patients in ACT III, one of the two pivotal efficacy studies, those patients were specifically queried about congestive heart failure upon entry into the study, and the case report forms were designed to capture this information.

In ACT I, I believe the history was more spontaneous, past medical history, if they said congestive heart failure, it was written down. But it's ACT III where we actually have a good idea of background, congestive heart failure. And you see the percentage of patients here.

So in total there were only 17

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percent of the patients in ACT III with a history of congestive heart failure, and 23 patients total with congestive heart failure in ACT III received vernakalant.

It's not a great deal of experience.

Probably 30 years ago we wouldn't have cared too much about race as far as being generalizable from one race to another, efficacy and safety. And maybe after BiDil we care more about it.

But if we care about it, we certainly don't have any data, because 97.7 percent of the patients in the pivotal studies were Caucasian.

So this is an area where we have a knowledge gap.

Okay now in this slide I have shown the conversion rates by various durations of atrial fibrillation. So it was recorded when a patient had the first symptom. Then you could calculate the time

from when the first symptom was reported to when they actually received the drug.

So these are divided into bins by day. I placed the Ns down here in white, and probability of conversion is on the ordinate.

So within the first day, 65 percent, 60 percent, then 40 percent. And you can see after day three the efficacy falls off in a very significant way.

So roughly a fifth of the patients after day three convert with vernakalant within 90 minutes.

This, you have a 50 percent conversion rate out here between day six and seven, but that's based on four patients of who two converted. So not a lot of data.

This was the sponsor's slide, I believe this one is in the briefing package. We had asked the sponsor to do some kind of modeling to show us what the conversion rates were with respect to time in atrial fibrillation. And they obliged with this

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plot. This was based on a logistic regression model.

And you see what it looks like here. This is a slide people were asking for this morning, where I've taken those blue bars from the slide two slides ago and plotted them against the logistic regression done by the sponsor.

The sponsor showed essentially the same slide, but they included the data from ACT IV. ACT IV was an uncontrolled study. These are the ACT I data.

So my concern about this is, you could look at this graph casually. This is the probability of conversion, the middle line, with the confidence intervals above and below.

You could say, okay, day seven, it looks like about a 30 percent chance of converting. But the data don't really speak to that. I think this is a case where you have done some mathematical modeling, and you

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have a nice smooth curve, but it may not represent reality very well.

And so one question would be what the labeling might say. The bin as the sponsor described it was from a couple hours to seven days, and then seven days and beyond.

And if you look at the AAHA ACC guidelines for management of atrial fib there is a distinction made also at seven days.

But the actual data out here from four, five, six and seven days are pretty weak. So bear that in mind.

We wondered about the need for an additional of vernakalant in patients with heart failure. Again there weren't many patients, as I showed you earlier. There was cardiovascular depression in the animals at super-therapeutic doses. The sponsor showed you that this morning.

We had hypotension in some patients. Well, hypotension isn't magic.

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You have to understand what is underlying that, whether it's an effect on weight, or a vasodilator effect, it's a negative inotrope effect. There has to be some effect, but we don't actually understand what it is.

And patients with heart failure seem to be predisposed to developing hypotension.

So this is an area where I think more information would be of value.

Another question that comes to mind is monitoring. This is very important issue. We know that vernakalant prolongs the QT interval. The sponsor showed you some information about in terms of metabolism, and how it doesn't seem to affect the QT very much.

And I would agree with that. I would also say that the average doctor doesn't know whether a given patient is a rapid metabolizer or not. So it might be useful in 20 years, but it isn't very useful

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in 2007.

So we look at all of the data together, and we have to say something in labeling about how long a patient should be monitored after they receive one infusion or two infusions.

One proposal was one hour after one dose, and 90 minutes after two. I believe that was our clinical pharmacologist's recommendation. You could say monitor until the QT is normal. Maybe until the period of peak QT prolongation is passed. Or maybe some hybrid approach where you basically say monitor for so many minutes, or until clinically significant QT prolongation has passed. So that's something else we'd have to deal with.

The effect of the drug on atrial defibrillation threshold was a point of interest for us. The sponsor showed a slide, I'm not sure which one, but they showed you the median number of shots, which was one,

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and the median energy, which was 200 joules. That is not a particularly useful way of looking at this.

So I constructed what amounts to a dose response per energy and percent success in cardioversion. So this represents patients who received vernakalant and the whole slide basically is patients who received vernakalant, and it shows the success of cardioversion. But it's divided here. These patients basically had vernakalant on board. So this was within four hours of receiving vernakalant, and these bars depict success rate after by and large vernakalant levels had dropped.

And had there been an effect of the drug on atrial defibrillation thresholds, you would see a difference in success between vernakalant and placebo, and you don't.

So I think we are very satisfied that there is no effect of vernakalant, pro or con, on atrial defibrillation threshold.

A question though remains about ventricular defibrillation threshold. Obviously it's much less common to need to defibrillate somebody because of a ventricular arryhthmia, but clearly you need to be prepared to do it. It will happen, and we don't really know what the effect of the drug is on ventricular defibrillation threshold.

So in summary the evidence of efficacy as the primary endpoint was defined is strong, substantiated in two independent randomized controlled trials. And the results were robust to exploration.

But again the apparent effect size is largely a function of the study design. We said 90 minutes, in retrospect maybe that wasn't such a good idea. But that is the data that we have.

The safety concerns were discussed I think fairly by the company. torsades is a concern; hypotension, bradycardia and QT

prolongation. I can tell you that in some of the analyses you asked about this morning in terms of other drugs on board, different anti-rhythmic agents, I did those analyses very carefully. The problem is the subsets are pretty small. So if you want to know about people on sotalol you can look.

I was not struck by any signals in terms of safety problems in any particular subgroup based on medication use. But again the subgroups are limited in size.

We think more data would be helpful for patients with more advanced heart disease, and for nonwhites. And we would like to see the ventricular defibrillation threshold determined in preclinical studies.

And that's all I have. Thank you.

CHAIR HIATT: Thank you.

Questions from the committee?

DR. LINCOFF: I have several questions, if I can refer to some of your slides.

DR. UNGER: Okay.

DR. LINCOFF: On I guess it was the sixth slide, it was the one probability of converting versus duration of atrial fibrillation in ACT I.

DR. UNGER: Okay, I may need a little help here.

DR. LINCOFF: I think your sixth slide. So if you sum up those Ns that's 145 or close to that by my adding. Now there were more than 145 slides - I'm sorry, 145 patients, sorry. There were more than 145 patients who received active drug. So what is that, in that study?

DR. UNGER: In ACT I?

DR. LINCOFF: Are those just the successful numbers?

DR. UNGER: I would actually need my review document to tell you.

DR. LINCOFF: So then by that, less than half the patients were in the first day, 60 out of 145, day zero to one.

DR. UNGER: Right.

DR. LINCOFF: I just think that, because we keep coming back to what is reflected in your slide three, apparent effect size of treatments versus AF effect time prior to initiating others.

DR. UNGER: This?

DR. LINCOFF: You know I would challenge whether with no treatment that would be the case for anybody presenting after the first day.

Now we've said we don't have a lot of data. But realistically when patients come in that we see, not in the first couple of hours, but a couple of days out, and they usually don't spontaneous convert in the first day.

So I think this whole question of whether or not we needed - it would have been better to design - or we observe the patients for a full day, et cetera. I think that aside from patients who are showing up the

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first day, who represent what looks like roughly 40 percent of the patients in the study, I think most of these other patients would not have converted, at least within a day, maybe within a couple of days, maybe in a couple of weeks, but would not have converted in the first day if they had not received any treatment at all.

DR. UNGER: Another way to look at that, another way to interpret this, these patients selected themselves out. I mean these patients had had symptoms for two or three days, and had not spontaneously converted.

DR. LINCOFF: Right.

DR. UNGER: I agree.

DR. LINCOFF: So I think the odds are that they probably would not.

DR. UNGER: Probably less.

DR. LINCOFF: And then by the same token, sort of in terms of selection, where you talk about the lack of effect on atrial

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defibrillation, the threshold, you showed no difference between the before four hours, and the after four hours.

The patients who - but isn't there a selection bias here as well? In other words the patient who in the active treatment, in the active arm, the vernacular, those patients who then needed to go on to electrical cardioversion selected themselves - were selected in a way, that is that they failed the pharmacologic. So they may have had for whatever reason a more refractory arrhythmia. So to see the same defibrillation thresholds doesn't - it isn't the same as taking all patients, treating them with the drug, and then defibrillating them. Because the easy ones already fell out.

DR. UNGER: I think that's true. I think you could interpret this by saying, vernakalant doesn't worsen - makes it no worse. In actuality it's kind of easy to

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follow because about half the patients who got vernakalant converted, and almost none of the patients who got placebo converted. And most of those patients did in fact receive electrical cardioversion.

DR. LINCOFF: And then did convert later on?

DR. UNGER: Right, right. So the Ns for vernakalant are about half of what they are for placebo. And this is only people who were shocked.

DR. HARRINGTON: So as you've indicated, Dr. Unger, part of the challenge here will be, as it is all the time, is to weigh the risks and the benefits.

And as you've suggested the benefit is all pretty much concentrated up front, and particularly in the patients who have had a short duration in their arrhythmia. Is there any way, given the small event rates, that we can tease out where the risk occurs preferentially?

In other words is there any relationship between duration that you've been in AFib and risk of receiving the drug that you can tease out? Or are the event rates are just too small?

DR. UNGER: I think the event rates are pretty small. I did a number of subgroup analyses on safety, and I think they are not in that review document that I produced. But I did them. And I really didn't see - I did not do the specific analysis that you're mentioning, which is time in atrial fib. In part that's because that was only solicited for patients who were in I think ACT I, so you're only talking about half the patients, so it didn't seem worth doing.

And there was a question this morning about having a table of all the adverse events. The three tables in that review document, I think five, six and seven, that actually are all - I'm not suggesting you look at it this second - but they are

adverse events through 48 hours, common adverse events, severe adverse events, and serious adverse events.

So that may be helpful if the company can do their part of the homework.

CHAIR HIATT: Some question asked earlier that I'd like your opinion on is when you reviewed these data did you see any evidence of reduction in thromboembolic events, hemmorhagic events, hospitalizations, things like that, any kind of endpoint benefits that you saw from early chemical conversion?

I know the numbers are small, but did you see anything?

DR. UNGER: The numbers are small. The one thing I saw that was interesting was, there were complications. There were physical mechanical complications related to cardioversion, chest wall adverse events. I think the rate was 2.7 for placebo, and it was half of that - it was 1.4 percent - in

patients who received vernakalant. And in fact it converted half the patients. So it's kind of interesting.

But in terms of things that we really care about, embolic events, bleeding, no.

DR. HARRINGTON: So when I did look at the table it reminded me of a question I had this morning. And maybe the sponsor can help if you don't recall this.

One of the issues we talked about with Dr. Grainger is the challenge with electrical cardioversion is that you have to get anaesthesia, sedation, and some of the complications associated with that.

There is a significant increase here of nausea, which is also a complication of anaesthesia. Did the nausea lead to vomiting? Do you know? Or is this just a transient sense of GI upset?

Because vomiting would be a more serious side effect.

DR. UNGER: I think you would have to ask the company that.

DR. KITT: Not all the nausea lead to vomiting, but there was some; there was a slight increase in vomiting in the vernakalant group.

DR. HARRINGTON: So if nausea is roughly 7 - 8 percent, give me a sense of, is it half the nausea ends up vomiting?

DR. KITT: I think it's less than half.

DR. HARRINGTON: Less than half.

CHAIR HIATT: So just to reference the tables you mentioned, direct current cardioversion in the short term AF population, ACT I and III, Table 6, from the FDA document, at any time placebo 76 percent, vernakalant two doses, 63 percent.

So numerically less. And then you also commented that the drugs used weren't that different between two groups, right? So the other anti-arrhythmic drugs didn't seem

to differ a lot between the groups?

DR. UNGER: Well, not only did they not differ, but the adverse event profile didn't seem - within any given group in terms of concomitant medications received, there didn't appear to be important disparities in event rates.

DR. CANNON: Ellis, did you run across data, if you didn't, maybe the sponsor could help me with this, on duration of hospitalization? So were the patients treated with randomized vernakalant and successfully cardioverted, were they able to go home faster than, say, placebo randomized patients where they might have been more watchful, waiting, hoping for spontaneous cardioversion before doing something, whether it be electrical or ibutilide or whatever, and perhaps resulting in an overnight stay versus they might have gone home the same day with vernakalant.

Do we have any data on that?

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DR. UNGER: I'll Therese.

DR. KITT: We did not collect duration of hospitalization. If patients were stable they were allowed to be discharged within 24 hours after receiving vernakalant. They could be discharged as early as 20 hours afterwards, and we did not collect duration of hospitalization.

DR. MASSIE: I was going to - this is a little bit off the subject, but Bob just brought up something that I forgot, I think it's important, worth mentioning; probably not directly to your presentation.

But there is actually considerable data now and growing, and actually I authored a paper that is likely to come out fairly soon on racial differences in atrial fib, and I hadn't really thought of in that context.

But the racial differences we are talking about are prevalence of atrial fib, which are substantially lower in African-Americans, despite the fact that they should

have more risk factors.

We have analyzed the ALLHAT study. There are people from NIH that are involved in this. And it's up 30 - 40 percent just by equivalent levels or higher blood pressure. And we've seen the same thing in several heart failure trials.

So I don't know that that has any relevance to a drug effect or a conversion, but it does tell you that it's something that one would like to make sure that it looks the same in African-Americans, or find out whether it does or not later.

It has nothing to do with these particular issues. I am not aware of any data about cardioversion and things like that.

DR. UNGER: Well, I think if in any way it's a different disease in African-Americans, then we want to know. Different prevalence, I understand what you're saying; I'm not sure that means it's a different

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disease.

But they do have - I mean the risk factors, you would think that they would have at least as high a prevalence.

DR. MASSIE: No actually going back, I never really thought of this, but one of our coauthors went back to autopsy data which actually identified lower rates of atrial fib as a comorbid condition of people who died in African-Americans, despite what you would think is the most prevalent risk factor of all is hypertension.

DR. HARRINGTON: So could maybe since Barry and I were just starting to talk about that, could maybe Peter, Ed or Jeremy help us with that?

Is it the same disease in African-Americans as it is in Caucasians? Do we know? And should we care about the fact that there is, what did you say, 98 percent Caucasians in the data set?

DR. KOWEY: I think we are going to

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have to plead ignorance on this one. I agree with exactly what Barry said, which by the way, Barry, my recollection is that that is separated by gender; that is that African-American men have a pretty low incidence of atrial fibrillation, but women with hypertension, African-American women with hypertension, specifically with metabolic syndrome, actually have a fairly high incidence of AF.

DR. UNGER: I'd have to go back and look.

DR. MASSIE: Well go back and check your data, because that is the data that has come out of a lot of epidemiologic studies. I know that we treat a lot of African-American women that border our hospital. And it's an epidemic in our emergency department of AF.

But to answer your question, Bob, I don't think that we really have a handle on that at all. And I think anything we would

say would be speculative.

But I agree with what Ellis has said and what everybody has said, that clearly there is a need to study an African-American population specifically with this drug and this disease.

MR. SIMON: If I could ask one question with regard to your third slide.

No treatment versus drug. I hope I can say this correctly.

Was there data collected that showed patients who took any drug or no drug before treatment - no treatment I should say - and any drug or any treatment before the drug? Is there a relationship between no treatment and drug and the results? Does that make sense?

DR. UNGER: I think so. So you're asking whether drugs that were taken by patients before they showed up for the study, drugs that were in their systems, had any effect on whether they could be cardioverted

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with the drug or with placebo?

In the analyses that we did, we didn't see a difference. In other words, your chances of being cardioverted were about 50 percent almost no matter what, and that included drugs on board or not on board. Is that -

MR. SIMON: Yes, thank you.

CHAIR HIATT: Other questions?

I think if we deliberate our questions, as a committee, if the sponsor, Dr. Kitt, has some additional information to give us, this would be a good time to do it if that is convenient?

DR. KITT: Over the lunch break we created four or five slides to help address some of the issues that were raised by the committee.

Slide up, please.

I think one of the questions was, conversion based on country. And we've got this broken into two slides, ACT I and ACT

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III. So here is the conversion rate, all sites, 4 percent in our placebo group, and in ACT I it was a 52 percent conversion rates.

And here's the conversion rates by the different countries, essentially no difference. And the conversion by placebo. And the next slide shows ACT III again. And here's the conversion rates by country. Chile and Mexico, there were no patients who converted.

We were attempting to get non-Caucasians.

The next slide I think is the question you had asked about a sort of a cumulative efficacy, broken out by zero to two, two to 24, and 24 to seven days.

So here's our primary endpoint, the conversion rate of 51 percent versus 4. These are the number of patients in sinus rhythm now, at 24 hours, 86 and 83; and we did a 12 Lead ECG on day seven, so this actually represents day seven data, 73

percent of the vernakalant patients compared with 78 percent of the placebo patients.

And here is the percentage of patients that were asymptomatic at those time periods. Once again this would be the 90-minute time period, this is the 24-hour time period, and this is the seven day when we did our symptom checklist.

And this is the number of attempted electrical cardioversions. This is not successful cardioversions. So you'll see that because more patients converted with vernakalant, there were less attempts at cardioversion compared to placebo during this period.

And this is - this data here is a little - not quite so robust. This is other anti-rhythmics used. However, I don't know if that was given to maintain sinus rhythm, or if those were given to convert. But this is the data that we have that at 24 hours about 26 to 28 percent of the patients in our

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studies had received other anti-rhythmics.

CHAIR HIATT: Just leave that up for one second if you don't mind.

Great, thanks. That's very helpful.

DR. KITT: And then we put together a safety slide also at your request.

Next slide up please.

And here are the events you had asked about. So within the first seven days there were two deaths in the vernakalant group. The one patient with a critical aortic stenosis and the hypotension and ventricular fibrillation. And this patient here, who was the lady who had the dissecting aortic aneurysm.

CHAIR HIATT: You're just leaving out the assumed, attributable, possibly attributable deaths?

DR. KITT: Right, well, the only one that was considered related by the investigator was this one. So these are all

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not - these are not related. These are all events.

CHAIR HIATT: All right.

DR. KITT: We're ending here at seven days. There were the two reports of ventricular fibrillation that occurred within the first two hours. There was the one torsades that occurred within the two to 24 hours period, in the patient who had also received the ibutilide.

And then there were two reports within the 24 to seven day period, one in the vernakalant, and one in the placebo group.

Embolic events, which were strokes, one within the zero to 24 hour period, and three in the - three in each group. But remember, once again, this is a two to one randomization, so there is a higher incidence of stroke in the placebo group compared to the other vernakalant group.

And these are significant bleeds.

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So there are was one GI hemorrhage in the zero to two-hour time period. There was another bleed in the two to 24 hour period. And between 24 and seven days 1.3 percent in the vernakalant versus .6 percent in the placebo group.

Do you need that up a little longer?

DR. HARRINGTON: Are these events mutually exclusive? So the v-fibs, does that include the patient that died? Or are they two separate events?

DR. KITT: No, that is the same, this v-fib is the same patient here who died. They are not mutually exclusive.

DR. KITT: Okay, ready? Here I think is the last slide. And this is the incidence of congestive heart failure or pulmonary edema. Two reports within the first two hours within the vernakalant group; one in the two to 24; and then 24 to seven days one in two, and this is atrial - adverse

events of atrial fibrillation, 11 in the zero to two hour time period, five, one. And then eight and three out here.

And this is the total number - excuse me? Why did I say fib? Sorry, flutter.

And the serious adverse events, 2-1/2 percent in the vernakalant group compared with .6 percent in the zero to two hour time period. About 2 percent in the two to 24 compared with 3 percent; and then 24 to seven day, three and six percent.

DR. CANNON: I'm sorry, explain what the atrial flutter, what are you showing on that row?

DR. KITT: This is an adverse event of atrial flutter that developed after the administration of vernakalant.

DR. MASSIE: One of the things that bradycardia and hypotension were -

CHAIR HIATT: They did this on the fly and didn't pick all the things, but I

think that's extremely helpful. Is it possible to even get those last three slides printed up before the end of the day?

DR. KITT: We can get copies of those, yes.

CHAIR HIATT: Okay, that's extremely helpful.

Does the committee have more reactions to that information?

Thank you very much.

DR. KITT: All right, you're welcome.

CHAIR HIATT: Any other comments so far? I think the next part of the meeting we actually transition into the questions, which usually involves mostly deliberation within the committee.

But before we do that, Norman, any comments? Anyone from the sponsor have any - we will certainly continue a dialogue. I just wondered if anyone has any other general comments they'd like to make before we do

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this.

Michael, do you want to talk about process a little?

DR. LINCOFF: There's been a lot of talk, discussion here, about the symptoms, and whether or not we should be cardioverting, et cetera, which is all very relevant, but I think we need to focus on the issue here of sort of a one-day journey, or a two-hour journey really.

The destination for 80 percent of these patients was sinus rhythm. They just got there on different pathways.

And it seems to me, and I may be wrong, but the symptom status, the quality, et cetera, was ultimately dependent upon whether or not they achieved sinus rhythm.

So I think it's less of an issue for those, and more of an issue of what happened during those two hours.

What was the journey? Was one safer than the other, et cetera?

There is certainly controversy regarding whether or not in the net it's necessary to convert some patients, but I don't think that is something we are going to affect. Eighty percent of these patients were converted, one way or the other; mostly converted, very few spontaneously.

So I think, at least for this population of patients, it shows fairly clearly that the physicians wanted to convert these patients. They wanted them in normal sinus rhythm. Whether or not that's data driven; whether or not that's evidence-based medicine, that's the practice.

So given that that's the practice, and that the current available modality to do that is electrical cardioversion or ibutilide, for the most part, and overwhelmingly electrical cardioversion is favored, I think what - at this point what we need to focus on is whether or not it is a more unsafe journey one way or the other

using the drug as compared with electrical cardioversion, because in the end you are going to achieve the same effect.

And I think the issue in particular, we haven't talked about it much, but I'm concerned about the issues of hypotension, et cetera, and how those offset or balance out the advantages of not having to put a patient under sedation for cardioversion, having to deal with the fasting state and the relatively minor complications that happen as a result of cardioversion.

So at least in my mind that's where we ought to be focusing for the rest of this discussion on approval.

DR. HARRINGTON: I don't think - that's consistent with the way I'm thinking of sort of a strategy. I thought the pool information presented was very helpful, because the figures that I wrote down, if we are looking at the drug group versus the

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placebo group, a third of the drug patients get electrically cardioverted; two-thirds of the placebo group gets electrically cardioverted; and roughly the same percentage get some other anti-arrhythmic drug.

So yes, what happens in that first two hours is relatively safe, but you do have to say, what is it contributing to the overall - the totality of benefit for that journey to use your phrase?

So I don't disagree with that. I may disagree that the focus has got to be two hours, or 90 minutes.

CHAIR HIATT: Yes, I think we are trying to set ourselves up here to address some of these challenging questions. Because clearly in the context of what the sponsor has provided us we have very robust data, reasonable safety information.

Now I think actually it is significantly helped by looking at what the groups are looking like at 24 hours.

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But the questions are also going to focus on, does that matter? Does that have any outcome that patients need to have, because you converted them quicker with a drug and save them from cardioversion?

DR. HARRINGTON: Norm, this morning you said - you chose your words as expected very carefully, that you wanted us to consider the data and be less concerned with the policy issues and the precedent issues.

But can you give us some perspective as to how you came to this endpoint? Because a lot of what I think Bill's remarks are getting at is, do we think this endpoint matters? Or is that not our task?

DR. STOCKBRIDGE: No, I don't think that should be your task. If you think that this is the right way to develop a product in this area. And you can make a rational data-driven decision about the approval of a product based on a trial like this; that's

fine.

And if you think that wasn't a great idea, you should say what you think a reasonable basis for approval is, and what happens in terms of a regulatory decision here may not follow that. But at least we can figure out what a rational course would be.

DR. MASSIE: I'd like to add just, I mean this is a way of quantifying conversion, and I think it's as reasonable as any other.

I think in the future, if we are talking about that, there is a lot of data we'd like to collect in addition to knowing what happened at 90 days - I mean 90 minutes. I got my days and minutes confused.

And in addition it would be nice if there were some way to enroll a population in which we could look a little bit more about the natural history, early on, over a period of time. That may be unethical in

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