DR. CANNON: Is that really true? I'm looking at Table 23 and there's a patient H10 and a patient H12, and if I'm reading this correctly, "Time from start of first infusion to hypotension," both of these were about six hours.

DR. PRATT: So the H10 is the cholecystitis patient I mentioned.

DR. CANNON: Okay. I'm sorry. What about H12?

DR. PRATT: And H12 is placebo.

DR. CANNON: Oh, yes. Thanks.

CHAIR HIATT: But it seems that the -- perhaps the electrocardiologic and the hemodynamic effects of the drug are reasonably well characterized, which corresponds reasonably well to the PK of the drug, but we don't really have a sense of if there really are any outliers that might pose special safety concerns, but the population seems to be pretty well characterized, and, does this need to be adjusted for 2D6

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inhibitors or poor metabolizer phenotypes? Anybody vote for that?

(No audible response.)

CHAIR HIATT: I don't think so, not from what we saw.

Okay. Number 8, "How much of a safety concern is bradycardia?"

Yes, Michael?

DR. LINCOFF: Only to my mind, I wonder how many of the hypotensions were -- there are the hypotensive events and the bradycardia events in these tables. I don't know how many are the same patients because there aren't patient identifiers. So, to my concern, bradycardia would be of concern, if it was -- to the extent that it correlates with the hypotensive events.

DR. KITT: There were two.

CHAIR HIATT: And this is bradycardia that's being monitored, so how much of a concern is it? Not a big concern?

DR. MASSIE: Along Mike's point,

bradycardia is often a premonitory sign of death, or it could just be anything else, you know, so people get BGLed before they die. The aortic stenosis patient, I think, got bradycardic before they died, and then there's just bradycardia. You got lots of drugs? Well, they give you bradycardia, you know, so it's a little hard to know, but it's also a little bit hard to totally dismiss, and if it's with hypotension, then I think it has to be taken seriously.

DR. HARRINGTON: I mean if you just -- you know, these tables, these are concerning. I mean the heart rates are 30, 30, 36, 19, atropine, atropine, atropine, neosynephrine, atropine. These aren't -- I think somebody just said it, you know, these are the SAEs. I mean these are bad events and we've already made the comment that it's not a large sample size, so I would agree with Barry that I don't think we have these totally characterized because of the

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limitations of the infrequency and the small sample size, but the ones that have occurred aren't trivial in terms of their clinical meaningfulness.

DR. CANNON: Can I get clarity on this and the bradycardia? In looking at the paragraph on the top of page 67, is it true that the bradycardia associated with conversion to sinus rhythm as opposed to bradycardia with a patient who did not cardiovert, they remained in atrial fibrillation? It appears, in quickly reading this, that that frequency was no different from placebo, that the increased frequency of bradycardia was associated with conversion to sinus rhythm. Is that correct?

DR. KITT: Yes, that is correct. Can I have the slide up, please?

We did look at this and the incidence of bradycardia looking at adverse events and ECG Holter data defining a heart rate of less than 40 and there is a higher

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incidence of the vernakalant group compared to the placebo group. Once again, this is in our zero to two hour time period. And if you look at the number -- or the percentage of patients who converted to sinus rhythm after receiving vernakalant and had one of these events considered a bradycardic event, it was 7.8 percent, compared to none in the placebo group, but, please, once again, the numbers are small here. Only 15 patients in the placebo group converted to -- spontaneously converted to sinus rhythm. And then, when you look at the patients who remained in atrial fibrillation, it's four percent in the placebo group, 4.3 percent in the vernakalant group.

So we believe the excess bradycardia that we saw was due to conversion to sinus rhythm, and down here, this gives you the event of the bradycardia event post-conversion for those 21 patients, and you can see that 15 of those 21 patients had that

event of bradycardia occur in less than five minutes, four was in five to 15 minutes after converting to sinus rhythm, and in two, it was more than 15 minutes after converting to sinus rhythm. So we believe that the bradycardia is associated with conversion to sinus rhythm.

DR. LINCOFF: Well, that should be fairly easy to test. I mean you've disadvantaged yourself by confining this analysis to zero to two hours when essentially all the conversions were in the vernakalant group. So if you extend it out, we know that by 24 hours, virtually 80 percent or an equal number of patients have converted. So what were the bradycardic rates if you encompassed that entire time, which would then speak to the question of is it the conversion or is it the drug that causes the bradycardia.

DR. HARRINGTON: Well, then they should be equal, Mike, because at the end of

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24 hours, the same number of people are in sinus rhythm, but if you look at Table 21, which is 24 hours --

DR. LINCOFF: But that's zero to -- oh, that's 24. Okay, zero -- because Table 20 is zero to two hours.

DR. HARRINGTON: But Table 21 is the bradycardia SAEs within 24 hours and there's only two in the placebo group.

DR. LINCOFF: But -- so that had to lead to discontinuation of study drug, since after two hours, the study drug was done.

DR. HARRINGTON: Or an SAE.

DR. LINCOFF: Right, but I'm saying some of those -- I don't know how these were classified. Some of these may have been -- in other words, if they didn't stop -- if there wasn't a study drug to stop, it became an SAE by virtue of the fact that you had to change your therapy. If there was a study drug to stop, it may not -- the same

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event may not have qualified as an SAE.

DR. KITT: No, these were SAEs at either prolonged hospitalization or were considered medically important by the investigator.

DR. LINCOFF: So did you not have the same number that -- so what happened to all those people in the control group, in the placebo group, who converted between hours two and 24? Did they also experience bradycardic events?

DR. KITT: Slide up, please. I may need some help from my statistician on this.

So here is, once again, looking at the different data sources and here's the incidence of bradycardia in the placebo group, 11.1 percent versus 5.6 in the vernakalant group, comparing those who had electrical cardioversion/vernakalant versus those who received placebo and had successful electrical cardioversion versus other.

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DR. HARRINGTON: But what I'm still not sure of is that -- is the bradycardia different with the drug than it is with electrical cardioversion? Ellis, are you going to help us with this?

DR. UNGER: Yes, thanks. Let me just backtrack to one point in the briefing document, page 64. I'm not sure we would all agree with the definition of bradycardia that you used in terms of the adverse event data. If you look at the bullets there, you put in AV block, bundle branch blocks, and things like that. I'm not sure they necessarily mean bradycardia.

But I did an analysis using the AE data set and using all of the Holter and all of the AG data, every RR interval, and I have a license to explore the data, so this is good. And I looked at the zero to two hours after drug, and I also looked at zero to two hours after a shock and I looked at shocks with vernakalant onboard and with vernakalant

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not onboard, and there was a trend towards more bradycardia with vernakalant. Unfortunately, I don't have a slide and it wasn't in the document. It's on my flash drive and that doesn't help us here.

At any rate, there was slightly more bradycardia, but the inescapable fact was that there were more patients who received vernakalant who had SAEs for bradycardia and that's a regulatory definition of an SAE, and so, because of that, I think you just have to -- you know, myself, I err on the side of caution when I say there's more bradycardia, but, in fact, there was quite a bit of bradycardia just from a shock, within the two hours after a shock.

DR. MASSIE: But I'm just looking at that Table 21 and at least B2 and B12 and B13 occurred three hours, four hours, and five hours and 43 minutes after the study drug. They may have been related to

cardioversions at those times. One says attempted and two of them did happen, and there's one in placebo that also is four hours afterwards, but the numbers are small. I just think that this is not adequately defined and that, you know, I sort of have this lingering feeling that you may be happy that you monitored them in the long run, at least until you were more sure it's safe.

CHAIR HIATT: Yes, so trying to summarize that, it does sound like conversion is associated with cardioversion, that there may be a drug effect on top of that, and that, again, that just documents the importance of an adequate monitoring window.

Should we move on? Number 9, "How much of a safety concern are thromboembolic events, including strokes?"

So, actually, I think this additional analysis provided by the sponsor helps us and actually I think the embolic events at the -- well, if you go out to 24

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hours, there's reportedly one on placebo and none on vernakalant, and if you go out to 24 to 70 hours to seven days, the rates are 0.89 percent on placebo, 0.3439 percent on drug. So there doesn't appear to be a signal thromboembolic event. I mean we kind of hit that early in the discussion in terms of potential efficacy. So we could say that we don't know if there's a signal there of safety concern either.

Anybody disagree with that?

(No audible response.)

CHAIR HIATT: Are there other safety concerns?

DR. LINCOFF: Hypotension.

CHAIR HIATT: Hypotension. The one case, a sort of fatal VF, which might have been the wrong patient, but, still, they died, and it would seem to be really clearly drug-associated.

DR. HARRINGTON: Yes, so maybe -- could we talk about that?

CHAIR HIATT: Yes, please.

DR. HARRINGTON: So, as Mike pointed out and I was raising the question, and I don't know what is the chicken and the egg here, but the fact is that there was a patient who was -- who sounds pretty sick when he or she -- it was a he -- got into the trial, had critical AS. Whether or not that was known at the time he was randomized -- presumably it was, got hypotensive, and as we all know, when critical AS patients get hypotensive, it's very -- it can be -- they can get real sick, real fast, and then it degenerated into VF and death.

I worry greatly about how well the drug safety has been characterized in a group of patients that might get treated in everyday practice. I worry greatly about that.

CHAIR HIATT: Well, I raised similar concerns earlier in the morning, because I think as the -- as any drug gets

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deployed into the population, there are going to be sicker patients who will be exposed to the drug and there's a possibility that patients like this could have a drug-related death, directly linked to the drug being infused, and I think we talked about that earlier. Can you really mitigate against that? Perhaps partially, but not completely.

So that's an event that just stands out there, in my mind, as clearly something that had the strategy -- had that patient been randomized to placebo, I don't know what would have happened to them. They might have died anyway, but maybe 90 minutes later.

DR. MASSIE: You know, this -- unfortunately, not every -- I mean, I've watched, at least from a distance but not close enough distance, people who had come in with tachycardia and aortic stenosis given beta blockers and died. It's stupidity and malpractice, but it's associated with the

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drug, nonetheless. So I share your concern that -- but we were talking -- wasn't there something in the label or a proposed label about hemodynamically stable? I mean, I think there's a couple of things we -- you know, hemodynamic stability and now they're being conservative about heart failure. Well, I think, in fact, probably get -- minimize certain high-risk groups if people read the label. I mean that's, you know, of course, an issue, but I think those are concerns that one would have giving a drug that has some hemodynamic effects.

You know, what do you when somebody's going at 180 in AFib and, you know, their blood pressure's low? I don't -- I think I'd rather convert them electrically than give this drug, even though it's tempting to reach for it and give it. But -- so I think those things need to addressed in the label. Hemodynamic stability, you know, is, I think, important, and talking about --

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at least emphasizing the risk of heart failure or saying it's not for those patients.

DR. LINCOFF: And I'm not disagreeing that, clearly, patient selection is an issue, but this patient was 64. I don't know if his aortic stenosis was known. His blood pressure was normal 130/90 when he came in, and his troponin was elevated, but I don't know if they knew that, you know. So this wasn't a red -- one of these obvious, glaring red flags of, you know, hemodynamically markedly unstable patient. They may or may not have known about the aortic stenosis. Certainly we should be listening to patients' chests, but they don't always.

You could see this kind of thing happening fairly often, a relatively young guy comes in with a blood pressure that's okay and a heart rate of 150 beats per minute may fib and he gets treated this way. The

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only thing that you can fault in this management of that particular patient is he got profoundly hypotensive and he still got the second infusion and then became profoundly hypotensive, but --

CHAIR HIATT: See, I totally agree with that assessment. I just don't think we're -- I think there's the risk of possible direct drug-related events that could occur with this compound. Kitt?

DR. KITT: The investigator did know that he had critically aortic stenosis before they dosed him and they did give him both IV and oral metroprolol, following which he became hypotensive, which he required saline resuscitation. He got the first dose. He became once again severely hypotensive and they once again resuscitated him, and after they gave him that fluids, he actually was up and sitting in bed and then they went ahead and gave him the second dose, after which he had his fatal ventricular arrhythmia.

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So I don't know, if he had not received that second dose, once again, purely speculation what would have happened, but, you know, our -- the hypotension that we have seen in our clinical studies have all, except for, of course, this case, responded to stopping the infusion and giving them saline and is fairly readily reversible and manageable in a monitored setting.

CHAIR HIATT: Right, and I think, you know, having read all that information, too, and I think we all appreciate that, that in hindsight, this is the kind of patient that a lot of things occur that contributed to their demise, as is the other patient with the -- that there were other contributing factors and there are certainly deaths that occurred that were not apparently drug-related, but they still happened on the drug group. And so my concern is, is that, you know, this hasn't changed. I think that there's -- in that situation, had the trial

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been a head-to-head electrical cardioversion versus drug, you know, we don't know if those patients might have survived had they been cardioverted. We don't know that, and so we have to accept the possibility of a drug-related increased risk. A small rate, but when you extrapolate to tens of thousands of patients, that risk is probably real.

DR. HARRINGTON: And for me, this is, you know, it's sort of you can't regulate good sense and I don't worry about Peter, Jeremy, Ed, Craig, the rest of the guys back here using a drug like this. I don't -- that wouldn't keep me up at night, but I do worry about the general guy just trying to make it through the day and you have a drug for which the -- you know, it's overall effects has not been well characterized in the broader population of patients with atrial fibrillation, and the uncertainties here, I think are great, that with a small -- you know, this comes up frequently at these

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meetings. Norm doesn't ask us to come talk about the easy ones. It's when there's -- there's just this sort of situation where there's just not a lot of data and you're dealing with a lot of uncertainty and you're dealing with a group of patients that things can go bad in a hurry.

DR. MASSIE: Actually, how many of these patients were treated in the ER? Was that part of this protocol? Versus admitted to the hospital somewhere, presumably a monitoring unit, of course. Were people treated in the ER?

DR. KITT: Yes, they were treated in the ER.

DR. MASSIE: Do you know how many?

DR. KITT: No.

DR. MASSIE: I mean is it rare or was this the common way of doing it?

DR. KITT: It was country-specific and I don't know the exact number of ER docs versus cardiologists who are in the study.

DR. HARRINGTON: So tell us that. By country, where were they treated? If it was country -- for example, in the U.S., where are the patients treated?

DR. KITT: Just a minute, please.

DR. MASSIE: I say this, and I don't want to sound prejudiced, but ER docs don't have a great deal of time to review records. They don't tend to listen to the heart so regularly, and I am concerned about that as I am treating other types of patients in the ER. It's just a whole different setting where there's not as much time to think about things and there are a lot of other pressures that aren't there.

I don't think I've heard too much in the way of labeling that tells you where you get to use the drug and I'm not sure I'm proposing that, but I would try in your promotional and educational activities to say this is a drug that you have to be able to know the patient well and monitor them

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closely for a period of time.

DR. LINCOFF: And, I mean, I think explicitly one can say this is a drug that can definitely cause hypotension, can cause fairly severe hypotension. It's responsive to therapy, but in a vulnerable patient, a patient who may deteriorate in an exaggerated fashion with hypotension, that's where the contraindication is, that's where the medical judgment comes in, and I think that's a much more real risk or much more -- numerically more common risk than the pure arrhythmias -- than the ventricular arrhythmias, which, you know, has been the focus here and I understand for this -- these types of drugs, it often is, but I think the hypotension is a much more real risk because I think this case illustrates what could well happen when rolled out into practice.

DR. KITT: I'd just like to say that all the sites in Canada were emergency room physical sites.

CHAIR HIATT: Okay. So I think that there are some unresolved risk issues.

"Is the risk management plan proposed by the sponsor appropriate for the safety concerns?"

Do we maybe want to just hear what that's going to be again, the risk management plan?

DR. KITT: Okay. We need to go back to the beginning. There's still more, more. Try, like, 81. Okay, slide up, please.

So there are four components to our risk management and post-marketing studies. The prescribing information, healthcare provider education, pharmacovigilance and reporting, and post-marketing studies.

Next slide, please. Currently, our proposed package insert would have an indication of atrial fibrillation of short duration, less than or equal to seven days.

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Patient should be hemodynamically stable. They should be symptomatic, wherein, the physician's opinion that they -- the person should be converted to sinus rhythm. They should be adequately anticoagulated according to the HHA ACC/ESC guidelines. The QT interval should be less than 440 milliseconds.

Under warnings and precautions, we have --

CHAIR HIATT: What is that?

DR. KITT: That is an uncorrected QT. Warnings and precautions, do not administer to patients with an acute MI, acute coronary syndrome, or symptomatic and/or decompensated congestive heart failure. We did not evaluate patients with an MI or acute coronary syndrome within the previous 30 days, so we have no data to support that data, and then the last point is administer with caution to stable patients with a history of congestive heart failure.

Next slide, please. Vernakalant should be administered in an acute care clinical setting where resuscitation equipment is available. We have recommended a minimum of 90 minutes following the completion of the last infusion, or until the patient is clinically stable and ECG parameters have stabilized, and we have -- in our label, we've identified the -- we've identified risks and management of adverse events. The study drug should be discontinued if clinically significant ECG changes, if the patient becomes bradycardic or hypotensive, and these events should be treated symptomatically with appropriate medical management.

Next slide. Our education plan is going to be comprehensive for what we believe is the targeted specific audiences. We'd be -- this drug would be used by cardiologists, critical care or emergency room physicians. We would also educate allied healthcare

personnel, such as pharmacists or critical care nurses or the ER nurses, and our education, the basis, then, would be the package insert.

Next slide, please. Next slide, please.

Oh, okay. Next slide, please. Oh, wait. I'm sorry. It's getting late for me.

Our pharmacovigilance plan, routine adverse event reporting with emphasis on events of ventricular arrhythmia and deaths, reviewing the literature for reports of adverse event, data mining using the FDA AERS database or other commercially available databases. We, of course, would follow regulatory requirements in terms of periodic adverse event drug experience reporting to the FDA, and we have computerized signal detection, looking for signals and analyzing those signals.

Next slide, please. Okay. We

have ongoing study on effective vernakalant on P-glycoprotein transporters. We have planned a study on the effect of ventricular defibrillation threshold. Ongoing clinically, there's a PK study in hepatically impaired patients, as well as in renally impaired patients, and we have -- some studies that we have planned: efficacy and safety trial to be done in Europe. We have a plan to do a study in non-Caucasian patients and patients with a history of congestive heart failure, as well as an observational study, which is on the next slide. And this observational study would be done to assess the real world adverse event experience, focusing and looking at events of torsade, not just ventricular fibrillation, but ventricular arrhythmia, bradycardia, hypotension, and death, and the design of this study has yet to be determined or to be designed, in discussions with the FDA as well as with external experts to see if it would

be a registry and/or would it be a mining of managed care or hospital care databases, and we would anticipate that this would be about 2,000 patients.

CHAIR HIATT: My only comment on all that is the observational study and I think, I'm no expert on that, but I would worry, in real life situations, that decisions about treatment choice and comorbidities and things that might affect outcomes that we've highlighted here, such as VF death, torsade, you know, interpreting those safety signals is going to challenging. So I think it needs to be not kind of a registry but a formal, observational study where lots and lots of variables are gathered on each patient and are used in statistical models to adjust for both treatment decision and potential variables that might affect outcome, and I think it would probably inadequate just to rely on kind of standard reporting mechanisms or just registering

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patients in a registry. Those are my only comments.

DR. MASSIE: There are registries and registries. I think a rigorous registry might be helpful and would probably be better than mining databases. I'm not sure, but I thought, based on the experience, and we talked about that hemodynamically significant obstructive valve disease is one I might put there if there's only one case, you know, or emphasize the hemodynamic stability. This person failed both those criteria, the one that died.

DR. KITT: We actually do -- I'm sorry. We do actually have that in our proposed label. It's just not -- it's not on that slide.

DR. MASSIE: Okay. And I don't know about size. I think, you know, you'd have people to advise, but the pharmacovigilance, I would certainly look for reports of hypotension and bradycardia and

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related things like AV block and sinus node dysfunction too, not just the arrhythmia ones.

CHAIR HIATT: Okay. So, what's some caveats? It sounds like a particular focus to the formal studies, looking at safety events.

Any other comments on their proposed --

DR. HARRINGTON: Let me just ask one question, Bo.

CHAIR HIATT: Yes.

DR. HARRINGTON: How big do you estimate the market is? How many patients do you estimate would get treated over the next -- per year, over the next several years, you know, understanding there's a ramp-up and all of that? I'm just trying to gauge what the population effect might end up being. I suspect some smart marketing person has figured this out.

DR. KITT: I have no idea.

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DR. HARRINGTON: I don't believe that somebody from the sponsor hasn't looked at that.

DR. KITT: I'm sure our marketing department has looked at that, but I don't know.

CHAIR HIATT: Well, obviously he's getting at kind of the sense of exposure. You know, how hard is it going to be find patients for a quality kind of observational study? You know, will this be something that is promised and then fizzles and fades post-approval where we don't get any meaningful information --

DR. HARRINGTON: Well, then I have another question, which is, is a sample size of a couple hundred patients adequate to categorize safety for a drug that might be given to 100,000 patients a year? And if you told me there was only going to be 500 patients treated, then I weigh the availability of a patient population to do

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further studies. If you told me that the patient sample size is 100,000 patients and you have a sample size of exposed patients of a couple hundred, I'd think of it differently.

CHAIR HIATT: Well, you know, one of my early calculations this morning was, you know, if one in a 1,000 patients is irrevocably harmed by this drug, then how many -- you know, at what point do you start saying there's a number of people dying on the drug over, maybe, the conventional approach, would you get concerned? And so that exposure is relevant.

My guess is, given the magnitude of the problem, easily available drug. It's kind of a nice alternative. There's lots of ways to use it. It might get used more than you think.

DR. HARRINGTON: No, I'm actually thinking it would get used as much as I think. That's why I asked it.

CHAIR HIATT: Any other comments on the monitoring for safety? Okay.

Question 12, "Is another study necessary to confirm the appropriateness of the dosing recommendations? If so, in what population should it be conducted?"

DR. HARRINGTON: I was looking at that last night. Could you rephrase that, Norm? Do you mean that, specifically, the dose that they chose, because they had the phase II dose and then they reversed it for phase III, or do you just mean are there other studies that we think should be done?

DR. STOCKBRIDGE: No, this specifically had to do with addressing the particular regimen that sponsors were --

DR. HARRINGTON: The three followed by two?

DR. STOCKBRIDGE: Are you happy with that? Do you think that needs to be replicated? That's all it asks.

DR. MASSIE: There was also a lot

of discussion in the review about the difference between men and women and that potentially not being justified by clinical data. Is that something --

CHAIR HIATT: That's tomorrow.

DR. MASSIE: Because there is a difference between men and women here. No? Okay, take it. It's getting late. Sorry.

DR. HARRINGTON: Could you put up -- there was a slide from the phase II data that showed the dose effect and I'm trying to find it.

CHAIR HIATT: CRAFT?

DR. HARRINGTON: Yes, from CRAFT. It's not a lot of patients, but there does appear to be a -- you know, that there is an effect of the two that you don't see with the one or the 0.5, but it's a very small number of patients. So is it definitive? No. It suggests that the three followed by two is a reasonable dose, but if you told me that it needed to be better defined, I wouldn't argue

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with that. On the other hand, it seems like a pretty good place to start, three and two.

CHAIR HIATT: Yes, I agree. I mean I think if things are to move forward, it's good enough to go for clinical practice.

Okay. We have to distribute some voting pads, so why don't we just break for five or ten minutes?

(Whereupon, the foregoing matter went off the record at 4:08 p.m. and went back on the record at 4:19 p.m.)

CHAIR HIATT: We're coming up now to the voting question, and the process to do this is a little different than maybe years past meetings, but it's standard now, that we're going to have a -- I'm going to ask the Committee if there's any other issues, or concerns, or information you'd like, and then once that's done, we'll actually do the voting, and that will be projected. Then we'll go around, I'll ask you to state your vote, and give a short rationale for your

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decision.

So, Rob, let me start with you. Is there any data on safety or efficacy that you think needs to be further deliberated before we vote on should this drug by approved for the conversion of atrial fibrillation?

DR. HARRINGTON: No, I'm okay with the discussions we've had.

CHAIR HIATT: Okay. So no further qualifications or anything. Okay. Please go around the room. Barry.

DR. MASSIE: I think we've brought up all the important issues, and I think there's --at least I get -- I have a feeling, and there may be others that we do need some additional information down the line, at least. But I think there's nothing else I would ask for right now.

DR. LINCOFF: I agree.

CHAIR HIATT: Yes, I have no further questions.

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MR. FINDLAY: No, fine.

MR. SIMON: I'm fine. Thank you.

DR. CANNON: I think all the important issues have been discussed.

DR. KASKEL: I agree.

CHAIR HIATT: All right. So now what you're going to do is take your little voting pad, one is yes, two is no, three is abstain. So let's go ahead and vote now, and I guess you wait a few seconds until everyone has voted. Should Vernakalant be approved for the conversion of atrial fibrillation is the question, and the voting is occurring. And should we -- has everyone voted, can you tell?

Okay. So let's go around the room the other way, and just state your vote, and give a short explanation why.

DR. KASKEL: I voted yes, and I think we've reviewed in pretty good detail the indications for the use.

DR. CANNON: I voted yes. I think

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there is a need for pharmacologic conversion of atrial fibrillation in symptomatic patients, and in the post-operative setting for patients who have heart surgery. I think we've discussed the safety issues, and I think they're reasonable, and I think there will be appropriate surveillance after marketing.

MR. SIMON: I voted yes, and I like the idea of either electrocardio version or a pharmacological. It gives the patient an option, as well as his physician. And I think the safety issues and what it will do are adequate.

MR. FINDLAY: I voted yes, as well. I felt from the day's discussions, which I thought were very, very good, that on balance this drug ought to be an option for doctors and patients out there.

CHAIR HIATT: I voted no. I felt that the safety concerns were not fully defined, including mortality concerns. And I

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felt the efficacy was very short-term, and included symptomatic relief, and prevention of electrocardio version, which is an acceptable alternative.

DR. LINCOFF: I voted yes. I think within the -- it should be -- it's a worthwhile addition to the armamentarium to the conversion of atrial fibrillation given that although the limitations need to be highlighted in terms of which patients for whom we do not have adequate safety data, and that overall the safety data set should be expanded with a post marketing study.

DR. MASSIE: I voted yes, as well. I do have concerns about who it should be used and other things. I think we know enough, however, to craft a label that would at least be the appropriate guidance with all the provisos that the guidees don't always read the label. And I think we need to collect an important amount of post marketing data to get further information. But I

thought it does convert, and I wasn't as concerned about safety to say that it overrides it at this point in time, if used appropriately.

DR. HARRINGTON: I voted no. I think that this could be a useful drug for physicians. I don't believe that a drug that potentially could be used in a very large population of patients should count a couple of hundred patients exposed as adequate to define both the benefits and the risks. I don't believe that these kind of data can be obtained in a post marketing way as reliably as they can in a pre-marketing way, because of the incentives that are involved pre-marketing versus post-marketing.

CHAIR HIATT: Okay. Thank you. So the majority said yes, two said no.

DR. LINCOFF: A question and comment. With the new legislation, the FDA has the authority now to mandate a post-marketing study of a specific type with

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penalties associated with failure to do so. Is that correct?

DR. STOCKBRIDGE: It is my understanding that the details of how that might get implemented have not been worked out, so theoretically that's true. But I'll point out that it's been theoretically true that we could enforce a commitment made under Subpart H, and we patently failed to do that in some cases, so we'll have to figure out how this -- I would not rely upon that being a method of insuring that something gets done.

MR. FINDLAY: Yes, I'll comment on that. I think the sponsors have been responsive to that today probably in response to the legislation. And I believe going forward over the next few years that all the FDA panels should get in gear around that issue once the policy, and the way the FDA is going to implement that is clarified.

CHAIR HIATT: Okay. So Question

14, let's just try to wrap up. If you conclude that Vernakalant should be approved, to what range or duration of atrial fibrillation should approval apply? And you've seen the sponsor's recommendation. Richard.

DR. CANNON: I would limit it to 48 hours, and I say this for two reasons. I think beyond 48 hours, I think the efficacy may diminish, and they're exposed to the risk. And I think the risk-benefit ratio may change after 48 hours.

And the second reason is that, for some of the reasons I stated earlier, it may create confusion to a practitioner to have a drug that's labeled for five, six, seven days and a patient who has not been anticoagulated. That goes against the guidelines regarding the need for anticoagulation beyond 48 hours, and I'm afraid there will be confusion that it's not necessary for a patient to be anticoagulated

if they've been in atrial fibrillation for five days, or six days. So I would recommend limiting it to 48 hours.

DR. STOCKBRIDGE: Is that zero to 48 hours?

DR. CANNON: Yes.

DR. MASSIE: Well, at least three, I mean --

DR. CANNON: To get to the hospital.

DR. STOCKBRIDGE: He said zero.

DR. CANNON: Okay. Three hours to 48 hours.

DR. LINCOFF: I certainly think we ought to -- I mean, as you pointed out, part of the reason that -- Dr. Cannon, part of the reason that some of these patients in this trial may have been done later is that they were in the hospital, they may have been anticoagulated, so I don't think we want to remove the physician's right to say, have a patient, observe them for a day or so on

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anticoagulation, decide that they're not going to convert, and then on 72 hours to cardiovert them with this, rather than using DC cardioversion. So I don't think -- I mean, the issue of anticoagulation and guidelines is separate from how you approve the drug. I think we ought to approve the drug on the basis of what we think is the efficacy and safety, and hope that practice guidelines and other ways will enforce the proper use of anticoagulation.

Certainly up to 72 hours it appears that even with the subset analysis to be a fairly high rate of conversion. And my bias, as I had mentioned before, is to take the overall point estimate, and not be overly influenced by a small subgroup exploratory analysis, so I would say three hours to seven days.

DR. MASSIE: I'm a little torn on this. I think at the very least, as I said earlier, the label should indicate that the

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data do suggest that there may very well be less efficacy beyond 48 hours.

Now I'm much more ambivalent about saying it should only be used from three to 72 hours, because when you look at it, that's a pretty arbitrary cutoff, if you look at the bars. But I think when you put all the bars after 48 hours together, that seems less arbitrary. And, therefore, I think it should be clearly stated how low the efficacy is beyond 48 hours.

CHAIR HIATT: Okay. I think we fleshed out that duration thing pretty well. Should it extend to patients with recent MI or heart failure? Again, we saw that data pretty clearly.

DR. CANNON: Certainly not recent MI, even the sponsor doesn't advocate that. And heart failure, I think they have told us that certainly Class 3, Class 4 heart failure, certainly Class, and I think they said Class 3, as well, that they would not

advocate its use. But I think it should be clear in the labeling that the efficacy in heart failure, I think even in Class 1 and Class 2, may be less than patients without a history of heart failure.

DR. MASSIE: Okay. I would agree with that, and I think we should also emphasize that in terms of the hemodynamic stability part of the label, too, in terms of heart rate, blood pressure, and heart failure status they should be hemodynamic, be stable.

DR. LINCOFF: I agree. I think if the FDA is going to approve this drug on a relatively small number of patients, we ought to take the potential safety signal seriously and make it a fairly narrow indication label.

CHAIR HIATT: Should a claim extend to atrial flutter? No, the sponsor didn't want that either. Are there any post-marketing commitments appropriate, such as a study to study use with beta blockers? They were con meds in the trials you saw. Any

formal study on beta blockers? No?

DR. MASSIE: Well, actually, I hadn't realized they were totally contraindicated, but if they are, I think --

CHAIR HIATT: No, they're not. They were in the --

DR. MASSIE: They were in, yes.

CHAIR HIATT: They were concomitant medicines in the study.

DR. MASSIE: Right. And I don't remember any analyses that actually showed any particular problem in people with both, but I'm not sure I saw any that showed it was safe either.

DR. KITT: About 70 percent of our patients were receiving rate control medications, and we saw no safety signal in those patients.

CHAIR HIATT: So no one is strongly recommending that. To study the effect on ventricular fibrillatory threshold. I think you all commented about a study to do

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that.

DR. MASSIE: This would be an experimental study, presumably in a dog model or something?

DR. KITT: It would be a dog model study.

CHAIR HIATT: How about in non-Caucasians?

DR. MASSIE: I really think that we need data. There would be control data in a post-market study, which control data is always better than registry data. That can be authorized, but not unique to them, but that's an area where we need to have data.

DR. HARRINGTON: So let me be provocative here then, given the Bidell experience, do you want to confine its use to Caucasian patients, given that only Caucasian patients were studied? You have no evidence that it works or hurts non-Caucasians.

CHAIR HIATT: You don't have any evidence on how to use this drug in non-

Caucasian people. You just don't.

DR. MASSIE: I don't know whether we want to propagate errors. I didn't see any rationale for one, and I don't see a rationale for this.

CHAIR HIATT: So the label would probably be somewhat restrictive on that point until further randomized trials could show --

DR. MASSIE: I mean, it could certainly make it clear that there has been essentially no exposure in African Americans.

DR. LINCOFF: Not necessarily randomized trials. I mean, if larger registry experience shows similar rates of conversion, and similar rates of torsade or not, then I think that would be --

DR. STOCKBRIDGE: What exactly are you asking for? I mean, disclosure is one thing. We'll say who was in the trials. What exactly do you want to say about --

DR. LINCOFF: I think we've heard

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clearly that there's a desire to have a large number of patients in a post-marketing, some sort of registry that gives better experience for the point estimates of the safety events. And so that could -- if in a broad enough population, which would include non-caucasians, I think you would have information on what the rates of conversion are at various time periods, and the rates of the important complications that we have some idea what the point estimates should be.

CHAIR HIATT: You see, I would disagree a little bit, because my discomfort with approval now was that I thought that there could be a safety signal that hasn't been fully fleshed out. And, therefore, I would recommend randomized trials to understand that, and doing different populations would gain you both extending the label, potentially, and really more fundamentally give you a better risk assessment. How about studying patients with

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structural heart disease?

DR. STOCKBRIDGE: I guess I want a little bit more conversation on this. Tell me again why this is a marker that catches your attention? What is it about race that you think is a predictor of responsiveness to a therapy, to a therapy in this arena?

DR. LINCOFF: I don't think it necessarily is, just as I don't think that there's a substantially elevated risk of torsade, but I also recognize that there's a limit in the data set, and that that's why I think there should be an obligation to do a large number of patients in a carefully collected data set of a registry that would allow us to say now no longer on 800 or 900 patients, but on maybe 3,000 patients that we have a pretty good idea what the point estimate of torsades is, we have a pretty good idea what the point estimate of ventricular fibrillation is, and we've seen in patients other than Caucasians that we

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have similar rates of conversion in the first three days, which is where we expected to see the efficacy. And I don't think a randomized trial is necessary for that, because we know the spontaneous rates of conversion are low. I mean, we have a pretty good idea what we should be expecting, and that's why I voted for approval, because I don't think we need more randomized data, but we need more safety data. And I think that to get the large number of patients to get that safety data, because these are now the infrequent events we want. I think those are better done in the observational -- as an observational study with an available drug where there is mandate, though, that they collect careful collection in a prospective registry.

CHAIR HIATT: Yes, but in a post -- in a sort of an open-label administration like in ACT IV, you basically have to assume all the events were drug-related, and they may not be. And so when you're trying to

assess safety, particularly with low frequency events, you're stuck. I mean, the placebo rates are really important.

DR. LINCOFF: And that's true, particularly for events like hypotension, but for torsades, I mean, where there's not much spontaneous torsade with atrial fibrillation, I think you can get a reasonable assessment, again, of the conversion rates, and of the rare complications that are fairly unique to a pharmacologic conversion, as compared with in the spontaneous, or with electrical conversion. I mean, how many torsades do we see post electrical conversion?

DR. HARRINGTON: So let me just push you a little bit, Mike, -- so the regulations say effective and safe. Do you believe that you can get safety information uniformly from observational data?

DR. LINCOFF: I think we have safety information now. We have an upper limit of a confidence interval for some of

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the most feared complications that is low, and is within the limit of, for example, Ibutilide, which is approved. People know that they have to be cautious with it, they have to monitor, these are correctable events. And this is an alternative to another non-trivial procedure that is D/C cardioversion.

On the other hand, I think it would expand one's ability to be confident of the use of the drug in other settings, perhaps to better define the length of time that one needs to monitor the patients afterward, and maybe get a better idea of just how many hours or days out from the onset of atrial fibrillation this is an effective drug, if one expands the database. So I think we've proven effectiveness, and we've proven a degree of safety commensurate with other accepted therapies, accepted and approved therapies, but I think there's more information we can get, but I think that

information is better obtained in the large number of patients enrolled in real world settings, rather than the narrow clinical trial randomized design.

DR. STOCKBRIDGE: Okay. I hear that you want more post-marketing safety data. What I didn't hear is why you particularly wanted to target one of, I don't know, a hundred different demographic characteristics about which you know nothing. Why was that?

DR. LINCOFF: And I didn't. I said this is -- to me, this is one of the multiple subgroups that one could look at in more detail if one had more numbers, and get some appreciation for is there homogeneity in the treatment effect. But I don't particularly think that this -- if you said women, or other groups, I think that it would all be the same.

DR. HARRINGTON: Yes. My remarks earlier, and I brought it up to limit the

label to Caucasians only. My remark was intended to be a comment on the lack of information in multiple groups of patients that might ultimately, or probably will be treated. So, for me, it was a discomfort with the relative paucity of data, given the commonness of the disease. You specifically asked non-Caucasians, and I agree with you, that that's representative of a subgroup that has not been well included in the studies.

CHAIR HIATT: Okay. Patients with structural heart disease? Anybody want that? And how broadly do you want to define that?

DR. MASSIE: Well, I do think it would be nice to actually do a study in heart failure patients, and I think if we did do a study in heart failure patients, it would have to be controlled, because I wouldn't know how to compare that group to the data they have now, because the heart failure is not very well characterized, and so on.

This is a big issue in heart

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failure, race and recent data have actually suggested, unlike some earlier data, that people in sinus rhythm probably don't do better than people in atrial fib with heart failure. That's been in controversy, there's been issues of trying to convert it, but I don't think we really know the answer. But people do want to convert some of these people, and I'm not sure that this drug is unsafe, but I'm certainly not sure I know it's safe in this group either, so it would be a worthwhile study. I don't think it's mandated.

DR. STOCKBRIDGE: Worthwhile study is not post-marketing commitment.

DR. MASSIE: Right. Well, I think the label essentially goes a long way toward excluding heart failure. And if they've excluded heart failure, then it isn't a post-marketed commitment. To change that label, I think you would need a post-marketing study in that group.

DR. HARRINGTON: So, Barry, then the comment in the proposed labeling from the sponsor says "Administer with caution to stable patients with a history of CHF." Would you say that should be strengthened to say do not administer to patients?

DR. MASSIE: You know, that's walking a fine line, because it did say excluding Class 3 and 4, and I think there was something about not very symptomatic. And there's a lot of words there, but it doesn't close the door on heart failure. And I wouldn't be against saying that you should not use this drug in heart failure until proven otherwise. But I'd probably use it off-label in certain people with heart failure that I think meet all those bills, honestly, but I think that it should certainly -- there shouldn't be anybody out there saying this might be a reasonable drug for heart failure.

DR. LINCOFF: Yes, I would be very

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straightforward. I would exclude it in heart failure. I mean, they excluded Class 4, Class 1, 2, and 3 were presumably in, but I think that there's too few patients, and too much of a question of whether risk versus benefit is appropriate in that group. So, I mean, I would be very clear. And if they wanted heart failure, then it's a randomized trial. I was never suggesting observational study for that.

Do we have any -- but on the other shoe, structural heart disease. Did we see any data on how many of these patients had valvular disease, or other ideologies? There's actually remarkably little information on the characteristics, so I don't really know if that's an issue. If nobody had mitral regurgitation in the study, which is a very common cause of atrial fibrillation --

CHAIR HIATT: Well, the question I think is, particularly in some value of heart

disease, is there may be higher risk of hypotension, and higher risk of safety concerns that we already talked about. That does seem to be kind of an area where there may be sort of a knowledge gap.

DR. MASSIE: And there's the issue of LBH, which we know that there are a lot of hypertensives there. I presume there are a fair number of people with LBH. I don't think we have any data on that. There should be ECG data. I'm sure it was classified and read, but probably no echo data. Right?

DR. CANNON: So, Barry and Mike, I want to make sure I understand. If you wanted to exclude heart failure patients, you mean systolic low ejection fraction heart failure, not heart failure with normal systolic function. They showed us some data on that. I mean, I would think that's a group that would probably benefit from restoration of sinus rhythm.

DR. LINCOFF: I actually don't

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recall the data for preserved systolic function and "history of heart," because my understanding is the diagnosis of heart failure was, "Did you ever have heart failure?" So that would be a history.

DR. CANNON: No, they had ejection fraction measure.

DR. LINCOFF: They had in a subset. And if it looked like fine with diastolic, then I would --

(Simultaneous speech.)

DR. MASSIE: -- is one of the issues. We only saw the efficacy for heart failure. Right? Above and below 50. And so I don't think that answer was good. I don't know what the issue is. Just as if they potentially could benefit in diastolic heart failure, because the atrial kick is important.

DR. CANNON: Do you have those data immediately available? I recall seeing a slide earlier today in the -- which one of

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the ACTs? I forgot whether it was I or III, where they did measure ejection fraction, and you showed the partition of patients with ejection fractions above or below 50. Because I think this is an important issue, if we're thinking about restricting it for heart failure, what kind of heart failure?

DR. KITT: Okay. The slide up, please. So these are -- this is the data in the studies in which we collected ejection fraction data, and we split it into greater than 50 percent, or an ejection fraction of less than or equal to 50 percent.

I'd also like to remind the Committee that our post-surgical patients, ACT II, all those patients had structural heart disease. They either had valvular surgery, or they had coronary artery bypass grafting, and we've got 107 patients in that study who received Vernakalant.

DR. MASSIE: So this is a little tricky extrapolating to heart failure,

because if you look at it, there's a lot of people who had ejection fractions, but when you get down to the ones that had a diagnosis of heart failure, it comes out 39, 40, about 50.

DR. LINCOFF: Yes, I don't think we could make the heart failure exclusion with or without. I don't think there's enough ejection fraction data, but I wasn't suggesting that we exclude based on structural heart disease. I was sort of asking if there was any data.

CHAIR HIATT: So it sounds like there's a need for some more information in that area. And it sounds like there's a particular concern raised around heart failure, how that might be defined, how that might affect the label. Any other comments on that?

DR. DICKINSON: We do have some data on efficacy with left ventricular ejection fraction, if I can have the slide

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up. In a subgroup of the patients in ACT II, ACT III, and ACT IV, we did have echocardiographic data. And the patients were classified, their left ventricular ejection fraction was classified as normal, mild, moderate, or severely dysfunctional, severe would be less than 25 percent. And, as you can see, the numbers in the moderate and severe category were very small, and the confidence intervals are huge. But, overall, the efficacy was very similar.

CHAIR HIATT: Thank you.

DR. MASSIE: Now, I'm a little -- this is not heart failure, so this is just by EF.

CHAIR HIATT: Yes. Right.

DR. MASSIE: So I don't know that it really informs the discussion on heart failure at all. Severe LV dysfunction in heart failure could be the same or they could be different.

CHAIR HIATT: Is there any need to

study this in patients with hepatic impairment? And, by the way, we saw some data with renal impairment, and at least to the degree that they were included, there didn't seem to be much of an affect on drug metabolism or outcome. A need for more severe hepatic impairment to be studied? No overwhelming cry for that.

How about the study with inhibitors P-glycoprotein or other transporters? That was touched on a little bit in the development program, as well.

DR. HARRINGTON: What's that one trying to get at? Is that the drug interactions?

DR. STOCKBRIDGE: The drug interactions have been well characterized.

DR. HARRINGTON: I mean, this gets to the point we had them show the clinical pharmacology. I'm not convinced that at the outer end of -- do we know enough about the metabolism, how long you should monitor these

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patients, et cetera. And when patients are going to start coming in on multi-drug therapies, I do think you probably want to define those interactions a bit better.

CHAIR HIATT: Yes. Remember, I think, and correct me if I'm wrong, but all this DDI stuff came from population PK kinds of experience, not from formal studies. Right? So it may not be known with confidence.

DR. MASSIE: Wasn't there some data, or some mention not being treated by P Grade glycoprotein mechanisms somewhere in the clinical pharmacology?

DR. KITT: No. What I had mentioned is there is an ongoing study. I think one has been completed, and there's one ongoing study.

DR. MASSIE: So we don't know at this time whether that's a relevant mechanism of excretion. I guess that would be the first question, we should know that. And if

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we know that and it is, then the next question --

DR. BEATCH: The information we know at this time is that it's not an inhibitor. We don't know whether it's a substrate.

CHAIR HIATT: Okay. And that data continues to be gathered. All right. We've gone through all the formal questions. Does anyone else have any other salient comments to help Dr. Stockbridge at all with their further deliberations on how to move forward here? Comments? No? Are we adjourned then?

DR. STOCKBRIDGE: That's been very helpful. Thanks, everybody.

CHAIR HIATT: If we are, then I want to thank the sponsor, and your responsiveness over the lunch hour to give us more data, all of you attending. Thank you very much.

(Whereupon, the proceedings went off the record at 4:49 p.m.)

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