some cases, and impossible or impractical in others. But certainly we'd like to know more, be collecting more data along the way that we did systematically or was done systematically there.

CHAIR HIATT: Well, and Norman, if we could try to characterize a bit more what your struggle is. If this is an acceptable way to develop a drug using this very short term endpoint then we must believe at some level that that has a larger benefit, that in some ways being in sinus rhythm would translate in fact to fewer drugs used, less bleeds caused by anticoagulation, fewer thromboembolic events, and those kind of adverse events associated with atrial fibrillation including a better functional performance and better quality of life.

And that this development program falls short of that, but it is certainly a stepping stone -

DR. STOCKBRIDGE: Well, they're not

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in this program, most of those things aren't in this program.

CHAIR HIATT: Correct.

DR. STOCKBRIDGE: But if you thought, nor are the sequelae of hypertension in a hypertension development program.

So you could take the position that you know well enough what you are doing with treatment of AF to know you are going to by treating prevent some events you are going to tell me what they are, and you know, you can say, I don't particularly need every development program to demonstrate that particular effect. I just, I could go with modest amount of safety data and a clear demonstration of effectiveness, which you sort of have here.

So that's really at the crux of this is whether you think you know well enough how to characterize the - if you had to write a label for this, an indication for this, where you said this is for the

conversion of AF in order to - what would you say there? That is really where we are trying to get to, what is your expectation of what the nature of what you have achieved here is.

DR. LINCOFF: But why is that necessary? Because if all you accomplish is that you have an alternative to electrical cardioversion to achieve the same end, and electrical cardioversion is practiced, then isn't that enough? If you can do it safely?

Because there is no question that there are disadvantages of putting a patient through electrical cardioversion. There's utilization of resources, there's putting patients under sedation, there's the burns. There's the requirement for a fasting state. There's the potential for aspiration. And those are difficult to quantify to my understanding, because there have not been any good numbers on them. But do you have to quantify it? If you can, with an awake

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patient on a monitor, and a physician in the room inject a drug and within a number of minutes, a relatively short period of time, do the conversion and not have to do electrical cardioversion, I think most clinicians would say that's an advantage.

So just as before there was the FDA meeting recently that linked the reduction of hypertension to the reduction of the mortal events - or morbid events. But before that the drug was to reduce hypertension.

Why can't this drug to convert atrial fibrillation with no other consequence, because it's the medical decision whether or not atrial fibrillation should be terminated, or whether one can manage it with rate, et cetera, based on other data.

DR. STOCKBRIDGE: Well, if you somehow can conclude that - I think there are two steps. The first step is to figure out

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whether - whether conversion by any means of somebody who's been in AF for a short period of time is worthy anything, is worth doing at all, since a lot of those people will convert spontaneously in not very long. So you got to first decide whether somebody is truly worth converting, and I don't think that's necessarily reflected by the practice that was - that is either done commonly or is part of the protocol that was within these development programs.

But even if you get to the place where you think you understand why you should get somebody converted sooner rather than later, then you have to deal with the business about how this sits relative to some other means of forcing conversion to sinus rhythm.

And you know if you think the risks - I'm sure there are risks of electrical cardioversion. And there are risks associated with this drug. You have to

help try to put those things together, and say, well, it's perfectly obvious to you perhaps that this is a safer way altogether to get somebody converted once you've made that decision to do that.

That's not obvious to me from these data.

DR. MASSIE: Why safer? I'm a little perplexed by that? It seems to me that although this may not fulfill your usual way of - what it does to the patient things, like a heart failure drug would be to improve survival or improve exercise tolerance, those are pretty easy to understand. But what we've really done is, we've found a drug that appears to be effective as a possible alternative to electrical cardioversion, which doesn't really say what it does to the patient, but it does sort of say why you would use it.

In other words, others have said that this is a group of people who the

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doctors decide that they had to cardiovert. We can't put ourselves in their head, and I'm not sure we always want to be in their head. We may not agree with those reasons. But they've made the decision to cardiovert a patient, and this is an effective alternative to be considered.

I mean I can give you lists of people I would rather not cardiovert. They have been mentioned before. I can also give you lists of people that I would rather not give this drug to right now; that would include people with poor LV function until more data are available, who are more at risk of hypotension. They include a large group of people who were not included in the studies, people with hypokalemia, people with prolonged Qts, people with maybe very wide QRSs, I'd begin to worry about giving electrical drug - so there are two alternatives. One is to say what we do for the patient. Well, what we do for the

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patient is, we have a way to get him into sinus rhythm, but it doesn't necessarily make him feel that much better, and it doesn't - we don't have any other data on outcomes.

But why would a doctor use if it he felt that in this patient electrical cardioversion would be something he preferred not to do or the patient not to have?

CHAIR HIATT: The problem with that thinking, and to Michael's point too is, these trials weren't designed to compare head to head cardioversion to drug, we don't really -

DR. MASSIE: So we can't answer that. But we know it's an alternative.

CHAIR HIATT: Well, it's probably standard of background therapy which could be applied at some point in time.

So the question is really, is the delay in need and actually reduction in need for that therapy. We don't really know head to head whether one therapy would be better

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tolerated and have less risk than the other therapy. We are just making some assumptions.

Let's be careful, because we have to stay within the study design.

So I think we've framed things a bit, and we will certainly have plenty of time to flush these things out.

Perhaps we could turn to the questions.

QUESTIONS TO THE COMMITTEE - PART 2

CHAIR HIATT: So I'm going to read this again.

The advisory committee is asked to opine on the use of vernakalant to effect conversion of atrial fibrillation to normal sinus rhythm.

There is no question that vernakalant is effective in converting atrial fibrillation to normal sinus rhythm. This was demonstrated in two studies where in patients mean age 63 - 68 percent male, 96

percent Caucasian, 15 percent with history of heart failure - in AF for three hours in 45 days, parentheses, seven days for the primary endpoint - were randomized to study drug or placebo, and conversion was assessed within 90 minutes from the start of the infusion.

Although the endpoint was - only required maintenance of normal sinus rhythm for one minute, the durability conversion was clearly longer in the lifetime of the drug in the blood.

Given time the rate of spontaneous conversion of atrial fibrillation is highest among the very patients among whom vernakalant is most effective; those in atrial fibrillation for a short duration.

So the question becomes, how long one should wait for spontaneous conversion before resorting to a drug. And that is a function of the risks of waiting and the risks associated with the drug.

The challenge to the committee is

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whether the available demonstration of activity and characterization of safety suffice to identify a population with a compelling case for net benefit.

Question #1: What clinical benefits were demonstrated in the development program for vernakalant? For which of them are there beneficial and meaningful trends?

So we have these six bullets: reduction in thromboembolic events; reduction in hemorrhagic events; reduced need for warfarin; reduction in the need for hospitalization; reduction in symptoms attributable to atrial fibrillation; avoidance of electrical cardioversion; and others.

So let's go around and try to wrestle with this first question.

DR. HARRINGTON: Well, I'll kick things off. I think we had a good discussion this morning about oral anticoagulation, and except for the patients who had AFib of very

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short duration, I don't think the conversion eliminates the need for anticoagulation. And certainly these studies didn't set out to show that.

So I would say that for the first two we don't have any evidence that the question that has specifically been asked, what would demonstrate in the program. Theoretically you might say, if you are converting people who have symptoms of very short onset, perhaps they can avoid warfarin, but we don't have any data for that.

As far as the reduction in the need for hospitalization -

CHAIR HIATT: Wait, don't go too much further. So which is why I kind of thought this new safety information was helpful.

So if you just kind of look numerically at these percentages, embolic events are numerically greater on placebo, and bleeding events are numerically greater

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on placebo.

Now I am not going to draw any conclusions. These are all going to be small number things. But we have to look at kind of trends and whether there is any overall signal here.

Does that change your opinion?

DR. HARRINGTON: No, I think that the infrequency of the occurrence is just such that it doesn't change my conclusion on that.

CHAIR HIATT: Okay, so you'd say that these numbers then don't demonstrate either protection from or cause of bleeding or embolic events?

DR. HARRINGTON: That's my view of the data displayed.

CHAIR HIATT: Okay. Anyone else on the committee think differently?

So we don't know?

DR. HARRINGTON: Exactly. Or probably, how's that?

CHAIR HIATT: Yes.

DR. LINCOFF: But we don't have any reason to believe, there is no mechanistic reason to believe it would reduce thromboemboli or bleeding, given what we've discussed.

DR. MASSIE: Well at the exposure. I'd say clearly no.

CHAIR HIATT: Yes, I mean one could look at this and say, well if you treated tens of thousands of patients, and the interval of atrial fibrillation was shortened by a few hours, would you expect ultimately a clinical benefit from that?

DR. MASSIE: Well, again, the people who are actually responding to it are in a window which we think they are not at high risk for these things. So I guess I would stick with no until somebody tells me something else.

DR. CANNON: Well, I think it would depend on the practice. So if an option

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would be, if you are going to take the conservative route, and you are going to send somebody home maybe on a beta blocker to slow the rate, and then have them come back in a day or two and see if they are still in atrial fibrillation.

And then at that point, as opposed to giving this drug or ibutilide and just terminating it right then and there, in someone who is otherwise reasonably stable.

It seems like you could be exposing someone to a day or two of not being anticoagulated, and therefore the possibility of a thromboembolic, and in fact, numerically, there was a greater incidence of thromboembolic events in the patients treated with placebo. I don't know if it was because of the strategy I just outlined, but I could foresee that as being a possible reason why there would be greater thromboembolic events if you go an alternative route to quickly terminating the atrial fibrillation.

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As far as the hemorrhagic events, I could foresee that if you decided to take a conservative approach and keep somebody in the hospital and treat them with Lovenox or heparin, you are going to wait a day or two on a beta blocker to see if they convert on their own, well, you are exposing them to an anticoagulation that could cause bleeding risk over that day or two as opposed to rapidly terminating the arrhythmia.

I mean I could envision, depending on someone's practice, how you could by not rapidly terminating the arrhythmia with this drug or ibutilide or electrical cardioversion that you could put them at greater risk.

DR. HARRINGTON: Let's make sure we're talking about the same thing though. I am looking at the data here that embolic events, three in the treatment arm from 24 to hour - hour 24 to - god, Barry is wearing off on me - 24 hours to seven days, versus four in placebo.

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DR. CANNON: Be careful, the denominators are different.

DR. HARRINGTON: She told us it was statistically significant. It's .39 percent versus .89 percent. And I could envision how that might be true, and if we have thousands and thousands of patients how that might actually turn out to be a significant difference, depending on how you approach, if you take a conservative route versus going ahead and doing something about it right away.

DR. CANNON: I'll buy that.

CHAIR HIATT: But there was a little bit of a split here. Now let me just challenge you on that one.

So if you were to design a trial to prove that hypothesis, and now you are saying that I've gained two hours of sinus, or maybe 24 hours, that I didn't have because I waited to convert someone electrically, and I want to now demonstrate a clinical benefit

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to that, how many patients do you think that would take?

DR. CANNON: It would be huge.

CHAIR HIATT: Huge.

DR. CANNON: But you are the one that points out, looking at small numbers to try to envision what might happen in community practice if this drug is approved.

CHAIR HIATT: That's what I'm trying to do.

DR. CANNON: But to prove that point would take many thousands of patients.

CHAIR HIATT: It would. So I mean I think both as a biologic reason to believe that it would spare you from the anticoagulation bleeding risk and the thromboembolic events of being in AF during that time, but the effect size might be really small.

DR. STOCKBRIDGE: I would just like to point out that we are mostly addressing question #2 now and not question

#1.

Question #1 asked you what had been demonstrated in the program, and question #2 asked you to fantasize.

(Laughter)

DR. CANNON: Well, but question #1, they did show us data, I've got it here in front of me, and there were fewer thromboembolic events, and there were fewer hemorrhagic events. The numbers are small; the percentages are very small. But this is what we have to work with.

DR. LINCOFF: But in this study the rates of conversion by 24 hours are exactly the same. So it's not like there were long periods that you could - I realize this is an observation, but there is also a multiplicity of endpoints here.

DR. CANNON: I'm looking at 24 hours to seven days.

DR. LINCOFF: Right, but that's cumulative. But if you look at two to 24

hours, 86 percent and 83 percent were in sinus rhythm by that point, so it's hard to attribute much of a delay that was saved by having received the active drug as a mechanism for preventing embolic events.

So I think a parsimonious approach here is to say that without a mechanistic reason to believe that this is real, and -

DR. CANNON: You know, again the clot that had formed in the left atrial appendage at hour 18 and dislodged at hour 36; I don't know.

DR. MASSIE: Let's stick with demonstrated. Because AFFIRM pretty much disproved a lot of this type of logic, too. There are factors that we just don't know about, and unless we see it, I don't know how we can go very far to saying it's likely to occur.

DR. HARRINGTON: And Norm's question goes on further to ask, you make the point, well, there are numerically more. But

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then he says, which of them are beneficial and meaningful trends. I think he's asking us then to say, okay, there are small numbers here. Which ones might you believe could be sort of possible?

CHAIR HIATT: And so actually to stay within the context of question #1, then, the weight of the evidence for those first two bullets that you see before you? You have to say that there is no signal there.

DR. HARRINGTON: Not using the word, demonstrated, and beneficial.

CHAIR HIATT: In italics, you notice that?

Okay, reduction in need for hospitalization.

DR. HARRINGTON: Well, we didn't get that data. Somebody asked it, didn't they?

CHAIR HIATT: They were hospitalized. I don't think sponsor knows, right?

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DR. MASSIE: The design wasn't designed to answer this question, because everybody had to be admitted to get in the study. So and if they didn't collect the number of hours, I think the answer is, we don't have any - nothing demonstrated.

CHAIR HIATT: Well, and then I guess again you speculate further, well if you converted maybe you don't need a repeat hospitalization within the week. But you - you guys don't have that information.

DR. MASSIE: Well, at the end of the day, the numbers were converted, so you'd have to decide that the way you got converted has a downstream effect days later. And it sounds like from the data they have in a week that that is the case; that they are still mostly where they were.

CHAIR HIATT: But the actual number of hours in hospital during that week is not known.

DR. KITT: No, we didn't collect

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that data.

DR. HARRINGTON: But as Barry pointed out, in fairness, this wasn't the study they set out to do.

CHAIR HIATT: Okay, so I guess the answer there is no.

The next one is avoidance of electrical cardioversion, clearly, I mean sorry.

Symptoms, I'm sorry. Yes.

DR. HARRINGTON: I'm just to figure out how clever Dr. Stockbridge was being here. Does this refer to the development program? Does it refer to the 90-minute time point? Does it refer to the seven-day time point? The 24-hour time point? To which point in time are you referring?

DR. STOCKBRIDGE: Describe for me what you think we have accomplished here? I mean if you think that it was important, if you think there was convincing data that the symptoms were improved at, say, 90 minutes

you can say that.

But you pointed out some properties of the way that was assessed that make it hard to interpret. But say what you think you've got out of this in terms of symptoms.

DR. HARRINGTON: So my view of what's been presented is that there were methodological flaws, perhaps, at least in what was described in the way that symptoms were ascertained at the various time points, without demonstration of blinding, et cetera. So I do think that there were some flaws.

Despite that I thought that Dr. Pritchett spoke convincingly that there is a tie between symptoms and sinus rhythm. Clearly there are more patients in sinus rhythm at 90 minutes than there are - with the drug than there are with placebo.

So in the totality of it, Norm, I would say that there is a reduction in symptoms attributable to atrial fibrillation

at 90 minutes alone; and that after 90 minutes I see no other data that says that there was superiority of the strategy.

Although as Ellis points out, perhaps if you had left those patients alone in the placebo group we might have seen that emerge. But we didn't do that.

So I would say, for me, demonstrated that there were symptom reduction at 90 minutes with the drug.

DR. MASSIE: I'd like to qualify that, though. I think that's true. I think they demonstrated that. But of course the study design did not allow you to cardiovert them at time zero, and cardioversion would have probably we know reduced the symptoms similarly if they were fully awake anyway at 90 minutes afterwards.

So again this is part of the structural study. I do believe it reduced symptoms. And I do believe that when people go from AFib into sinus rhythms they can

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often recognize that and they probably do feel better even if they are still in bed.

But I don't know that we can answer - so I think the study demonstrated that, but it's perhaps an artifact of the study design.

CHAIR HIATT: I think it demonstrated symptomatic benefit, and it reflects the design. But I think it was pretty clear.

And it also avoided the adverse symptoms of cardioversion. So I think the problem with the symptomatic benefit, whether there are methodologic flaws or not, is, it's very short lived. The advantage.

Okay, avoidance of cardioversion.

DR. HARRINGTON: Sure, cut it in half, or more than that, 69 - what is it, 69 percent get cardioverted in the placebo versus 31 in the other.

CHAIR HIATT: So it was very effective at short-term avoidance of

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cardioversion. And if you avoided it it looked like the effect was durable.

Any other demonstrated benefits? Did we miss anything?

MR. SIMON: The fear of cardioversion, electrical cardioversion.

CHAIR HIATT: We kind of assumed that avoidance with symptomatic - okay. So what kind of clinical benefits do you believe should be expected through the use of vernakalant? Compare with what treatment, electrical cardioversion, rate control and other drugs. Are these clinical benefits expected?

So here maybe we could go back through these points and kind of flesh them out a little bit further. I think we already sort of dove into the first two points. So if we truly get patients in sinus rhythm quicker, is there going to be any long term clinical benefit to that in terms of thromboembolic events or avoidance of

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anticoagulation?

And I think it was a biological possibility that there certainly could be, but we said that the sample size needed to prove that might be infinite.

DR. HARRINGTON: So isn't here where we have to really talk about the strategy? And Barry alluded to this in his previous remarks, that, say that this drug will make it to the marketplace. And you have a patient in front of you with symptomatic AFib of appropriate duration that you want to embark on cardioversion.

You could give them a drug, or you could electively cardiovert them, or you could watch them. And let's say we've decided you're going to do one of the first two.

So in that situation, the clinical setting, I have trouble believing, our consultants have all told us that cardioversion - once you get in sinus rhythm

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you've in sinus rhythm. So I don't see a benefit for the thromboembolic prevention in the clinical setting in which this drug would be available.

About the only benefit I see is that you avoid electrical cardioversion, and to me that might qualify. I've said earlier, a couple of times today, live longer, feel better, avoid unpleasant things. Avoiding cardioversion sounds to me like avoiding a pretty unpleasant thing.

So that might be - I don't think the trial was set up to demonstrate that necessarily, but that may be a real clinical endpoint that you could prove in a clinical trial.

DR. LINCOFF: I don't think we should underestimate the logistics associated with doing cardioversion. It's one thing for an emergency situation where a patient is hemodynamically unstable. But in general outside of that it usually takes a little

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while to set up even in most systems. You know you take them to a procedure room. You may not be able to do it that day. Again, there is the issue of the fasting state, et cetera.

So I think in practice, where it's not as contrived as a trial has to be, and this trial was, there may be a substantial delay that could be avoided by just having a drug that you could give in the ER. And so for the potential, whatever benefit that would be, maybe for emboli. Again, I think the only advantage for anticoagulation would be if a patient presented so early that you made the decision, well, I won't need to give them the six weeks afterward. And I think that would be a very limited number of patients. But that's a potential as well.

So I think in reality, in practice, the elective cardioversion that we'd be thinking about these patients for, because they'd be the stable ones, may in

fact save a fair amount of time.

DR. HARRINGTON: But don't you have to have the same set up? Don't you have to have the same set up to give the drug? You'll have to have them appropriately monitored. You'll have to be prepared to shock the half who don't convert. So does it really save you - I mean it saves the half the people who don't get it, but do you have to have - do you save on the set up?

DR. LINCOFF: Well, I mean the approach would be, in an emergency room, you have the ability to do emergency cardioversion if they have torsades or VF. But otherwise you would give them a drug, if it didn't work, you do whatever it is you do in your hospital, schedule them to go to the procedure room or whatever.

But I think most hospitals are not doing elective cardioversions in the emergency room; electrical cardioversions.

CHAIR HIATT: Yes, so I think

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because the sort of standard background therapy of cardioversion is not one that in most patients is mandated on presentation, I'm not sure if the resources are going to be delaying that by another six hours or 12 hours.

DR. MASSIE: Let me just ask, it's probably coming a little bit later, but there is this concern we're going to talk about later presumably of potentially torsades, potentially VF.

If you had your druthers, would you wait until the person was in PO for a certain amount of time before you give them the drug? Before you would cardiovert them and potentially have those risks? If you were really cautious?

DR. HARRINGTON: So would you have them all teed up?

DR. MASSIE: Well, not necessarily teed up, but not in a way where it might be contraindicated, where you'd have to intubate

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them and all the rest.

DR. HARRINGTON: Particularly for a drug that has an 8 percent nausea rate.

DR. LINCOFF: We haven't talked too much about the risk.

DR. MASSIE: That's coming I think. But since we are talking about - one of the perceptible advantages is that it gives you an alternative to cardioversion. But the strategy of how you would use it might expose patients in whom cardioversion would be more risky than if you waited.

CHAIR HIATT: Well, remember, we're delaying it. The alternative is delaying, not comparing -

DR. MASSIE: And we're talking about this delta time, too.

CHAIR HIATT: Right.

DR. MASSIE: And the delta time, if you actually said, well, this is purely elective. He's only been in AFib for 18 hours. Wouldn't it be safer - I mean I've

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done this with ibutilide, I can tell you - is I say, the guy just had a meal. Let's wait until I feel comfortable in case something goes wrong. And it looks like it's less likely to go wrong here is my view than ibutilide, but I treat ibutilide often in terms of time and set up, although I don't have an anaesthesiologist on hand, because I figure if the bad things happen with ibutilide, the patient will be conscious, and won't need the anaesthesiologist.

But that is an alternative question is, does it really get you all that worth if you are cautious and you perceive this as purely elective.

DR. LINCOFF: Well, again, perhaps not going into too much detail until it's in the questions. But I'm not convinced that the risk of arrhythmogenic complications is the same as ibutilide.

Granted, there have been ones here, but I think there are fairly good

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explanations. Also, granted, the data set is relatively small, and this emphasizes the importance of a post-marketing evaluation.

But I think there is a very real possibility that this isn't associated with nearly the risk as either approved drugs or drugs that we might be talking about at some point in the future. So this may well be an advantage that you don't have to be as prepared to do an emergency cardioversion.

Again I am if anything more concerned about the hypotensive effects.

CHAIR HIATT: Well, all these inherent comparisons are speculative. And in some ways what we should try to do with these questions is focus not just on how you'd handle an individual patient but what does it mean for the population of people that will get exposed to this drug.

So if you think about the clinical benefits of these things above, in my opinion is that the thromboembolic and hemorrhagic

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event avoided by a quicker time to conversion is probably not clinically going to be relevant.

It could reduce the time in the hospital. It can shorter the symptomatic state by a few hours, and it clearly can avoid cardioversion.

So to me the clinical benefits are mostly symptomatic not morbid/mortal kinds of things.

Anyone disagree with that?

So the expected benefit, I think, summarizing these first two questions, is that this drug would play a role in the acute setting to achieve a symptomatic endpoint for patients who are symptomatic with atrial fibrillation.

DR. HARRINGTON: But being very careful how you phrase that, because if the strategy was electrical cardioversion or this drug, you don't reduce symptoms at all. But if the strategy is drug versus watchful

waiting, you might.

So in terms of saying, reduce symptoms, I like the way you phrased it near the end when you said, you know, reduce the duration of symptoms perhaps.

CHAIR HIATT: Well, it's symptomatic in a bit more global context. There are two components of this. One is the symptomatic state of being in atrial fibrillation, and relief of that, and the other is the symptomatic adverse effect of a cardioversion, which I think the committee sort of continues to highlight as potentially a clinically real issue, and the set up and the conscious sedation and that kind of thing.

So symptomatically speaking in a slightly broader context, those would be my interpretation of the symptomatic benefits of this therapy, but that I wouldn't expect, if we did a 100,000 patient trial that there would be any other clinical benefit achieved

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by this strategy deployed in the design of these trials.

DR. HARRINGTON: And we'll get into the side effects associated with the drug at some point, because while some symptoms might get better, there are other symptoms that occur, in the totality of things. I mean let's not ignore that either.

CHAIR HIATT: Nope. The charge is the overall risk-benefit.

Question #3: Cited conversion rates excluded patients who underwent early electrical conversion, those who converted prior to receiving study drug, and those who otherwise did not receive study drug. Are these exclusions reasonable? If not, how should these cases be handled?

DR. MASSIE: You know, we saw the data analyzed the other way. It wasn't really very different. I actually think people who spontaneously convert should be considered in the denominator and in the

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numerator for both therapies, but it doesn't really make I think a measurable difference in the totality of the data.

But it should be intent to treat. Really. Real intent to treat.

CHAIR HIATT: It doesn't sound like that, I don't think -

DR. HARRINGTON: Well, let me make a case for modified - or they actually use the treated analysis if I'm correct, is that it? They did an as treated analysis.

So there are certain conditions by which I would say that as treated analysis are appropriate. If understanding the - well, if knowledge of the treatment is blinded, in which case it is blinded, that would be at least a criteria that has to be met, so that the allotment to the randomized block did not affect the way that you subsequently went on to get the treatment. So I'd be okay with that.

DR. MASSIE: Well, I think an on

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treatment analysis emphasizes the efficacy signal, but it's probably a more conservative analysis in terms of safety.

DR. HARRINGTON: We were talking about efficacy here. So for efficacy I'm actually okay with your modified, as long as they also show us the conditions by which people didn't get the treatment, and as long as they show us the overall intention to treat analysis, and as it was suggested, the data there are certainly consistent.

So I have no objections. This is something that in the angioplasty realm we do a lot of. In the anti-platelet trials for example, 3 or 4 percent of patients undergoing angioplasty in the anti-platelet trials don't get the anti-platelet drug for whatever reason in the cath lab. And as long as the intention, the overall intent to treat analyses are done and are consistent, I'm okay with it.

CHAIR HIATT: Any objections? So I

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guess we are okay with question #3 that the data were analyzed appropriately?

Question #4: In a restricted sense vernakalant is clearly more effective than is placebo. Among patients who had been in atrial fibrillation for three hours to seven days, the rates of spontaneous conversion on placebo within a 1.5 hour window were about 4 percent in ACT I and ACT III while conversion rates on drug were at 51 percent at proposed doses.

How well characterized is the relationship between time in atrial fibrillation and spontaneous conversion? Note that 3 percent of patients converted spontaneously after randomization but before study drug administration.

So we have a lot of information on spontaneous conversion rates. And I think as was presented earlier, in a population that might have been predisposed by their physicians to treat them, because they

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weren't kind fo coming out of alcohol withdrawal or something like that, that spontaneous conversion rates over this very short interval were low, but we don't know what they would have looked like at 24 hours had they delayed the therapy 24 hours.

DR. MASSIE: Well, I think that is the answer to the question, is, we haven't characterized it at all. We've just characterized a very little piece of it by design of the study. And it happens. It maybe didn't happen as much as we imagined it might happen. But it's only 90 minutes. And if you came out of atrial fib 100 minutes before, then you weren't - you're excluded from the study, and a few people did that.

So I think the answer is, it really doesn't tell us in this population what we might have expected had we waited 24 hours. But the differences are so real. So I'm not sure.

CHAIR HIATT: Other comments on

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this? I mean I think, you know, in the FDA presentation it was clearly a speculative line that if you wait long enough you will reach a certain level of conversion. And I remain uncertain what that is. Because you are now talking about therapy today, not natural history studies from 10 or 20 years ago.

So I don't know if these trials would have been insignificant had they waited, or would they have shown the same strong signal benefit. We just can't judge it, because we don't know.

DR. MASSIE: Well, I think the big thing is probably the one I think Ed brought up, which is, these were selected for some reason to admit them to the hospital. It could have been to get the study payment. But it looks like they really did mean to convert them one way or another when they admitted them. And I don't know what that means, but I would lend a lot of credence to

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say it's different from the AFib patient who just comes in the emergency room saying my heart is racing. More of those, I think, are much likely to convert spontaneously than this group. But I don't know how to quantify it.

CHAIR HIATT: But you don't know even in this population, had you waited 24 hours, if you would have gone from 4 or 5 percent conversion to 20 percent conversion.

DR. HARRINGTON: I think the answer is, how well is it characterized in this population. And the answer is, it really wasn't characterized.

DR. HARRINGTON: Yes, so let me - and maybe the sponsor can help - one of the things that can frequently help in a clinical trial, these were obviously very selected patients, is, was there a concurrent registry or screening log of the patients who were examined for potential enrollment, and reasons why they weren't ultimately enrolled?

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That kind of information could be helpful. I don't know if that exists for this.

Did you have some sort of screening log where you collect the universe of -

DR. KITT: Yes, we do. We're pulling up that slide for you. Okay, slide up, please.

We did look at this. Hold on just a minute. Okay, so there were in our two pivotal studies, 31 patients were randomized but not dosed; 4.4 percent of the placebo group, and 5.6 in the vernakalant group.

And as has been mentioned previously the largest reason is, between the time of screening, and by the time they got the drug mixed, and they were able to get the drug infused, about 3 percent of the patients had already converted to sinus rhythm.

The majority of the rest did not meet inclusion or exclusion criteria. Between screening and randomization I think

you know some of the inclusion-exclusion criteria, they were doing histories, physical exams, and during that process some of the patients did not meet the inclusion or exclusion criteria. In one patient they were randomized, but they realized that there was no more drug available in the pharmacies.

DR. HARRINGTON: So this helps me with my defense of your modified intention to treat, but it doesn't help me with - think about it like in a consort diagram way that you screen how many patients to get to the number randomized. Do you have that data?

DR. KITT: No, I don't. We don't have the number that were screened. This is just all that we have.

CHAIR HIATT: You know that is sort of the same thing. Did you screen 10,000 people? Do you have some sense of how many people were kind of consented, and then initially screened, and then didn't go forward?

DR. KITT: No, we don't have that data handy.

DR. STOCKBRIDGE: Could I just interject something on this particular question. I mean this is sort of getting at the problem that you are going to have to identify some window, patients who have been in AF for at least 30 seconds, and not more than six months. I mean you are going to have to name a window at some point, if you think you are going to approve this, that says who you think is a reasonable candidate for getting it.

So as you think about the spontaneous conversion rate, and the difference between what you think the spontaneous conversion rate is and the on-treatment conversion rate is, and you know, integrate what you think the symptoms you've saved somebody and what the electrical conversions that you've saved. You are going to have to be able to name both the beginning

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and end of the interval over which you think you are operating. That is what question #4 is mostly about.

DR. MASSIE: I could see you going there, and I could see trying to craft something.

The real issue is, you want people who you don't think are likely to convert spontaneously. It's hard to put a time window on that, but you want the physician to realize that that can occur, and on the other hand you are going to look at these data and say, well, you know, they asked for approval for three to seven days, but at least the doctor has to know that if it's not within 48 hours the success rate falls off quite a lot, even by seven days.

You could describe that, but if you want a definite number, I have a feeling we are going to have a hard time coming up with people who - because the doctors may know something we don't know, or they at

least may think they know something we don't know, about how likely they are to convert, and they may think this patient is different than all other patients.

CHAIR HIATT: But it might affect risk-benefit thinking that.

DR. MASSIE: No, I think it's very important to address those issues somehow in the label. I'm just not sure it's going to come out in precise - or it would be very hard to come out in precise two days to whatever.

CHAIR HIATT: In fact, why don't we go to the second component of this, how well characterized is the relationship between time in atrial fibrillation and conversion on vernakalant? And it seems to be relatively well characterized, in that - because I think then this gets at what is probably a more critical issue, which is, you get a lot of benefit early. You may have not as much benefit late. And you still have the same

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risk I would assume across, whenever you give this drug.

So if you believe there are patients who could be harmed by this drug, and you have shortened the symptomatic window significantly in the patients who had really early onset AF, your response rates are really dwindling off after 48 to 72 hours. And is any risk acceptable in that context?

So I think it's actually extremely important question.

DR. HARRINGTON: That's what I was trying to get at when I asked Ellis the question of had he been able to look at an analysis where you would be able to parse out the risk as a function of duration.

Because hypothetically you could create a situation where the patients who are most refractory to conversion, the later patients, perhaps they are also more susceptible to the side effects, I don't know. But that would be nice to know.

Because otherwise, if you take your case, Bill, that the risk is going to be consistent, or independent of the duration, then you do raise the question of well what exactly is the benefit we're getting in a very narrow window, say 48 hours, when a lot of them might convert anyway.

CHAIR HIATT: You could ask that - you could even assume that the risk got worse if you were in AF longer. That's okay. But you have to integrate those two numbers at some level. And because the benefit tapers off so dramatically over time in AF, that I think that is part of the consideration.

DR. CANNON: Could I ask a question? I don't know if it's appropriate now, but I was going to ask it later, so I might as well ask it now.

And that is the rationale behind the strategy of using this drug on somebody who has been in atrial fibrillation longer than 48, certainly 72 hours, unless they are

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in the hospital, and somebody is just watching, hoping crossing their fingers on a beta blocker that they would spontaneous convert?

And the reason I ask that is if somebody knows that they went into atrial fibrillation at 10:00 o'clock Sunday morning and now Wednesday they decide to go to the doctor, well, by the guidelines you'd have two choices. One is to anticoagulate for three weeks, bring them back and then do something, hopefully spontaneous to convert, or if not then you'd do something.

The other is to use TEE guided therapy. And as long as you're going to do that, you might as well do electrical cardioversion, because you got them sedated for the TEE.

So what is - beyond 48 hours where the efficacy appears to drop off, what is the compelling rationale for extending use of this drug out to seven days? Does that make

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sense?

CHAIR HIATT: It does because the sponsor declared it. It's a short duration cohort, and I think that's okay. Now we may not agree with that, but that's how they cut the data.

DR. HARRINGTON: I mean that was their primary analysis cohort, up to seven days, so I don't fault them for trying to push that forward. Their primary analysis cohort was three hours to seven days. They have an overall treatment effect in the three hour to seven day cohort, so the first principle is look at the overall trial result. That is their overall trial result. So I don't fault them for asking that.

But now you are asking the more important question, which is, okay, now that you have seen the overall trial result as positive, is there a differential treatment effect within the overall trial?

And at least these data suggest

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that there is, that all the effect is in the first 48 hours. I think that's what you're getting at.

DR. CANNON: But I think we have to be cautious. There are 29 patients after day three, which is approximately a fifth of the total population in that group. So just from a methodologically and statistical standpoint I don't know how much confidence we can place on that subgroup analysis saying there is heterogeneity, when the overall trial result for the defined population was positive.

CHAIR HIATT: But did they test that? I don't know if we saw that. Or did you test that, Ellis? Is there an interaction term here? In other words, did you test effect by time, using time continuously?

DR. UNGER: I mean that was really just an exploration, and you see the analysis in the slide. And part of the limitation here is that we only these data for ACT I.

So we are really - and that is part of the reason you only have, what was it, 29. That's the problem.

DR. LINCOFF: But I think making a regulatory label decision on the basis of an exploratory underpowered subgroup analysis showing a result divergent from the overall result, the main estimate from the overall group, is worrisome.

If we want to make it on the basis of medical judgment, based on practice, for the points that Dr. Cannon pointed out, that may be different. But just to do it on the basis of this, and say, well, I don't see a benefit after three days in this exploratory analysis I think is somewhat hazardous.

DR. MASSIE: It's somewhat hazardous, but on the other hand it should be known to the physician. It should be in the label somewhere whether it says you can only use it for the first 48 hours, and then after that it becomes off label, I don't know. But

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it does look like it's there. And the fact that the numbers are so small isn't the agency's fault. You know? So if we can't say that - I think frankly if you did an interaction analysis it would be positive for change in efficacy over time.

DR. HARRINGTON: Did the sponsor do that?

DR. LIU: No, we didn't. The curve was that we showed you, if you want to have that up there, was just an attempt to describe the response rate, how they change with time. It wasn't very much of a parametric model where we could test that.

CHAIR HIATT: I'd be surprised if there was a strong interaction here. Because to me interaction means one subgroup responds differently than another subgroup, and here the magnitude of the effect just wanes.

But I mean it's still there. It's just not as strong. To me interaction if, you know, half your population has diabetes

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and half doesn't, and the diabetics respond one way and the non-diabetics another way, that's interaction.

Here it's just that we're not seeing quite as strong an effect the longer you are in atrial fibrillation.

DR. HARRINGTON: Well, we have Jim here who could correct us nonstatisticians, but I believe what it means is that the difference that is observed is quantitatively appears - appears real, and that the interaction term is just a mathematical of expressing the difference between the two observations.

I don't think it means that they have to go in different directions, but that there - but that they are separate from one another, and that that separation is a real separation statistically.

CHAIR HIATT: So maybe we need to deal with how robust both the sponsor and the FDA's presentation is on this change in

responsiveness over duration of atrial fibrillation.

DR. HARRINGTON: So one other thing, Bill, is the last slide that the last slide that the sponsor put up, to me that adds to the credence that this is a reasonably robust finding. Because as Mike points out, with only 23 or whatever it is patients in ACT I, it looks a certain way. But when you add in ACT IV, the basic shape of the curve doesn't change.

DR. KASKEL: Bill, should we be more concerned about potential racial differences in responsiveness at this point in time?

CHAIR HIATT: I think we need to address that in terms of a variety of issues, but I'm not sure we are quite there yet.

So how well does the committee feel that the characterization of the relationship between time in AF and conversion through vernakalant, how well

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characterized is that?

I think it is reasonably well characterized. I realize, Michael, it's kind of a subgroup analysis, secondary analysis, but it's a positive, it's not a negative subgroup analysis.

So I think it's reasonably well characterized. Now the question is, does it rise to the level of a labeling restriction or not, is a little harder to wrestle with.

DR. MASSIE: Correct me if I'm wrong, I mean there is labeling, precise labeling is sort of needed, prescription. But there are also things in the label that are informational that aren't part of the indication.

And I mean I do feel strongly that given the total amount of data we have and what we see, and the fact that there is no reason to think that risk is going to get less, that it's something that the doctor needs to know, that it's not like anybody who

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comes in in the first week is going to have the same likely response.

So I think that somehow it should get in the label, whether it's - maybe the agency can figure that one out.

I would have a hard time saying it absolutely should only be indicated for people in the first 48 hours for the same reasons as Mike. I would also feel hard - making no distinction between people who were in the first 48 hours and those that are seven days out.

What length of time in atrial fibrillation is clinically meaningful?

DR. HARRINGTON: Well, we heard from Mr. Simon this morning that he knew right away when he went into atrial fibrillation. So what is clinically meaningful? If it's the patient's symptoms, I mean we heard - and we all know this from dealing with our own patients that people can feel miserable, or they can feel

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uncomfortable. And is that - the patient's symptoms are certainly important.

But if you are talking about what time clinically meaningful to then perhaps put that patient at risk for some other bad thing like a thromboembolic event, we believe that is a longer period of time, and Rich alluded to with the guidelines that say 48 hours for anticoagulation.

But I would say if the patient is symptomatic anytime after fibrillation is meaningful.

DR. STOCKBRIDGE: I think we have to divide this into those two cohorts, because in some ways I think this refers to this particular drug and this - these trials and how you maybe set this up.

I mean obviously we talked earlier about length of time in chronic AF can certainly mean certain things. But I don't think that's exactly our purview with this.

Rather it's length of time coming

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into a treatment decision.

DR. HARRINGTON: What are you trying to get at here, Norm?

DR. STOCKBRIDGE: I think all of these sub-bullets deal with the issue of how to set some advice about how long somebody should be allowed to sit in AF before you do anything, and then what your window of opportunity is for applying a drug, this drug, to get somebody out of AF.

CHAIR HIATT: So if you waited, based on what you just speculated, if the patient presented, and we waited a couple of more days, and we think we know that the drug might not work as well, we also think that the spontaneous conversion rate might have caught up to some degree, and so the lines might start crossing at some point in time here.

DR. CANNON: And also at about 48 hours you are going to have to make a decision. In my practice 48 hours is the

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tipping point. And you've got to do something. I mean either you are going to decide to keep them in atrial fibrillation just to be satisfied with the rate control, which is fine for many people, but you are going to anticoagulate them, get them started on coumadin, or presuming that they've been on heparin for some interval of time, cardiovert them.

So I think from a management standpoint 48 hours is pretty much the decision time. You've got to do something. You've got to make a decision. Crossing your fingers and - that's over. You got to make a decision.

DR. LINCOFF: And if we believe this rather steep fall in the efficacy of pharmacologic conversion with this agent over a few days or so, then there is a potential disadvantage to waiting.

CHAIR HIATT: Well, that's correct. Again as just stated, I think all the

comments sort of fall in line a bit. So the drug is probably maximally effective during that window, and it tapers off over time. Other things have to kick in at 48 hours that might affect how you'd use this drug. I mean maybe there would be other such compelling kinds of treatment decisions that the drug would have hard to market for people who have been in AF for longer than 48 hours. And so the decisions change.

So I think those are all very relevant. It still kind of comes back to shorter is better from a variety of perspectives.

DR. HARRINGTON: I like the way that Richard described it, 48 hours does sort of encompass a lot, doesn't it? There is a decision making that has to take place at the end of that time period that is really critical, in long term or even intermediate term. Anticoagulation is a big deal.

MR. SIMON: I've gone to 48 hours,

and I have not gone to 48 hours; 24 or 48 hours. And at the 48 hour I've been told by my physician that you need to get in here; we need to make a decision. And I'm on anticoagulant also. But if I'm that, they call it chronic, and it's 2 - 300 beats a minute, you are not really functioning too well. But if it drops down to 100 or so I can do things, but it's not like the other. But within 48 hours, I've been told get in there.

CHAIR HIATT: For patients who have been in atrial fibrillation for what duration is the time savings attributable to vernakalant clinically meaningful?

So we triangulated a bit, the sort of 48-hour timeframe, when the drug is maximally effective. It clearly beats placebo; has symptomatic benefits during that time and it avoids cardioversion.

DR. MASSIE: I'm a little confused about the question. I don't know what time

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savings we're talking about, because the only time savings is protocol driven. I mean if you are going to convert them, you are going to convert them. But in this protocol you had to wait 90 minutes to convert them.

I don't know how to quantify the time savings. I do believe that the patient will be converted quicker than my organizing a cardioversion for an elective. So there would be a time saving but it's not quantified in the protocol. It's driven by the protocol.

CHAIR HIATT: Well, the protocol said two hours. Then you could open up to other decisions, right? So you might have saved - would you grant two hours time saving?

DR. MASSIE: Well, it's protocol driven. If they had just came in -

CHAIR HIATT: But yes or no.

DR. MASSIE: I would two hours is about as early as I could organize electrical

cardioversion.

CHAIR HIATT: So at least you've saved that per protocol.

DR. MASSIE: But it is by protocol. It's not an effectiveness of the drug that you saved two hours.

CHAIR HIATT: Right.

DR. MASSIE: But since it does coincide with probably our best efforts at organizing a rapid cardioversion, I believe two hours if a patient is uncomfortable is -

CHAIR HIATT: In those 50 percent who responded, then you might have saved them a number of other things too.

DR. MASSIE: It's just that I can't put a number on the time savings, because the time saving is not something that happened clinically it's something that was driven by the protocol.

DR. HARRINGTON: Yes, that's the part I'm struggling with, in terms of clinically meaningful. What is, if I had to

have you wait two hours while you were going to be cardioverted, and you rate was reasonably controlled, you were a little - you felt your palpitations but you weren't that uncomfortable, is that clinically meaningful?

It's a tough one, and as Barry points out, you are only going to convert half the people, so you have to take into consideration that half the people didn't get converted, and that has to get entered into the - or quantified.

We are parsing pretty short periods of time here.

DR. LINCOFF: And it also depends upon a practice pattern that could be altered depending on where you are in that alternative. If you are coming up close to 48 hours, you may say well electrical cardioversion will do it right now. Otherwise you might say, tomorrow come back and we'll set up the room. So it's something

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you have control over.

DR. STOCKBRIDGE: I think we ought to probably move on. And if you vote in favor of approving this drug, we should readdress this question as part of the follow up to that, to try to get some sense for who it is you think you are approving it for.

CHAIR HIATT: All right, let's move on to some more questions.

What effect does unsuccessful conversion with vernakalant have upon subsequent attempts at electrical conversion?

That, I think, was answered: no effect. Everyone agree?

How was atrial hemodynamic function affected by vernakalant? Does this matter?

DR. CANNON: I saw no data on that. It could matter, particularly for patients that have very stiff hearts. Cardiomyopathies in which atrial systole is important.

I think our belief is that the shorter they have been - the shorter the time they have been in atrial fibrillation, the quicker we can get them back into sinus rhythm, but better the perversion of atrial transport; the longer they have been in atrial fibrillation, the longer it's going to take for atrial systole to recover.

But we don't have any data.

CHAIR HIATT: But isn't this sort of what the drug might do during that sort of acute exposure? And does it do anything adverse to the atrial function?

DR. CANNON: I saw no data.

CHAIR HIATT: That we might care about? Anybody else have any thoughts about how to interpret that?

DR. MASSIE: I saw no clinical data, but there were a number of animal studies trying to characterize the electrical effects. Did any of those look at atrial function in another way? Do you know? Put

crystals in or do echos or do something like that to see if there was a depression of atrial function?

DR. BEATCH: We did not assess atrial function in animal studies.

DR. KASKEL: I think there is a potential for some studies here at the cardiac physiological levels are very keen looking at with some patch clamping possibly doing some models to see what happens to the question of channels, the different sodium channels, subtypes and potassium.

It's possibly if they don't atrial systole the system, maybe it's a different gene expression of channels that don't turn off later. It means a host of things for an electrophysiologist and a molecular biologist, a lot.

DR. CANNON: But it could be a simple echo study. You know, does the atrium squeeze or not? What interval is important for recovery? Does a dark matter versus

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electrical cardioversion. I would think that that could be easily obtained just by echo.

CHAIR HIATT: Well, it'd be confounded a little bit by, whether you are in or out of sinus rhythm. So the question would be answered, of those who converted spontaneously versus on drug, was there a difference in atrial function.

DR. CANNON: Is there a difference between electrical cardioversion and pharmacologic cardioversion.

CHAIR HIATT: Sure, and is there a difference between those who converted spontaneously, electrically or by drug in terms of major function, we just - we don't have any data.

DR. STOCKBRIDGE: And do you care? That was part of this question.

CHAIR HIATT: Unless you think that the fatal case of VF or something like that was related to some alteration in atrial hemodynamic function, that to me is a

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speculation, I don't - I don't believe it, so I'm not sure I care a lot.

But does anybody else care?

DR. CANNON: Yes, well, for some patients it does matter. Again, patients with stiff hearts; patients with hypertrophic cardiomyopathies, atrial systole matters a lot.

And one of the justifications for restoring sinus rhythm in those populations versus patients with otherwise fairly normal -

CHAIR HIATT: Okay, but it doesn't seem to change the response to cardioversion. I mean I try to think about this as something that I can relate to clinically. Hemodynamic function could certainly be characterized a whole host of ways, right, both invasively and noninvasively.

The question is, do any of those measurements relate to anything that would clinically change as a result of giving this

drug, that would somehow affect - somehow induce more thrombosis in the left atrium, induce inability to respond to cardioversion, that's how I interpret this.

DR. LINCOFF: Well, it could. I mean you couldn't do it with this experimental design. But if you did an experiment where half the patients got this drug, and then if they failed went to electrical cardioversion, and the other half just went to electrical cardioversion, and then in the end you assess atrial function, is it different with these two approaches? And if it were better or worse with one approach or the other, that would be relevant information. Because presumably that might have an impact on the likelihood of developing a thrombus a few weeks afterward or something.

But you couldn't do it with any other design. You couldn't even do it just by looking at those who converted on drug

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versus those who converted electrically, because those might be different patients. The electric will be more patients, the drug might have been patients who had been function to start with.

You'd really have to take a pure strategic strategy approach.

DR. MASSIE: But we do have some relevant information. It did appear that hypotension was more common with the drug in the people who had heart failure. Isn't that right?

And so who knows the reason, but if in fact that would be a group that might depend more on their atrial function, first of all. And maybe hypotension is invasive dilation. Maybe it's atrial. But it's a lot of speculation.

But otherwise I don't think we have any way to answer this question, other than just that it raises some interesting points.

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CHAIR HIATT: And to your point, Michael, I think that there could be three groups - the spontaneous converters, the electrical converters, the drug converters. But again why would you care? It has to be driven by whether that will be so many long term sequelae due to alterations in atrial hemodynamics. And that is the link I'm having a hard - because remember, the drug effect is very transient. So whatever it did to set up some kind of cascade of events that might be bad or may be good, I think it'd be really hard to tease out.

Now I think to your point, Barry, I think that actually ties that back in to some of the safety concerns, and there it might be relevant.

DR. STOCKBRIDGE: So I didn't quite hear how badly anybody wanted to know the answer to this.

CHAIR HIATT: I don't feel strongly that that's something I would ask for. We

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are intellectually curious, but - so it doesn't sound like the, does it matter question, at least at this stage, it doesn't seem to matter a lot.

DR. LINCOFF: In part because we don't even know what the standard electrical cardioversion does.

CHAIR HIATT: Right. We don't know what any therapy does to that particular constellation of atrial function measurements.

How much of a safety concern is torsades? Have the rates of torsades been adequately characterized in the patient population, and at the doses for which vernakalant will be used? For how long, either hours or QT prolongations, should rhythm be monitored after exposure to vernakalant? Does this time need to be adjusted for the 2D6 inhibitors and for poor metabobolizer phenotypes?

Start with the rates of torsades,

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have they been adequately characterized at the doses used?

DR. MASSIE: They are somewhere between nil and ibutilide. I mean I think there probably is a risk of torsades. It's not really very apparent though. So I would say it's low.

CHAIR HIATT: But you don't really mean that it's as high as -

DR. MASSIE: No, no. It's a big window, but I don't think it's high. I mean there is a confidence interval.

CHAIR HIATT: Does anyone doubt that torsades is related to this drug?

DR. MASSIE: I'm not sure.

DR. LINCOFF: I do. I mean this is the limit, this is the limit of the small sample size. This is really where we run into the problem of small sample size.

But I think there is a very real possibility that there is not torsades related to this.

The one episode of torsades that was early was after a patient got ibutilide. And you know the other ones were later, and they were the same rate in the placebo group.

And the prolongation of QT is trivial compared to ibutilide and the other agents that are pure potassium channel agents.

So you know there is a real possibility that this is not an issue with this drug. It might be, and that's why we clearly need more data. But I think what we've got now does not provide a signal to me that -

CHAIR HIATT: So if the drug didn't prolong the QT interval, but if there is biologic plausibility, you still don't see a link? If it did not, that's one thing. But this drug prolongs the QT interval.

DR. LINCOFF: But the prolongation is very mild.

CHAIR HIATT: I understand. But of

course we don't know the outliers. We don't know the shift of curves if you will on those - the means and population changes aren't that great.

DR. MASSIE: It's not small. We were talking about 20 milliseconds, right?

DR. LINCOFF: It's much smaller than the other drugs.

DR. MASSIE: I know, but we're talking about a chronic drug exposed to people in the population, we are in a ballpark where the agency would be not even wringing their hands but say, go out and prove that this is harmless. It's not trivial. It's transient.

So I would say my default thing is it might increase the risk of torsades. It doesn't increase it hugely, and we need more data.

CHAIR HIATT: And remember that, I do think that that is real, but it's in an acute setting. It's highly monitored. The

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drugs wash out, and then one of the questions will be, how long do you have to monitor people, so that if there is QT prolongation, which we think there is, and if there is even the chance of related risk, then I think the answer to that is, you can monitor these patients until the risk goes away.

DR. LINCOFF: I'm not saying we have enough information to exclude it. I'm saying we don't have a signal, and certainly I think it's likely to be much less than a drug that has more substantial QT prolongation.

I mean QT prolongation with ibutilide, the estimated - point estimates are, what, about 3 percent? So this I think is clearly much less than that.

DR. HARRINGTON: That would be my perspective, that if you just look at the data that Dr. Ruskin showed us, one out of 700-and-some cases gives you an estimate of .13. You have a boundary on the confidence

interval of .61. You know, do I believe that there is prolongation of the QT? I did have a question for Norm. It mentions that they did not do a standard QT study.

With this type of drug, with the amount of electrocardiagraphic information they have, does that suffice in this arena? Or was it because they started this development program before you really launched full bore?

DR. STOCKBRIDGE: No, we do not ask for a classic thorough QT study a la ICH E14 for a drug that clearly prolongs the QT.

CHAIR HIATT: Okay. So back to the question, though. I mean, there are these events in the database. How well characterized are those events of torsade? I mean there --

DR. MASSIE: I strongly believe that they need to be. Post-marketing or whatever, I think we need more information.

CHAIR HIATT: Well, they exist in

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the database. They are characterized to the degree that they are in the context of a randomized trial.

DR. MASSIE: The torsade, you mean?

CHAIR HIATT: Yes. They just aren't that many.

DR. MASSIE: Right, and the worst one is actually associated with ibutilide, so --

DR. HARRINGTON: Yes, but still -- yes, I mean this is the issue. Mike just said that, that we have a small sample here. We -- if you just look at the two phase II trials, we're talking about low hundreds of patients exposed to the drug. Yes, we saw some baseline demographics with -- that suggested that these patients were -- had some characteristics of the overall AFib population, but in general, this was a pretty healthy population, and the one person who we know about that was really sick, got the drug

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and died. So --

DR. LINCOFF: Not primarily of arrhythmia. I mean that patient had two severe hypotensive episodes and then --

DR. HARRINGTON: And then had an arrhythmic event and --

DR. LINCOFF: Right, but, I mean, we know that you get hypotensive with an aortic stenosis. I mean I think that's a drug-induced death, but I don't think it's a VF death. I think it's a hypotension death.

DR. HARRINGTON: I would say that we have drug death and everything in between is open to speculation.

CHAIR HIATT: I think we cannot exclude the possibility that in a broader population, the torsade's going to be something to deal with and the question is not we can't prove it. It is in this database. There may or may not be a relatedness. I'm not sure I'm too obsessed about that because it's there and so it's

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going to have to be looked for very carefully.

DR. STOCKBRIDGE: Okay. So you're talking about, maybe, some kind of registry to follow rates of torsade in the future. Is that what I hear? Is that where you're going?

DR. LINCOFF: As well as other.

CHAIR HIATT: Yes. I mean probably more than just registry, you know, but really kind of looking at observational studies in more formal ways, you know, that allow you to adjust for treatment decisions, which might directly impact the risk of torsades, and other factors.

DR. MASSIE: I think there are complementary ways of getting at this. I think a consecutive series of people with a lot of data and some prescribed ECGs would be good, and I think the ones that come up as reports, then you have to do what you're saying, is use the observational whatever

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techniques we have available and if the two -- neither shows a signal, it's easy. If one shows -- if both show a signal, it's easy, and if you get half -- mixed results, then it's complicated.

CHAIR HIATT: So I guess we're saying that the rates of torsade have not been well characterized, that they are what they are in the development program of a very small number of patients with a very minimal amount of exposure, and that that's an unknown that would need to be monitored going forward as exposure increases.

"For how long (either hours or QT prolongation) should rhythm be monitored after exposure to a vernakalant. Does this time need to be adjusted for the 2D6 inhibitors or for poor metabolizer phenotypes?"

DR. LINCOFF: I don't think you can, in practice, do phenotypes. As Dr. Unger pointed out, I think that that's fairly

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easy. You know, looking at this graph, it looks like the maximum prolongation was about 20 milliseconds. Does your average practitioner have the ability to clearly read 20 milliseconds on a QT in a patient?

CHAIR HIATT: Okay. So then, you might actually need to think more about PK and just come up with some sort of guidelines that would -- because it didn't seem that the metabolizer status was -- had a big impact, but one might want to take just the worst case scenario for DDI kinds of things and metabolizer status and just fix that as the monitoring window, not -- and take the guesswork out of the clinical decision-making.

DR. STOCKBRIDGE: So the question really was mostly, should -- how long should the rhythm be monitored. It wasn't how long you should monitor QT particularly.

DR. LINCOFF: No, I only brought that up if one of your criteria, which was

proposed would be until the QT returns to normal or a time. I'm just not sure most of us, especially, you know, in the ER tracings, et cetera, is going to be able to measure that.

DR. HARRINGTON: Yes, I agree with Bill, either you're going to have -- for the average practitioner, you're going to have -- the above average practitioner, it doesn't matter, you're going to have to give him or her guidelines that says, X hours. I think Mike's right, that if you start requiring people to look at the Q, forget it. I mean maybe the physiologist will do it. I'll tell you, the busy general cardiologist, the busy emergency room physician will not do that.

CHAIR HIATT: Okay. So we all agree with that. So what are you -- you're looking at the data. What do you all want to recommend for any kind of a monitoring window here?

DR. CANNON: Well, last night I

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wrote, two hours, but I'm scrambling to find the data to justify that. I've got it underlined, two hours.

DR. MASSIE: You know, I think caution is good. I would -- I'd feel better with three hours and I have no data to justify that, but I am pretty worried about the emergency room use, because monitoring and monitoring (sic) and paying attention and not paying attention and the urge to get people out, you know, we can say anything we want and it is a drug that ER docs would probably like to use, you know, I would guess, on patients, so -- but I just don't think we know enough from the data set we have to be fully comfortable with two hours, although when I looked at, we didn't see anything after two hours.

CHAIR HIATT: If you think there's any safety concern at all, why would you compromise on a monitoring window here?

DR. MASSIE: Then you've got your

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registry and your post-marketing thing and maybe you could convince the FDA to cut it back when they've showed that nothing bad has happened.

DR. HARRINGTON: Well, Cathy, could you put up slide 33 from the sponsor's presentation? Is that possible?

So this is the -- well, maybe the clinical pharmacologist could explain this to us, that presented it, but it looks to me like the curve is truncated at two hours. So we don't know -- I mean this is all modeled data, but --

DR. KEIRNS: Sure, we could extend it beyond there. I've actually -- Dr. Kitt had also showed data on the QT for poor and extensive metabolizers, if you want to -- 72, I think it is.

DR. HARRINGTON: But the poor metabolizers still have a fair bit of drug hanging around at two hours.

DR. KEIRNS: Well, so do the

extensive metabolizers, actually. I mean it drops to about half of the concentration within about 30 minutes of the end of infusion, due to the distribution phase, and then --

DR. STOCKBRIDGE: That's not what the previous graph shows. The graph shows at two hours, you've got half of the --

DR. KEIRNS: No, I mean 30 minutes after the end of the last infusion, if you go back to the slide we just had a minute ago.

So if you're -- in our, you know, in our thinking, we've been recently thinking in terms of monitoring from the end of the infusion because, of course, some people will get one infusion, some will get two infusions, and in the clinical trials, we defined everything from the start of infusion, but if you look from two hours from the start of infusion, which -- or 30 minutes from the end of either of the infusions, the concentrations have fallen by about a half,

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and then the slide -- the slide that actually shows the QTcF changes from baseline for the poor metabolizer and extensive metabolizer population, really don't show any difference in the values between these two populations. There's -- as you see, there's 15 poor metabolizers, which is why the error bars for them are considerably wider and 360 extensive metabolizers.

CHAIR HIATT: And it looks like at two hours, the QT is getting back towards baseline.

DR. KEIRNS: Pretty close, yes.

CHAIR HIATT: So a minimum of two hours after the end of the second infusion, if not three.

DR. HARRINGTON: The broad confidence intervals around the poor metabolizers don't bother you? It's only 15 -- is it 15 patients?

DR. KEIRNS: Right, it's 15 patients. Well, the prevalence of poor

metabolizers in the population is about five percent. We were able to genotype about 40 percent of the patients in our studies, so that's the nature of the data you're going to have, basically, unless you do a huge study.

DR. HARRINGTON: But that's the point, that there'll be a group of patients who you can't identify prospectively who have a potential risk of having -- if I take the upper bound of the confidence interval, actually having substantial drug levels two hours later and I don't know who they are.

DR. KEIRNS: Well, the other thing we did do was look at PK outliers -- or rather QTcF outliers rather -- that Dr. Kitt presented, and I actually went and looked at the data for those 15 poor metabolizers and there were only two of them that had any QTcF values above 500 milliseconds and those were at the end of infusion. By one hour from the -- or actually, by 30 minutes after the end of infusion, they were back well below 500

milliseconds.

CHAIR HIATT: Yes, what Dr. Harrington's point, I think, is -- actually, I'm glad you reminded us of this. It really is the end of the confidence interval of risk that we worry about, not the average or the point estimate or the population mean. So if there were a subset of poor metabolizers who did have sustained drug levels past two or three hours, who could be at risk for torsade or other lethal arrhythmias, wouldn't we want to know that?

DR. LIU: Can I take a chance to comment on the confidence interval? Jeen Liu, I'm the statistician from Astellas.

Can I have that poor metabolizer slide up again, that we were talking about? So I think we are concerned -- the concern is about that last peak of the green confidence interval being pretty high. I think we have to take things in totality. What we have done here is to provide a confidence interval

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at each time point assuming that my QT at this minute had nothing to do with my QT five minutes ago. So if we integrate all that information, what you're going to see is the confidence interval will shrink. We have to take that into consideration.

CHAIR HIATT: So the question remains open, I guess, based on this whole issue about return of QT back to baseline, drug levels, you know, two hours post last infusion, and length of monitoring, is there -- there could be the potential for risk beyond a conventional time point, and so, therefore, longer might be better.

DR. MASSIE: Well, there's the other thing is where we focused on torsade and QT, but there's blood pressure and heart rate --

CHAIR HIATT: Yes, hypotension and bradycardia and that kind of thing.

DR. MASSIE: -- and, I mean, it's not like we know a huge amount about this

drug.

CHAIR HIATT: Yes.

DR. MASSIE: And so if there is to be more data to be collected to get us to know more, I would really want to take caution aside and then, you know, get less cautious when we have more information. That would be my -- it's really less than looking at confidence limits and curves. It's just --

CHAIR HIATT: Well, the amount of patients exposed does not exclude a bunch of outliers as to who could be at risk.

DR. KITT: Hi. Could I please have the slide up?

We based our 90-minute after the end of the last infusion on a couple of things, and these are the peri-infusional hypotension adverse events. The gray bars are vernakalant -- or, excuse me, the green bars are vernakalant and the gray bars are our placebo, and here are two infusions, and

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you see that most of the vernakalant-associated hypotension occurs peri-infusional or right after the infusion. Now, this right here is our 90-minute post-infusion time point, if you will, and you'll see from that time point on, once again, other therapies are allowed, but there is a higher incidence in the placebo group compared to the vernakalant group.

Can I have the bradycardia slide? Oh, okay. Slide up, please. And this is if you look at bradycardia and sinus bradycardia, and once again, looking at adverse events, a similar kind of curve. Again, we see that most of the bradycardia occurs peri-infusional, and here again is our 90-minute after the end of the infusion, if you will, and we see higher incidences of bradycardia in the placebo group.

Just -- wait. You just --

DR. MASSIE: That interval is labeled 120 to 240.

DR. KITT: Right. That --

DR. MASSIE: So that is either 90 minutes --

DR. KITT: Yes.

DR. MASSIE: -- or it's a lot more.

DR. KITT: What this is, these slides are created -- the way we had cut all of our data was the start of the infusion was time zero. So this was our two, our two from the start of the infusion. So in each -- each infusion was ten minutes -- a 15-minute observation period, so actually minute 35 is the -- is the end of the second infusion.

DR. MASSIE: Well, we can't micro-manage, but that'd be two hours after the end of the last infusion, which is probably the same as three hours.

DR. PRATT: Just -- Craig Pratt, Methodist DeBakey Heart Center, the fourth of the consultants that's here.

We all participated in making some

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tables. They're actually in your document and we're dealing with Table 23 for hypotension, which is on page 72, and those are the hypotension events that actually caused a doctor to say, "Serious adverse event and/or discontinue the drug." So they're the most important ones, and Dr. Massie might agree that, when we look at data, discontinuations and SAEs are important than AEs. All of those events started in the first 60 minutes, the hypotension events. So they'd have all been identified by 90 minutes. They certainly lasted longer, but they were all -- the only exception is the patient with cholecystitis and of course that patient wouldn't have gone home because they ended up with a laparotomy for cholecystitis.

So I think that if you look at Table 21 and 23, you'll see that these declare themselves long before 90 minutes in almost all patients, unless they were really sick anyway and they're not going home.

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