200 or malignant hypertension or --

DR. MASSIE: That VA cooperative study will never happen again. I mean, those were people who had diastolic blood pressures of 120 and above and were left off therapy in the control group.

CHAIR HIATT: Barry, the point is -- and, actually, I think Bob's point is -- is we actually talked about the risk of being on placebo in hypertension trials. And it turns out you were probably okay out to four weeks.

MR. SIMON: I want to make one remark regarding the blood pressure-elevating effect. We have seen this consistently in the pre-clinical program, but it was always very limited in extent, so about 10 percent increase, and it was transient, only lasting a few minutes.

And this is also what Dr. Straub told you today, that it was seen in the clinical program as well, but only transiently during the infusion. And mild.

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CHAIR HIATT: All right. Is the risk management plan proposed by the sponsor appropriate for the safety concerns? I mean, part of that is hard to answer, because we've said there maybe are still lingering safety concerns.

DR. MASSIE: I just don't think it -- I think it's not adequate, because I don't think we are at a point where we can look at uncontrolled data to understand the risks of this drug. So it's well thought out, and it has all -- nice attributes, but I think you have to know more than we know about a drug before you can go to this next step to understand safety.

DR. HARRINGTON: It's almost like that question should come after 13. That is one of the things if we vote to approve it, then shouldn't we ask the question; is the proposed management plan okay? Because if we say "don't approve it," it's irrelevant. If we say "approve it," we should have some

discussion about it.

CHAIR HIATT: Yes.

DR. HARRINGTON: I mean, is that fair?

CHAIR HIATT: That's fair. There's another study necessary to confirm the appropriateness of the dosing recommendations. If so, in what population should it be conducted? And this is one that came out of the FDA review, and that the dose is complicated, and maybe it can key off a little bit on how much do we know about the dose in men and women. And so does anyone think that another study is necessary to confirm the dose?

DR. CANNON: So I would say yes, to confirm in women, because I am concerned about the very narrow therapeutic window, that with just a slightly higher dose you can see a considerable increase in ventricular tachyarrhythmias. And that the decision to use .32 milligrams in women -- milligrams per

kilogram was based on exposure to I think 200 women. I believe that's right. Correct me if I'm wrong.

So not a very large number of women, so I -- I'm nervous about that therapeutic window in women. So I would propose another study at the least with women to confirm that that dose is the appropriate dose, and it's safe and effective.

CHAIR HIATT: Well, now, if you want to do that, tell me how many patients you think you need to study.

DR. CANNON: I don't know. A statistician would have to tell you.

CHAIR HIATT: Well, but you know enough about this. I mean --

DR. CANNON: Probably another 200 women, and maybe from North America where perhaps you'd have treatment that would be more comparable to what they would be exposed to in this part of the country.

CHAIR HIATT: So how many -- how

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many events --

DR. CANNON: But the question is to confirm. If I'm reading the question correctly --

CHAIR HIATT: Yes.

DR. CANNON: -- to confirm, that's what I feel.

CHAIR HIATT: Okay. And maybe -- I don't know if it's appropriate to sort of speculate about what it would take to prove or, you know, rule out a safety concern. But it's going to take acquiring a lot more events than we have here.

DR. CANNON: Right.

CHAIR HIATT: And that's going to probably take a lot more people. Now, if it included torsade, maybe you're going to get enough events occurring with the drug administration to rule that out, what --

DR. LINCOFF: I would have a dissenting opinion regarding singling out women. Again, I'm not -- not to say we have

enough data one way or the other, but -- so by my reading, I may be wrong here, but at the recommended dose there were 170 -- 171 males and 202 females, is this right? This was my reading of the -- who got active drug.

So, I mean, I think the exposure at recommended dose is relatively comparable, and then the safety population was 528 males and 403 women. I may have the numbers reduced, but they are fairly comparable reversed.

So, you know, I think that, as much as we have confidence in the overall result I think these dosing guidelines are reasonable for men and women to the -- again, emphasizing, to the extent that we feel comfortable, with the overall development program.

And also, although I don't like the change in bolus speed or -- I am going to accept that there was a lot of work that went into this. And if there was an easier way to do it, I anticipate the sponsor would have

been all over it. So I think that, you know, it is what it is.

CHAIR HIATT: So based on what we know today -- and I think we have highlighted the things we don't know -- is the dose as well characterized as it can be, how it can be administered and using these algorithms that are posed on these different flow sheets?

I mean, I have to agree with you. I think that they've done a good job to try to -- to do that. It's certainly -- it certainly poses the risk of mistakes and overdoses and all the things we talked about.

I think the question could be looked at that way, and it could also be looked at, once again, going back to this whole risk-benefit ratio, and do we know enough about dose and risk and benefit?

DR. HARRINGTON: Yes. I mean, I think they have done a very good job. And I agree with Mike's comment that if there was an easier way to give it, I suspect that smart

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people there would have figured that out.

I am worried about the complexity. I mean, we know this from a variety of areas, that people are going to get it wrong, and no matter what you do they're going to get it wrong. So is there a better way to do it? I suspect that they are going to continue to think about it and try to make it better.

I'm not sure that imposing on them another study -- I agree with Mike -- it kind of is what it is right now.

CHAIR HIATT: Or if you were going to impose another study, is that the one you would impose?

DR. HARRINGTON: That would not be the one I would propose.

DR. KOWEY: Not to belabor this, but I think they have to put this in the context of the most frequently used drug that is used for this indication is IVM uterine. And we have no idea how to use that drug. If somebody has a -- knows the dose to use

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intravenously for AF termination, and if somebody knows how to avoid all of the consequences of adverse events that commonly occur with that, I'd like to hear them, because -- so I think you have to put this in some kind of context.

Yes, it's not the easiest method of administration, but it has been very well studied. And I think within the -- with the way that they've studied it, I think that they've proven what they needed to prove. If you -- if this drug isn't available, and drugs like this aren't available, the default option is a drug we know nothing about.

CHAIR HIATT: All right. Maybe I would suggest just a couple of minute pause, stand up, stretch, and then we'll go to the voting.

(Whereupon, the proceedings in the foregoing matter went off the record at 4:17 p.m.

and resumed at 4:28 p.m.)

CHAIR HIATT: So if all of the voting members could have a seat.

So there it is on the screen. So this is actually the voting question. Should tedisamil be approved for the conversion of atrial fibrillation? One, yes; two, no; three, abstain.

Everybody -- before we actually do this, anybody have any other questions that they want to address before we do the vote?

(No audible response.)

All right. So go ahead and vote.

(Pause.)

Push it again. It might take a couple of shots. Does that mean they're all in?

Okay. Then, I think we'll go around the room. I forget who went first. You get to go first this time. And just state your vote and then give a short explanation.

DR. HARRINGTON: So I voted no, and

the reason I voted no is that I do believe that this drug has some potential value. I think it has -- but I'm very concerned about the representative nature of the patient population, which included some of the things that Mike had brought up about the drug treatment.

I'm not entirely convinced that we've well characterized the safety. I think that the dosing and the monitoring has not completely been worked out. It's quite complex, and I believe that more information is warranted before approval.

DR. MASSIE: I voted no as well, and largely because I just don't think that I know how safe it will be in practice in the United States if it's approved. And I think we need more data by virtue of prospectively designed studies rather than risk management type of trials.

DR. LINCOFF: I voted no for the same reasons that have been stated, and that

I discussed earlier. That is, the imprecise estimate of the risk of particularly torsade in a population that I would consider relatively low risk for the events, or at least the population -- with little definition of what it would be in the population that would actually get the drug.

CHAIR HIATT: I voted no as well, and I -- now I will link yesterday and today. I feel that both programs had the same deficiency, which was, in my mind, I don't have a lot of confidence in the safety issues, both the events and the arrhythmias. I know that the efficacy is fairly clear, but short-lived. So I'm not as bothered by that, though I'm not sure how much patients are going to gain from that amount of efficacy, though the shocks avoided I think was a reasonable argument.

So my major reason I think to vote no is that the safety issues are -- to my mind don't allow you to make a proper, informed

choice that incorporates risk and benefit into a treatment decision for this drug.

MR. SIMON: I voted no. As a patient, the complicated nature of the regimen, as well as I just would not feel comfortable taking the drug myself, and for all of the other reasons that the doctors have mentioned, led me to this conclusion.

DR. CANNON: I voted no. I am largely concerned about the narrow therapeutic window, particularly in women. I'm also skeptical that this is a value in atrial flutter. Certainly, it's not in women.

DR. KASKEL: I voted no, and I think that, on the positive side, the sponsor has done a lot to develop this risk map, which could be used for subsequent studies, as well as observational studies that are needed to answer some of the questions that have not been addressed, such as safety.

CHAIR HIATT: All right. So I'm going to say something here, Norman, that I

think maybe will try to tie the two days. And I don't know if I'm allowed to do this, but it seems to me that with -- we had six yes and two no yesterday, and we had all no's today.

I don't think that the programs are that much different. In fact, maybe the no votes were influenced by more data today than we had yesterday. And so I would hate to send a recommendation to you all that somehow one drug looks a lot better than another drug.

And if the FDA feels that both of these drugs maybe could go forward at some level, then the yes votes from yesterday should count as much perhaps. And if the FDA feels that these drugs pose significant, unrecognized safety concerns, then the dominance of the no's today should be considered.

In other words, I don't think now today that we're done with the vote. We should take these votes in isolation. I just don't think that the difference here -- the

populations, the indications, the way these drugs work -- are so much different that we should dissociate now that this drug doesn't work and shouldn't be used and the other drug does. That's just my sort of synthesis of what has happened the last two days.

DR. CANNON: I'll respectfully disagree. I think these are different drugs. The drug yesterday does not have quite the same pharmacologic -- electrophysiologic effects, particularly with QTc prolongation. And I think the arrhythmias that we saw with this drug differ to some degree with what we saw with yesterday's drug. This is more torsade-defined, which is not surprising, given the effect on the QTc interval.

I don't think they are apples and apples. I think they were two different drugs.

DR. MASSIE: Yes. I would say, really, pretty -- very much the same thing. I think that we don't really have the risk

quantified from the drug from yesterday, but I think we have a feeling that the events that occur are less mechanistically related and perhaps less life-threatening.

And so I think it's that distinction that Richard just talked about, together with the fact that I think the experience was a broader experience worldwide, and perhaps because of the large number of people in Western Europe, as well as the moderate number in North America, more reflective of what we might expect to see in the United States if the drug was going to be used, whereas that really was absent here.

And while, you know, I'm involved in a lot of trials -- and this is -- enrolling patients in this country we know is expensive and difficult -- it can't be avoided totally.

CHAIR HIATT: So let me just finally say that I voted no both days. And I voted no both days because I think the safety concerns are largely undefined.

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DR. LINCOFF: But as someone else who voted yes yesterday and no today, I also would like to courteously provide a rebuttal, that I don't think that the programs are the same either. In addition to the points that have already been raised, there is also this important issue of concomitant medications.

And yesterday's program had a goodly proportion of patients who were on representative other meds that you use for atrial fibrillation, not enough to do subgroup analyses, but enough to say that this population represents the type of patients that we would be treating.

DR. HARRINGTON: So as someone who also voted no the last two days, I'll also disagree with you, Bill, that I voted -- I voted no for some of the same reasons. I don't think that either program had well characterized their safety profile of their agent, and I made that comment yesterday. I thought the numbers overall were insufficient.

I'm still not sure what this early conversion endpoint really means. I think we've come to some sense, as a Committee, that avoiding electrical cardioversion is good, and that has been a -- I think a healthy discussion.

FDA might want to consider having a meeting with more experts, not necessary a panel meeting, but to have a full discussion about what should constitute meaningful endpoints in this arena. But there were some other things about yesterday's drug that I think were different than today's drug.

So for me if it was -- if this were a Venn diagram, the two days overlap largely for me, and maybe that was the point you were getting to. But I do think that there are some distinguishing characteristics of each drug that I felt were lacking.

CHAIR HIATT: But I did that intentionally, Norman. And I think -- I wanted to flush out what was similar and what

was different. And I hope that's helpful.

DR. STOCKBRIDGE: Yes, I think it was. Could we take maybe a minute or two and have people just sort of sketch out exactly what they think they would expect this sponsor to do to earn a yes vote?

DR. HARRINGTON: Well, I would like to see, number one, more patients, more representative of global practice. That could include Western Europe, North America, but more representative of Western practice.

I think Mike has come to it several times, and I agree, I'd like to see patients who are on anti-arrhythmic therapy get treated with this drug. I think Peter has also pointed out that a lot of these patients are going to get anti-arrhythmic drugs, and I'd like to have that in the mix. Largely, Norman, for me I would like to see just a lot more patients, where I'm more confident in the estimates.

DR. STOCKBRIDGE: Powered to do

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what exactly?

DR. HARRINGTON: Well, I think that would be an interesting discussion. I like the endpoint of avoiding cardioversion. And if we could somehow figure that out, maybe it is this 90-minute or 2.5-hour conversion time, and then calculate how many cardioversions do you actually avoid to get -- because that to me is the clinically meaningful thing, that, you know, you're avoiding something that's -- I've not had it, but I've done plenty of them, and it looks pretty miserable.

And so, avoiding those to me would be a meaningful endpoint, and maybe that 90-minute or two-and-a-half-hour conversion is a biomarker for the ultimate clinical endpoint, which is -- or surrogate for the ultimate clinical endpoint, which is avoiding cardioversion.

And then, I think you'd have to have the discussion, as Barry had said, how do you count the failed drugs, the torsades that

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you have to convert? And those probably ought to count against you if you get cardioverted anyways.

CHAIR HIATT: Well, this is hard, because if, in fact, you sort of shift into, well, I'd like to know more about the efficacy, a couple hundred more patients might answer that question. You know, give them a little bit different background therapy, allow more things in, but it may not answer the safety question, will it? And so the other thing you might do is sort of sit down and add up, in this population, with these therapies, what are the events that matter?

So the torsades matter, the thromboembolic events matter, and, you know, we're not probably as worried as much about hypertension, et cetera. But I would maybe make constellation a bundled endpoint, because I want to get as many of those as possible. I'd like to acquire -- and you probably heard this number -- 150 of those events to exclude

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a certain amount of risk, you know.

So if you had a lot of those events, then you could go back to the physician and say, "Well, I know now with a point estimate of X and a confidence interval that's fairly narrow that this drug does a certain amount in terms of the risk side." That to me is what's missing. You can always flush out more efficacy issues.

But I guess the thing to recommend to the sponsor might be a little hard, which is you need more events.

DR. MASSIE: I'd like to propose -- people are going to throw me out of here maybe, but I think it could be very difficult to do what we need to do, which is have a large study in a practice environment. And I'm not sure the way to go, isn't to randomize to the drug or cardioversion. We know it prevents cardioversion. We have a handle on that.

But what we don't know is what

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happens to the patients, and we don't -- you know, and we are assuming that it is going to avoid cardioversion. Only by doing it head to head can we decide it's good to avoid cardioversion.

But it will give you the size, it will give you the real population that comes into the world, and I think it will answer something about the risk, because, you know, the torsade is going to be a risk, and we'll be able to quantify it from the number of people who get randomized to the drug.

So it's a little bit between an observational study and a randomized trial. Now, what's your primary endpoint? You're going to have to sit down and micro-manage that. But there's a way to get the information we need to get. I think that that might be a viable alternative.

CHAIR HIATT: So you didn't need that yesterday?

DR. MASSIE: What?

CHAIR HIATT: We talked about, you know, you could really redesign the development program and say it's got to be a head-to-head comparison. But we didn't request that yesterday.

DR. MASSIE: Well, your -- how are we going to get the information we want? We didn't seem to want it as badly yesterday as we do today. And I think it's a real important question is: how can somebody get this data? Are we sending them off, you know, like Don Quixote?

I think this is a way to get the information I would want, which is, what are the outcomes in patients treated this way? And it's also a very important study, because what we're saying is we're trying to -- using this pharmacological approach to avoid cardioversion. Now we'll actually decide whether -- how important it is to avoid cardioversion. Maybe these people aren't as miserable or aren't staying in the hospital as

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long and having all this as we thought. Maybe it isn't even something we want to do.

I do believe it's good to have an alternative. A patient may just not want it. But so -- because I think if we're going to do a placebo-control trial, it's going to be very hard to do, and we're going to still have the looming effect of cardioversion and how to build that into the protocol.

You know, but I don't think -- one thing we don't need to do, I think, is to spend a huge amount of effort characterizing the -- avoiding whether or not this drug prevents cardioversion. And I think we pretty much know it doesn't do many of the other things, so -- it's a thought. People may think it's a stupid one.

DR. LINCOFF: I actually thought about that quite a bit yesterday and today. And in the end, I've actually gone back to the idea that the placebo-controlled structure is almost the same thing, assuming you don't

constrain therapy otherwise, because what you're really asking for is about two and a half hours of delay your cardioversion.

And what that accomplishes, it allows you to blind, because so many of these endpoints are very difficult to assess in an objective fashion. And it also gives some time for these patients to convert spontaneously, and so it almost more models practice.

So what I really want to know is if you -- when you hit the patient, if you've got two strategies, I'm going to kind of poke along a bit and decide if I have to cardiovert or just give them the drug right away. And I think you are almost going to get to that, because I think the most important issue is numbers.

I think as little as you interfere with practice, it allows you to get numbers, big numbers, so that you can get a better estimate, because what I would really like to

hone down on is, give me a confident estimate of what the event rate is at the doses -- now you've settled on doses, don't need to do dose ranging, put every patient into the right dose and tell me what the likelihood is of torsade.

CHAIR HIATT: Okay. So you are still looking for safety events. And I agree with that; we need more safety events. But I think the idea of completely changing a development program strategy, they have already invested a lot of money in this. I mean, you have to talk about what's feasible, too, here. the strategy is probably still defensible, but it may be that the events are not adequate to judge safety.

DR. CANNON: I think another benefit of extending the trial, but pretty much in the same design, not changing design radically, is to get more information about late -- or prolonged atrial fibrillation.

This issue of how far out can you still show efficacy or show a very reasonable

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therapeutic window, and I think if they just simply continued to enroll patients -- men and women -- again, I say I'm more concerned about the women than the men perhaps, but we need more in both, but I would keep the same design.

DR. HARRINGTON: But would you keep the patients greater than 48 hours, Richard, or would you just --

DR. CANNON: No, these are patients coming in that have had atrial fibrillation -- or maybe -- and they're already on an anti-coagulant, for example, so you don't have to worry about putting them on anti-coagulants, sending them home, or using TEE-guided therapy. So they've had atrial fibrillation for longer than 48 hours.

I think we're still -- yesterday and today we've wrestled with the efficacy of a pharmacologic approach after about 48 hours. I think we're agreed that within 48 hours it's reasonably effective. But I think thereafter

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the numbers tail off, and we're less certain about how efficacious it is.

So more people enrolled in the study, you would have more people that have had atrial fibrillation for a longer period of time, and presumably are on an anti-coagulant, so that you can give them a treatment and not have to send them home on anti-coagulant therapy that is going to require yet three more weeks.

DR. MASSIE: I'm not sure I would restrict it to that group, because I still think we need more information.

DR. CANNON: No, not to restrict it, but that would give you more people that have had atrial fibrillation for a longer period of time, so that we just get more data on longer duration of AF and does the therapeutic window make sense at day seven as it does at day -- in 24 hours or 48 hours.

CHAIR HIATT: Does anyone else want to recommend what to do? Does it make any

sense to go through 14? Probably not.

We can wrap up. I'm just wondering, then, if it's kind of more no today than yesterday, and more work needs to be done. How far away are they? I mean, do you want to wrestle with that, Norman, or not? I mean, is this just getting enough more safety data to know that you have some confidence to rule out certain bad things, or is this truly a redesign of a development program?

DR. STOCKBRIDGE: Well, I mean, that's -- that's not my decision to make. But I certainly heard what the Committee has said about -- and the source of their discomfort with this program having largely to do with fully characterizing the safety data.

It's a little unfortunate, I think, because I do think this company did a better job of characterizing both torsade risk and the dose response than the one we saw yesterday did. So they are -- in some ways I feel like they are victims of a better

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development program.

DR. HARRINGTON: Yes. And perhaps --

DR. CANNON: They had to go through several doses to find a therapeutic window that seemed optimal. Yesterday that wasn't that necessary. I think that's just -- they are different drugs.

DR. LINCOFF: And I think that's the key. I mean, I think the company did -- has done a very thorough job and a very transparent presentation, but it's a different drug, and their stock or whatever -- I mean, they can deal with this drug, but they have the intrinsic difficulty associated with the mechanism of this drug and the risk of torsade and the necessity, because of that, to provide a better estimation of the safety issue.

I mean, the only methodologic issue that I would suggest might have been avoidable was the issue of concomitant medications, and even that, in and of itself, with these

numbers may not have answered all the questions. So I don't think it has anything to do with the conduct by the company. It's just in the intrinsic properties and mechanisms of the drug.

MR. SIMON: If I can mention one thing -- as a patient, I can't add anything to your presentation. But as a patient, I'm always looking for drugs that will help an atrial fibrillation.

The only thing I could see over the last two days is that yesterday I would feel comfortable taking that drug. Today, with all of the uncertainties and the different things that physicians have mentioned, I didn't feel comfortable. And I don't know how to quantify that or qualify that any further.

CHAIR HIATT: Well, it's always what you don't know that you're worried about, isn't it?

So any other comments?

(No audible response.)

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If not, we're adjourned.

DR. STOCKBRIDGE: Yes. Thank you, everybody.

(Whereupon, at 4:49 p.m., the proceedings in the foregoing matter were adjourned.)