You haven't' said anything about the acidosis. Clearly, that will set up for toxicity.

Many of these patients with CKD in the states will be on an ACE, an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker or both and, therefore, are set ups for hyperkalemia and other electrolyte disorders as well decreased kidney function. The role of this agent in interaction with those two drugs, I don't know. And in the sense that this agent is cleared by an organic acid pathway in the kidney makes interaction with these other organic acids very high and very likely.

So there's some food for thought here plus also the fact that on one of your slides, you show that renal vascular resistance was increased in some of the patients. And therefore, not only can you see hypotension but you might see hypertension. So this milieu of uremia really tells us that we have maybe a different group that needs to

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be examined very carefully if it's going to be applied to a large population in the states.

CHAIR HIATT: Thank you.

Responses?

DR. STRAUB: Yes. I can only agree that these are all valuable concerns, and I think, especially in terms of potassium, we have given pertinent instructions in the package leaflet that we would like to get this controlled before we actually examine the patients. With respect to ACE inhibitors, another concomitant medication, we have huge experience in the dossier about giving that drug concomitantly.

Yes, we do believe that even though there are slight increases of AUC in patients with impaired renal function, if it's mild to moderate, we don't think it's a big concern because we see that the differences are not very huge and that we see, especially with QTc returning back to baseline, that there is not a large difference between these groups.

We would agree, though, and we have evidence on that, on the oral part for of tedisamil development that if you apply the drug in severe kidney failure, that this requires dose adaptation. So that's why we propose to contraindicate it in severe kidney failure.

CHAIR HIATT: Yes, Norman?

DR. STOCKBRIDGE: Can you describe the timing of the torsade-like events with respect to the start of the infusion?

DR. RACZKOWKSI: Yes, we have that slide. That was one of the core slides. There were two slides where we listed all the torsade events in men and in women, and I believe those two slides showed when they occurred. They all occurred within 48 minutes. There was one outlier at 18.5 hours.

DR. STOCKBRIDGE: Yes. The process by which you picked those up, was that just the first event that everybody had, or were there really no events after 48 minutes?

DR. STRAUB: No. The whole Holter was screened for ventricular tachycardias. And if there was a torsade, this was traced and the most severe events were brought into the attention, so the fastest one, any torsades, any sustained ones, these were brought to the attention of the committee. So what you see here is really a true reflection of the number of patients with torsades.

DR. STOCKBRIDGE: So it's the number of patients with an event?

DR. STRAUB: Yes.

DR. STOCKBRIDGE: It is not the distribution of all of the events?

DR. STRAUB: That is correct.

DR. STOCKBRIDGE: Okay. I mean I was struck by the fact that all of them occur except for this guy out here at 18 hours. On the rising phase of the -- well, the plasma levels are going up.

DR. STRAUB: Yes.

DR. STOCKBRIDGE: It would have

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been kind of interesting to see -- and now I understand why that is. You actually don't report the ones that happened on the following phase. But that might be of some interest as people are trying to figure out how long you should monitor.

DR. RACZKOWKSI: So the question is is if a patient had a subsequent event of torsade, was that detected in any of these patients? Is that the question, Dr. --

DR. STOCKBRIDGE: Well, what I hear is sort of no, the answer is no, that people who had an event that got reported during the infusion, in fact, don't have an event that was reported subsequently after the infusion was terminated.

DR. STRAUB: It was part of the evaluation process, but what we report her eis the earliest onset of the first event.

DR. STOCKBRIDGE: Okay. All right.

DR. STRAUB: And then there are also only those which were serious were having

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cardiac intervention. I tried to make that point. So the sustained polymorphic VTs, which were sustained torsades, these were all receiving d/c cardioversions, all ended up in normal sinus rhythm.

And you see here the sustained events happened maximally 40 minutes thereafter. And in female subjects, there were two sustained events which required d/c cardioversion. These were the first two here. They appeared 20 and 30 minutes after start of infusion. All the others were solved and were not requiring intervention.

DR. MASSIE: Can I follow up on this because it really just brings up the Table I wanted to mention. This is the Table 12 in the reviewer. But what it is is it's a list of subjects in whom the study drug was discontinued during the initial infusion. There were 18 of them; 17 were on the active drug; and most appeared to be for VT, torsade de point or prolonged QT. And while some were

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above the recommended dose, 12 of the 18 were at the recommended doses.

So the number turns out to be a small number, I guess, with a big denominator, but the connection between the infusion and adverse events, which, had the infusion not necessarily been discontinued, which it should be, but, you know, might have led to more severe consequences. I'm not sure whether the people who had d/c cardioversion were included in those. I assume that they probably are included in that group, because it seems unlikely you would start back the infusion.

DR. RACZKOWKSI: I'm not sure that we can reproduce the FDA Reviewer's Table, but we do have some, I think, granular data that we can share with you.

DR. STRAUB: Let me show you a couple of slides in the main studies by study what were the reasons for stopping the infusion prematurely. We start with the male study. You see here a threatening change in

rhythm or AV conduction. There is QT interval more than 550 which was one of the stopping criteria. Because it was a dose-defining study including .64, we didn't want to over shoot the response and, therefore, said if you see more than 550 milliseconds, then you stop the infusion. So it was a stopping criteria. So these are the majority of the reasons in that study.

There was one systolic blood pressure less than 90 and QT interval more than 550 and/or a 20 percent increase from baseline under .64.

In females in that study, remember that study has been amended to include only males at the end, but there were a couple of females in that study. And there was systolic blood pressure less than 90 in one case and a threatening change in rhythm of AV conduction here.

The next study was given this picture. That was pretty equally distributed in terms

of, again, QT interval change, conversion to normal sinus rhythm. Here, that was a misinterpretation because we didn't say once somebody should convert that they should stop the infusion regimen. But in that patient, it was done that way.

Then you have conversion to sinus rhythm or bradycardia. Again, a misunderstanding from the investigator in that case. Due to administrator reason for protocol violation and onset of ventricular tachycardia in one case.

In the next study, these were the reasons for discontinuations. And there was one under drug and one under placebo patients converted to normal sinus rhythm. Again, erroneously done. And then QRS duration increased more than 30 percent in one placebo patient.

In this study, 16, you see this picture - QRS duration increased with .032 in three cases here; placebo one case here; one

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case under .24 conversion to normal sinus rhythm. And in the study 18, which is the last study, you see adverse event not otherwise specified.

So this completes the picture, and from my perspective, it's the majority of the cases are QT discontinuations or a misinterpretation of the study protocol, namely that the patient cardioverted and the full dose was not given.

DR. LINCOFF: Can you explain the monitoring of the QT, what the protocol was? Were they supposed to do 12 leads or were these read off a monitor, because in the midst of an infusion, it might be difficult --

DR. STRAUB: It was 12 leads but if local 6 lead was done in order to control the environment, that was allowed. But normally, all ECGs were 12-lead ECGs. But for monitoring purposes, the QT should be followed, there were specific leads given likely to --

DR. LINCOFF: And it was just continuously monitoring during the 30-minute period?

DR. STRAUB: Absolutely, telemetry and Holter.

CHAIR HIATT: So, let me get to your point, Norman. I think there does appear to be kind of a dose administration relatedness for these arrhythmias, and it also is occurring at does at or below the recommended doses, but there clearly seems to be a dose response.

Okay. We're nearing the noon hour, and I'm thinking from just a logistical perspective, we might take an hour off for lunch, come back to the open public hearing, which might be quick, followed by, if sponsor is prepared, to do their data summary of the integrated sort of numbers of safety events, et cetera, then the FDA review, and then we'll got to the questions. Does that sound okay? Thank you very much.

(Whereupon, off the record at 11:56 a.m. and back on the record at 1:03 p.m.)

CHAIR HIATT: Once again, I have the privilege of reading you a script. This is for the open session.

"Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision making. To insure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it's important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the Committee of any financial relationship you may have with the sponsor, his product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your

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attendance at the meeting.

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

The FDA and this Committee place great importance on the open public hearing process. The insights and comments provided can help the Agency and this Committee in their consideration of the issues before them. That said, in many instances, and for many topics, there will be a variety of opinions.

One of our goals today is for this open public hearing to be conducted in a fair and open way where every participated is listened to carefully, and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the Chair. Thank you for your cooperation."

Do we have anyone in the public hearing portion that would like to come forward and make any comments? No one? The open public hearing portion of this meeting is now concluded. We will no longer take comments from the audience. The Committee will now turn its attention to address the task at hand, careful consideration of the data before the Committee, as well as the public comments.

I think what we're going to do now is just get just an update from sponsor, if we could, on the sort of event considerations, and any other kind of final comments they'd like to make. And then we'll turn to the FDA presentation.

DR. RACZKOWSKI: Over the lunch break, we were able to pull together some analyses of the distribution of D/C cardioversions over time between the placebo group and the medicinal group. And we also have some of the adverse event data that you

had requested by time, by treatment group. So Dr. Straub will present them.

CHAIR HIATT: And if this is going to be summary information, if there's any possible way to have that printed just so we can kind of have a look at it as we go through the questions, that would be appreciated.

DR. STRAUB: Some numbers are coming up. So this is a slide showing you in males, and in females those proportion of patients being in normal sinus rhythm at 24 hours. These were under .48, 51 percent versus placebo 47 percent. If we exclude those patients who have the C cardioversions, we still have a proportion of 46 percent conversions under Tedisamil, and 30 percent under placebo. If we add these with D/C cardioversions, you won't find a relevant difference any more. Although it doesn't tell you anything about successful cardioversions, we have had these numbers in a separate slide.

If we look to females, 40 percent

are in normal sinus rhythm at 24 hours, 40 percent versus 34 percent on the placebo. If you exclude those patients with D/C cardioversions, then we have 30 percent on the Tedisamil versus 18 percent on the placebo. If we count all the D/C cardioversions in there, the conversion rate at 24 hours being patients in normal sinus rhythm at 24 hours is 79 versus 84 with the placebo.

CHAIR HIATT: Do you want to pause on that for a just a moment, let the Committee respond to what you're seeing?

DR. MASSIE: Two things. One is, you've captured what Norm was making us think about, and there's a lot of people without the cardioversion mandated or happening clearly. Beside D/C electrical cardioversion, was any other type of attempted cardioversion allowed?

DR. STRAUB: No.

DR. MASSIE: No other pharmacologic strategy?

DR. STRAUB: No.

DR. MASSIE: So this is either spontaneous, or as a result of electrical cardioversion.

DR. STRAUB: Yes.

CHAIR HIATT: So a little over -- well, around half the men are still in atrial fibrillation then. Correct?

DR. STRAUB: Yes.

CHAIR HIATT: And 60 plus percent of the women are still in atrial fibrillation.

DR. STRAUB: If we do not count the D/C cardioversions, yes. I mean, if no D/C cardioversions are counted, you have 46 percent on the Tedisamil, and 30 percent on placebo.

CHAIR HIATT: But you take all the ---- now we go out 24 hours, you take everything.

DR. STRAUB: Yes, we take everything, including --

CHAIR HIATT: And you're in sinus rhythm --

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DR. STRAUB: -- D/C and that is 69 -

CHAIR HIATT: Wait a minute. These are sub -- I'm confused. I'm assuming the top line is everybody.

DR. STRAUB: This is everybody. That is correct.

CHAIR HIATT: All right.

DR. STRAUB: This is the proportion of the D/C cardioversions.

CHAIR HIATT: Okay.

DR. STRAUB: I'm sorry. Yes, it was a little bit misleading. So those without the D/C cardioversions, there were 61 patients from 133. This is 46 percent were converted by --

CHAIR HIATT: See, the denominators are changing as you go below.

DR. STRAUB: Yes.

DR. LINCOFF: But that's remarkable, that 30 percent of men without cardioversion in the 24 hours converted

presumably spontaneously, unless there was much off protocol violations --

DR. CANNON: So I'm confused. So why is that number so much higher than was quoted for placebo sinus rhythm in the data? I mean, it was less than 10 percent.

DR. LINCOFF: That was the first two and a half --

DR. STRAUB: In the two and a half hours. We now count the 24 hours.

CHAIR HIATT: In fact, I was speculating that low spontaneous conversion rate might have been maintained, but it looks like there is one that continues to occur after the two and a half hour window. But it's also remarkable that half the men are still in atrial fibrillation at the end of all this, and 60 plus percent of women are still in atrial fibrillation at the end of this.

DR. STOCKBRIDGE: You're picking up about 3 percent an hour. It's 3 percent of the people who couldn't even get the therapy

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by the time they converted, and then it's another roughly 10 percent in two and a half hour post randomization. And, so, it turns out to be about 3, a couple of percent.

DR. LINCOFF: So it would be -- I mean, I realize the subgroup is a subgroup, but it would be interesting to see how many of those spontaneous cardioversions were actually the people who came within the first day or two days of duration of Afib, because if it's the first day, then that wouldn't be surprising. If you got patients out at two days, three days, four days converting like this spontaneously, that would be surprising. But I think it is striking that if we look at these drugs, as I have advocated, as a way of preventing D/C cardioversion, without D/C cardioversion, 46 percent of patients, or incremental 16 percent of patients end up being affected by the drug, men, and 12 percent women, unless you bring cardioversion into the equation.

CHAIR HIATT: So your interpretation of the avoidance of cardioversion here at 24 hours is what?

DR. LINCOFF: Well, it's hard to put a percentage. You don't know how many wouldn't have had it, but if you say in a strategy that avoided cardioversion, you got an incremental 12 absolute percentage points of women, and 16 absolute percentage points of men into normal sinus by 24 hours.

DR. STOCKBRIDGE: Right. Assuming you're willing to wait 24 hours.

DR. LINCOFF: Which I think is clinically reasonable. Waiting several days isn't, but waiting 24 hours I think it's hard to argue.

DR. STRAUB: Okay? So the next data requested were sorts of what is the curve? We don't have a curve, but we wanted to re-emphasize what is the Afib flutter duration percentage conversion, and you have here three to 48 hours. We have 48 hours to

seven days, and eight days to 45 days. You see that how the conversion rates, there's 52 percent, 28 percent, and 13.1 percent, and we have the change, and between the placebo and the active, so this is 40 percent, 28.6, and 13.1. These are the males. And if you look at the females, we have 32.4 percent, 16.3, and 8.0, placebo 10 percent, zero, and 3.3, that speaks for a change of 22.4, 16.3, and 4.7 percent.

MR. SIMON: Can I ask a question? With regard to Afib and atrial flutter, do you have data that shows who had just atrial fib, who had just atrial flutter, and who had both, and is there a difference in conversion?

CHAIR HIATT: And then in terms of kind of the series of requests, I'm assuming the next thing we'll see is the safety, cumulative safety data.

DR. STRAUB: This is first for the baseline characteristics about atrial fibrillation and flutter. You will see 85

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percent have atrial fibrillation, 15 between 11 and 16 percent have atrial flutter.

CHAIR HIATT: Maybe if we want to keep the train of thought going, perhaps, a delay on that response, and if you wouldn't mind getting back to the things, the new information you prepared for us.

DR. RACZKOWSKI: Dr. Straub, could we pull up the safety analyses, the distribution by time?

DR. STRAUB: Okay. We start with the males, these are the serious adverse events time to onset which was requested. We have here the day one events, day two to seven, and day eight to twenty-eight. You see the deaths in males, which occur late. Hypotension, one late placebo case, myocardial infarction between two to seven days, also here a placebo case, pulmonary edema, one case here, thromboembolic events between days two and seven, and one case later, and bradycardia two cases from day two to seven.

DR. MASSIE: Are these patients?

DR. STRAUB: This is patients. This is patients.

DR. MASSIE: This is patients. But a patient couldn't be listed as several events, like an MI, and then a death, or something?

DR. STRAUB: Theoretically, yes. I will comment on the next slide, there is a double counting.

DR. MASSIE: Okay.

DR. STRAUB: Actually, this is in females. You see here one death case, which was the same like pulmonary embolism, which is also counted here. There is -- so this one is early, and happened on 0.24 as you might remember. All the other events were occurring late. Hypotension, we have two cases on the Tedisamil, one on placebo here, one on placebo there, so that seems to be balanced. Myocardial infarction, one placebo case and three other cases. Pulmonary edema, one case

here. Thromboembolic events, one case early, three, two, and two later. Torsade de pointes, one case early. Bradycardia, one case on the Tedi, one case on the placebo, and two for other cases later. So in our understanding, as this was sort of a balanced type of observation, we are left with torsade de pointes, a known risk, hypotension, the death case of the pulmonary embolism, which we thought is not related, thromboembolic events which is the double count, so we are left with torsade, one case, a known risk, and the sorts of balance observation of bradycardia, which we had called earlier. These were the four serious adverse events.

CHAIR HIATT: Yes. It is sort of how you would anticipate that would have sorted out. I would -- my sort of simple numbers would say that there are a couple of extra thromboembolic myocardial infarction death events, major events, and the torsades that we've talked about earlier, trying to go

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back and forth between males and females, early and late, that kind of thing.

DR. LINCOFF: In the FDA Table 12, there appear to be a couple of more hypotensive events that led to discontinuation of therapy. I mean, the number looks like three or four here. How was hypotension captured for your analysis?

DR. STRAUB: Hypotension here was only counted as serious adverse events. If you want to look for the treatment discontinuations, I can pull up a slide for that one, too.

DR. LINCOFF: So discontinuation alone, if it wasn't coded by the investigator as an SAE, would not have qualified.

DR. STRAUB: Correct. So this is the time to onset of the serious adverse events in males. There were four cases of ventricular tachycardias. Other than that, this cohort looks pretty clean. In the mid-part we have myocardial infarction, three

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cases here, one case there, one case very late, and tachycardia, also delayed case -- three delayed cases on the placebo, three thromboembolic events in the time spent of two to seven days, and one case between eight and twenty-eight days, plus three bradycardia cases in the bin of two to seven days, and twenty-eight days.

And, finally, the observation in females, I think we have seen it, haven't we? No. Okay. So we have one death case here, which was the pulmonary embolism. I think I've lined that out already. I think you have seen that. The hypotension was two cases here, one case there, and placebo. That's an equal distribution, so the only thing to repeat was the torsade de pointes from our perspective to be the worrisome non-balanced event. You see the bradycardia here coming under placebo, but also under active with one case each.

CHAIR HIATT: So just to try to

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interpret what we're seeing then. It seems to me that the bradycardia hypotension events are relatively balanced, but that the broad definition of cardiovascular/thromboembolic events are numerically a little unbalanced. And then I think the other challenge we all just sort of look -- well, what do you think is a time frame that's appropriate for a drug with a very short half-life? But the sponsor, I think, intentionally chose seven days. It's kind of -- that was in your sort of primary adverse events sort of time window, wasn't it seven days?

DR. RACZKOWSKI: No, we collected adverse events for four weeks.

CHAIR HIATT: Right. But I guess I'm just trying to think, an MI that occurs at 28 days, versus an MI that occurred within 7 days, would we consider that relatedness slightly different?

DR. STRAUB: That's true. Our interpretation was, of course, we wanted to

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have a broad observation window, and we wanted to have this 28-day window to be absolutely sure we have captured everything what is serious, so it wasn't for us to concentrate on 24 hours only, so we also wanted to go beyond.

CHAIR HIATT: Yes.

DR. STRAUB: And then looking at individual cases, and making case-by-case evaluation, whether or not the likelihood was bigger or less likely that this was related to Tedisamil or not. And given the fact that we didn't see anything which we didn't know yet, so meaning bradycardia in the sense of a heart rate lowering effect is a known phenomenon with Tedisamil, and the other observation -- hypotension, by the way, looks pretty unlikely. And we know the drug behaves totally different, even in the other direction, so given that, and what we see here is pretty much what we know.

DR. WALDO: I'm Al Waldo from Case Western Reserve University, a consultant for

Solvay. This gives me an opportunity that I really wanted to get before, to get back to a case that Dr. Cannon was talking about before, and that's the one case here of the lady who died. And Dr. Cannon's last words were, she's not the same patient because -- and, of course, we all understand that. But I wanted to rise at the time and say, "Yes, she is the same patient." And the lesson really is, is to understand a little more about sinus node dysfunction, the presence of atrial fibrillation. I mean, unfortunately, two-thirds of patients with atrial fibrillation, one form or another have a sinus node dysfunction, and some of them have it extreme. And what happened with this patient is after conversion to sinus, after conversion of the atrial fibrillation, she had a huge pause, and sinus node didn't wake up, and she didn't have a junction escape, but a classic example of sinus node dysfunction, led to her arrest.

She survived that. She was

extubated, her blood pressure was normal, she was minimally supported on ventilation, and then she went back into fib. And the docs there, unfortunately, didn't learn the lesson, and it wasn't the drug, per se, that did it. Although the drug was there, it was the underlying mechanism, so had a severe sinus node dysfunction. And so what happened, they gave her Amiodarone this time, and the same thing happened. When she broke, she got hypotensive because she had prolonged asystole, and this time they couldn't -- she didn't survive.

So the only point I wanted to make is that it's the but-for argument about, as is often said, about if you hadn't taken the drug, this wouldn't have happened. But it's a little different. It's not the drug, per se. It would have been any drug. It turned out to be Amiodarone the second time.

I think in a small number of patients, they will have this extreme result.

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In fact, that gets back to what Peter was talking about earlier, which is the other reason I wanted to make a point, is that the notion of just waiting for sinus, the node function to return for spontaneous conversion of atrial fibrillation, send the patient home and see what happens, there are going to be some patients who this sort of thing happens to. And even spontaneously, they have exaggerated over-drive suppression of sinus node function with marked sinus node dysfunction, so huge portions of the sinus node waking up, no junction escape, and it can lead to terrible things at home, too.

DR. CANNON: So I would respectfully disagree. I think this drug contributed to her death. This is real world. There are going to be people with sinus node dysfunction, presumably, who get this drug.

DR. WALDO: That's my point. I agree with you.

DR. CANNON: And now the drug is on

board, and we talked about how it might affect metabolism of other drugs. We talked about that earlier, so if you're giving Amiodarone later, and perhaps with the cardioversion and the hypotension and so forth, their AV node dysfunction got even worse, so I would conclude that the drug likely contributed to her death, not unlikely.

DR. WALDO: We don't disagree, I don't think, if you hear my point. Of course, the drug contributed. I don't for a moment suggest that that should be denied. Absolutely, it did, but I'm suggesting it would have been any drug. That's my point. I'm suggesting it could either have been cardioversion, I'm suggesting it could even have been spontaneous reversion of the atrial fibrillation, because the intrinsic problem was not the drug or the D/C shock, but the intrinsic problem was markedly abnormal sinus node dysfunction, absence of a juncture escape rhythm, which is classically described.

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CHAIR HIATT: Will we be able to get some printouts of that new data?

DR. STRAUB: Sure.

CHAIR HIATT: That's wonderful.

DR. STRAUB: We're in the process ofo printing them.

CHAIR HIATT: I appreciate that. Do you have some more to present on that area topic, as well?

DR. STRAUB: Only to answer the question of Dr. Simon. And we have here the subjects with recurrent episodes, which we have differentiated also for the people who had both rhythms at the same time, with atrial fibrillation in about 80 percent of the patients, atrial flutter in about 10 percent of the patients, and between 6-12 percent had both.

CHAIR HIATT: Thank you for the extra information you provided us today. We very much appreciate that.

DR. MASSIE: I did have one other

question that I didn't answer this morning, but a lot of these people did get electrically cardioverted. And I would be curious as to, this will be anecdotal, perhaps. What type of adverse reactions may have occurred during the time of that cardioversion? It was just brought up that people may have sinus node arrest and dysfunction. Were there any difference in those types of things in the people who got electrical cardioversion? Is there anything to say it was equally safe, better, more successful cardioversion, or perhaps was there a safety signal the other way? By treatment group, yes, not cardioversion versus none, but in the people who were pre-treated with the drug.

DR. RACZKOWSKI: Well, let me just offer here for a moment that, of course, the patients weren't randomized, and so we're looking at a non-randomized sample here. And I don't know if we have immediately available the adverse events on those patients who were

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D/C cardioverted.

DR. MASSIE: But in theory it is an important issue, because we know a fair number of people will get cardioversions.

DR. RACZKOWSKI: Yes. Yes.

DR. MASSIE: I've seen some pretty long pauses after Ibutilide. I've seen some long pauses with Ibutilide without cardioversion. It will be anecdotal, but I think it's worth looking at.

DR. HARRINGTON: But, again, as the sponsor said, I mean, the challenge is that now the group of patients who get cardioversion in the treatment arm may well be different than --

DR. MASSIE: Right.

DR. HARRINGTON: -- than the group having a treatment, cardioverted in the placebo arm. But you just want just additional information.

DR. MASSIE: We're talking about -- one can perceive a risk. It's worth looking

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at. I would be actually quite comfortable and happy if, in fact, when they cardioverted them, there was no difference in bad outcomes, but I realize they're different.

DR. STRAUB: So we've got some adverse event information in those patients who cardioverted versus non-cardioverted. So if you want to see that? So here, converters versus non-converters. You see here the females, to start with, subjects with at least one treatment emergent adverse event. These are the subjects who converted to normal sinus rhythm, and these are the subjects who did not.

DR. RACZKOWSKI: Well, let me just ask Dr. Massie, is that the question you're asking? I think you wanted to know about D/C cardioversion. Is that correct?

DR. MASSIE: Yes, electrical -- I just -- the interaction between electrical cardioversion and being pre-treated with Tedisamil.

DR. STRAUB: We did not analyze that.

DR. MASSIE: Okay.

CHAIR HIATT: Okay. And there may be some other things that come up. I'm just wondering maybe if it would be appropriate now to transition to the FDA presentation. Thank you.

DR. MARCINIAK: Okay. I'm Tom Marciniak from the Division of Cardiovascular and Renal Products, and I'd like to give I don't think a drastically different perspective, but a slightly different perspective on this particular product. I would like to start with a disclaimer. This is probably my least favorite activity. And, in fact, when Norm said I'd have to do it, I said, "Norm, can I volunteer for a trial of direct cardioversion instead".

(Laughter.)

DR. MARCINIAK: And Norm being the very wise boss says, "No, Tom, why don't you

wait. You may need it during your presentation."

(Laughter.)

DR. MARCINIAK: But, actually, I was actually one of the ones I think internally who will take credit or discredit for actually encouraging having this Advisory Committee meeting, because I think it is a complicated issue. There's not a simple answer that I can say yes, I know what the answer on this one, prove or disapprove, whatever it might be, that it really is kind of a very difficult risk-benefit tradeoff. And I think -- I don't really have any questions that Tedisamil really works. Okay. And I hope -- that may not come out in my reviews, but I think actually I'll try to give you the data why I believe that to be true. But, in fact, there's this whole issue about whether it is a favorable enough risk-benefit tradeoff.

Now I think, to me, in terms of the

benefit, when I talk about net benefit, I don't mean the efficacy minus safety issues. I really mean what is a benefit that I, as a patient, might be able to appreciate. And I think the complicating factor is, as it was yesterday, as it is today is, I don't think converting a few hours early is a huge benefit. I think really the benefit is, if I do things like avoid that shock, or avoid treatment with Ibutilide. And so I think that's always the thing we have to look at, and we really have to try to get a handle on that to really understand what is the net benefit.

I also looked at the literature, similar to what Dr. Granger did. In fact, I did come up with exactly the same conclusions. The first article I'd like to quote is this one from the Annals of Internal Medicine, which basically said very nicely as we do in this country, well, the range is from zero to 76 percent in terms of spontaneous conversion

rates. And, actually, that article does go on to explain, in fact, it's this issue about what is your patient population? How many patients are recent converters, versus delayed converters is why you have such wide range.

I actually like our colleagues across the Atlantic who have, I think, a more simpler view of the world, if you like. And in terms of recent converters, there's a review from The Lancet that nicely pegged it at 20 percent at three hours, 60 percent at 24 hours, and 80 percent at 48 hours. And not surprisingly, that review actually recommends waiting 24 hours to see what happens before doing anything. They do support this with one reference.

I also looked at a recent meta-analysis, or not recent from JACC, which basically looked at Amiodarone studies, basically some of the -- including the two that Dr. Granger quoted. And for onset between 48 and seven days, typical rates of

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conversion were somewhere between 35 and 64 percent.

Now actually what starts to look fairly substantial to me is, is actually these things are actually very, very consistent. We don't see this consistency in clinical trials we get submitted on most drug products. And so I guess one of the questions is going to be, is how consistent does this fare out in terms of actually what happened in this particular study, because the zero to 76 percent is what we have to worry about. What was it actually here?

Now while we accepted in terms of looking at whether the drug has any activity, what was the conversion rate at 2.5 hours, I think what's more meaningful is to look at what I call the success rate. And by a success rate, I mean the patient was in sinus rhythm at 24 hours, and they did not have any other conversion attempt, either D/C conversion, or actually in this case there

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were a number of patients that did get prohibitive medicines. They did get Ibutilide at least the way we have interpreted the data files.

For this particular success rate, I count in the numerator patients who got an additional conversion as failures. This is what's talked about. It doesn't make much sense if they got converted because they had v-tach to count them as a success. I did still include them in the denominator for these particular numbers, but it's arguable which way you should look at that. If we look at then -- these are also for atrial fib. If we look at doing that, it's counting other conversions as failures. Looking at 24 hours, I get rates somewhere between 28-55 percent, not dramatically different.

Now, actually last night I thought okay, I should look at the other question that was asked yesterday, is what if I exclude everybody, now excluding from both the

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numerator and denominator of patients who got direct cardioversion, or some chemical that might appear to be a chemical diversion attempt. If I do that, would anybody hazard a guess what the number comes out to be? Look at all these studies, placebo group only, excluding cardioversion from both numerator and denominator, my number comes out to be 47 percent in those with recent onset.

I have to start concluding these studies are really remarkably consistent, and that their fact is, even in this population, a very, very substantial conversion rate, spontaneous conversion rate.

Now the other thing about -- these numbers here are all these subtracted numbers, placebo subtracted numbers, so these numbers here are already the net benefit. So at 48 hours, I start to see -- I see a dose response. I start to see actually not what you see with -- I shouldn't say with other drugs, a net benefit. I'd say somewhere in

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the range of 20 to 30 percent.

What I think is even, again, probably reinforcing, is now if I look at greater than 48 hours, now you see placebo rates virtually nil in spontaneous conversion. And I still see, perhaps a bit lower, but I still see an additional conversion rate, I called it perhaps 10-20 percent. I thought okay, this is 48 hours. This is what we were given in terms of the sponsor's standard categorical. So last night I looked at the other question.

What if I break this down by greater than seven days, and it made it a little difficult on us because we didn't get the -- we got categorical data on most of our study files. If you do pull it out for the patients that at least we have the actual days since onset, interesting, these numbers don't change dramatically. I still see a fairly good conversion rate, perhaps in the order of 10, 15, as high as 20 percent, even in the

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patients that had onset greater than seven days.

I think this is probably to me the best testimony that this thing is doing something more than just converting people a few hours early. So I think, from the efficacy standpoint, well, let's go on. There's also some peripheral issues. If I look at gender, if you look at the tables of all studies, remember some studies were gender -- were females, only some were males, not only, it looks like perhaps there is a reasonable comparability, perhaps, to rates in males. If you look at the two studies that actually did a head-to-head comparison of females, and that's 107. And, actually, there is also a small number in 102, 112 which were dropped from most of the analyses, you start to see that actually doesn't look quite as favorable for conversion rates between females and males. So I think there is still a lingering question of whether your efficacy is

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lower in females than males.

I might also note that, of course, that it's what - somebody correct me - one of these studies is a study which is largely in the U.S. population. We looked at that actual issue, and we don't typically, in looking at a first cut, we typically did not find any differences between -- differences by country, but the limiting factor there is, of course, there aren't large numbers in the U.S.

Success rates for atrial flutter, this is at 24 hours, sort of the opposite of what we see for fib. Really don't see much that says at 24 hours there's really a difference in success rates. The p-values that actually come close to being significant, this is a non-corrected post hoc analysis, you like; actually, are the ones that say that placebo works better than Tedisamil. So I think, really, I can't say that it looks like there's a lot of efficacy in atrial flutter.

So what's my conclusions on the net

benefit? For atrial fibrillation in men, it does seem to be at least 20 to 30 percent with recent onset, beyond what I might expect by just allowing them to convert on their own. With greater than 48 hours, and even greater than seven days, I still see at least some efficacy, 10 to 20 percent, somewhere in that range. And it's probably lower in women. And, in fact, in atrial flutter, I don't see any clear evidence of benefit at all.

That's what I view as the, if you like, the benefit to the patient side. Well, what does this balance off against? Well, I think there are two types of problems that I'm concerned with. Obviously, number one, what are the pro-arrhythmic effects? And, of course, then are there any other safety concerns? And you've actually touched upon all of them so far in your discussions.

This is just kind of a reminder that that one death you can argue, and I think it is correct, maybe this patient with another

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drug would have done as badly. Still have to probably count it as a treatment-related death, and I guess the feeling that if you do have any of these drugs go out into widespread use, unfortunately, you're going to see this. It's going to be, I think, impossible to avoid.

The ventricular tachycardia fibrillation or arrest on day one, this is my analysis based on day one on events reported, trying to look at them. And I think what started to be outstanding is, in fact, if you like, even at the to be marketed dosage, males at 40, starts to increase at three two milligrams, I think clearly elevated when you get to .48, and starts to look perhaps not quite as clear for women. But, obviously, if you get slightly higher, you see a very, very clear dose response. So I think it says that, again, given variability in levels, that this will be a problem in some patients.

The bradycardia and hypertension I

thought was worth looking into a bit more detail just because that was the mechanism of death, if you like, for the one patient that might be drug-related. And I looked at them in various ways, and for some reason, I came up with this slide, even though if you look at it, it doesn't look bad at all. It's mostly zeroes. There are no events. And this is on day one, an event of bradycardia, or hypotension that was reported. But what started to concern me is you do start to see this typical dose response where it goes up, and, in fact, you may see somewhat of an interaction where it goes up faster in the presence of a beta blocker, so there may be issues here with pre-treatment with beta blockers. And, of course, that's a great concern, almost 80 percent of patients were on beta blockers.

Finally, this is another version of trying to look at thromboembolic events. I happened to arbitrarily, and this is very

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arbitrary, cut them off at two weeks, and you seem to see this - even with some suggestion, perhaps, maybe of a dose response, maybe not, that thromboembolic events, and this is including Mis, strokes, peripheral embolism, pulmonary embolism in this case, within that time frame. So there's a suggestion here, kind of hard to say what it means.

Now, in fact, actually at first cut, sort of the reaction is okay, this drug has a very short half-life, that these could not possibly be related. But then one of our cardiologists reminded us that well, there's actually been some speculation on whether with some drugs that you see increased atrial stunting.

This happens to be one article. I do not put this forth as even being a good study. It does make the comment that the decrease in left atrial doppler flow actually was seen even in patients who did not have successful conversion to sinus rhythm. But

the whole point is, and it can be debated whether this is a real effect or not, is probably there is at least one potential mechanism where a drug with an extremely short half-life could affect thromboembolic events probably for at least a number of days in the future.

Now last, but not least, on the safety side is the issue of dosing of this drug. And this is actually the complete reproduction of the two dosing charts nicely put. Blue is for boys, and pink is for girls, I guess it is. And I guess it's really of great concern to many of us, is that -- I know it's almost like throwing a dart at this and saying what the dose should be, is that we're really concerned that it would be very easy to go wrong along one of these tables and columns and pick out the right dose.

Now, probably that won't lead to a dramatically wrong dose, but we just think it has problems in terms of potentially

increasing more dosing errors. The two-step infusion also raises issues about whether it will be infused right. And it's just something to see what will really happen to this drug when it's put out into the real world.

So my conclusions are with widespread use that, actually, yes, you will run the risk of having deaths from both ventricular arrhythmias, and from bradycardia and hypertension. And I think you've got to realize, if you approve this, this is what will happen. We see it in post-marketing reports with all of these drugs. It doesn't mean it is an absolute why not for approval. Is there an increased thromboembolic risk? That data, I don't know. I can't totally ignore it. Don't have the answer on it. And, finally, of course, the important question, what will happen in the real world, particularly considering this complex dosing scheme.

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And so, as I said at the start, it's not an easy question to answer, and this is actually the official FDA view on doing benefit-risk adjustments. And, of course, you're involved here, and we certainly greatly appreciate your opinions on this. Thank you.

CHAIR HIATT: Thank you. Would you clarify a little bit more your concerns about the dosing regimen, because I think you were recommending that further study needs to be done on that before approval? I mean, I appreciate your concern, but --

DR. MARCINIAK: No, it all depends. You can make your judgment. I don't think there's a simple black and white answer to that. You could argue that you can live with that complex dosing scheme.

CHAIR HIATT: Just to clarify your concerns about dose, because there was a lot in your part in the documents. So the first question is, do you think we know the dose in men and women?

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DR. MARCINIAK: I think in males you've got a good handle on what the dose is. I'm less clear in females whether I have a good handle.

CHAIR HIATT: Why?

DR. MARCINIAK: Why? Because I actually -- you're going to a lower dose, which doesn't seem to have much efficacy.

CHAIR HIATT: But do you know that. My question is, do you know?

DR. MARCINIAK: The size of the studies I showed there, the number of women involved was fairly small.

CHAIR HIATT: Okay. But the sponsor made, I think a pretty good effort to study both genders in a fairly rigorous way. And we recognize that the responses seem to be less, and there seem to be a few more bad things happening to women than men. But do you -- would you want another study at a higher dose in women to know that, or not?

DR. MARCINIAK: Probably not.

CHAIR HIATT: So you do know the dose.

DR. MARCINIAK: Well, I may not know the dose in terms of do you know what the interaction is with the dosing regimen.

CHAIR HIATT: So that's where I'm going, because it seems to me like there's multiple steps here to getting to a recommendation that we need another formal Phase III new dosing regimen before this drug could be approved. Or could that be explored as a post-marketing thing to refine the dose, because you've got -- I think you have the dose, mostly, and you have an algorithm the sponsors -- we have some nice PK data, they can generate a plateau and the drug levels. They have a good sense of what it's related to in terms of body mass and height, and it's complicated. I want to isolate what the issue is here.

So the issue is, I don't think it's that we don't know the dose. The issue is

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that it just may be prone to lots of mistakes in the field, because it's a complicated algorithm. It's not just a simple weight-based, or BMI-based dosing regimen. Would you agree with that, or no?

DR. MARCINIAK: Partially.

CHAIR HIATT: Well, what am I missing? What are your other reservations about your dose?

DR. MARCINIAK: Even at your -- I guess it's a question whether you think it is feasible to explore higher dosages, or higher dosages in a different -- or different dosages in a slightly different regimen.

CHAIR HIATT: Well, a simpler regimen is not an unreasonable request to make at all, I don't think. But it's driven not so much because you don't know the dose, it's because you think that the current regimen is so complicated that there may be lots of errors. And you add that to monitoring the QT back to normal, those other things we talked

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about earlier, and that -- just the nature of the management might be particularly challenging. And having a really simple dosing scheme, which you proposed, which I think was a reasonable proposal, makes a lot of sense. I just want to pin you down a little bit as to what you're really thinking, and particularly, if this drug were to be approved, are you -- how uncomfortable are you with the current proposed dosing regime if it were to go forward now or not?

DR. MARCINIAK: Oh, I think I'm not that uncomfortable. The issue might be is I think there's very little efficacy in women.

CHAIR HIATT: That's a different issue.

DR. MARCINIAK: Well, if you approve it for women, it's not a different issue.

CHAIR HIATT: Well, no. Sorry. I just don't want to dwell on the dose thing too much. I mean, when I read that, I felt well,

maybe we should consider a simpler dosing regime before approval to avoid narrow toxic therapeutic ratio kind of effect here. Maybe we should do that, but the sponsor has made a real effort to persuade us that they've got a really clear way to sort of inform the physicians, there'll be lots of education, and there'll be observational data coming forward that will tell us how it's being used in the field, and so what does the rest of the Committee think about the dosing regime here?

DR. CANNON: Can I ask, what do you mean by a simpler dosing regime? What do you mean by that?

CHAIR HIATT: Well, it's complicated by both weight, and then above a certain weight you have to factor in height. And, so, you've got these tables that do all that for you, but they're suggesting it could just be maybe be weight-based, I think. Am I right in saying that?

DR. MARCINIAK: No, it's not -- the

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dosing scheme is not only the weight adjustment. The dosing scheme is also this two-step infusion, too.

CHAIR HIATT: Thoughts about that?

DR. LINCOFF: Aside from simplicity, I think the issue of whether or not we could further explore and learn more about higher doses in women would be pretty difficult at this point. The data is not definitive, but I think you'd have a lot of trouble getting past IRBs or other ethical groups the idea of doing higher doses in women. So I think we're left with what exists, that is a fairly narrow therapeutic margin, and that's particularly relevant in women for whom, to get a dose that appears to be relatively safe, you give up what appears to be a lot in efficacy, and that's just the way it is.

I'm less bothered by the male-female, because it's really two cards, pink, blue, whatever, than I am about the two-step,

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which I think really introduces a lot of issue regarding dosing errors. And we've seen with this narrow therapeutic window how an overdose could potentially markedly increase the risk of complications. And I don't know how, on the basis of existing data, to address that problem. I don't even know how you could go into Phase III again and do it. You'd almost have to back up all the way to Phase II, and try to design something different.

CHAIR HIATT: So I do think the FDA's concern about this is very legitimate, and for the reasons you articulated, Michael. There's a couple of components to the dose that make it a little bit challenging. And because you kind of see these events occurring at these doses above the recommended in men and women, it makes you think that if there was a little bit on the high side -- I mean, you actually if it was on the low side, if you waited a little longer, it might have been okay. But on the high side, it might create

some problems, so I think that these are really important issues, that if a vote were to sort of recommend approval, what do we think about the dose, and how it's being delivered?

I mean, understanding all that you know, and that was specifically brought out in the FDA review, are we okay with the way the sponsor wants to do that?

DR. HARRINGTON: Well, I think that Mike has summarized my concerns quite well, that it is complicated, it is prone to error despite nice charts, et cetera, we all know the medical error IOM report. Medical errors will be made. I thought it was said very well, that it will happen. I worry about being on a very slippery slope. The female issue, I agree with Mike 100 percent. I don't think you could go back and explore higher doses in women given -- it might have been a run of bad luck that you got four or five significant arrhythmias in women at that dose,

but that's what you got. And you would be hard-pressed to go back to your investigators and say hey, we want a little more data at that dose, so I think Mike is exactly right. So what you're left with is less efficacy in women.

I worry about the two-step dose. I want to -- I know the sponsor wants to say something, but I also want -- if Tom could address the issue with dosing, there's the other side of dosing, which is how long the effect persists. And the FDA, I'm looking at your review, it says, "Monitor it for six to eight hours or longer". And the sponsor's pharmacology experts and QT says that no, a couple of hours is fine. And could you give us your perspective on that end of the dosing?

DR. MARCINIAK: I'm actually going to pass that on to our clinical pharmacologist for his comment on that.

DR. HARRINGTON: You don't have slides, or could you point us to the page that

it's in the briefing book?

MR. TORNOE: I don't have the briefing book at hand. We looked at the QTCF, not the QTCB, as the sponsor. And it takes about six to eight hours to return to baseline QTCF, so that's where the six to eight hours comes from. So the discrepancy might be that the sponsor looked at QTCB.

DR. HARRINGTON: And do you want to argue for one methodology over the other? You obviously chose one, but the sponsor chose the other. Could you give us the arguments that favors your --

MR. TORNOE: Well, QTCB has been shown to be less correlated with heart rate, so when you correct the QT, you want to remove the heart rate effect. And their QTCF is better than QTCB, so whether you should monitor all the way until the return to baseline, that's another issue. But when we did the analysis, it takes about six to eight hours before they return to baseline in QTCF.

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CHAIR HIATT: So the Committee -- let me see. Maybe this is my bias, I think we have a lot of information about the dose. We have dose response and efficacy, we have some dose response on safety. We totally acknowledge that there's this male-female difference, that pushing the dose in women might be a stretch, that you have a complicated dosing regime on a couple of points, and then we have a long monitoring window, which we haven't reached a consensus on. But as we sort of talked about previously, maybe the idea that the QT could be reliably assessed as an endpoint in practice is probably not a good assumption; and, therefore, it's easy to recommend longer. And at some point in time, you might bump into feasibility issues.

Okay. So if that's all true, then the question - again, I want to go back to the FDA about this - what more information do you need, either pre or post approval, to

understand more about the dose and its ramifications?

DR. MARCINIAK: I guess it's a question of whether, in fact, you can achieve, particularly in women, particularly actually in the unstudied population we haven't talked about, in blacks, a reasonable risk benefit for the conversion versus other events, adverse events. To a certain extent, I think it definitely is a judgment call on whether you have enough information with what you have.

CHAIR HIATT: So there's a couple of options I could give you then. One is, is that the sponsor's design of what seems like would be probably a reasonable observational study, and you could say we know enough about the dose, and how to give it, and maybe we can talk about a conservative window to monitor patients. And then just really monitor things in the field, let things go forward, and assess how it's being deployed, how many

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mistakes are made, if you can. And the more rigorous the observational study, the more formal the assessment of those things would be. And you get all the additional dose information you need in the field.

The other approach is to say well, we need all that information before approval, do another study. And a third option might be to go forward with what you've got and monitor it, but do a Phase IV trial where you refine the dose, and test that formally in randomized trial.

DR. MARCINIAK: Yes. I guess I don't have much confidence I would be able to get information, much information on true rates of dosing errors post --

CHAIR HIATT: In an observational study?

DR. MARCINIAK: In observational study.

CHAIR HIATT: How about a Phase IV, would you feel good about that?

DR. MARCINIAK: Phase IV commitments we always worry about getting done.

CHAIR HIATT: So then you'd want a Phase III.

DR. MARCINIAK: This -- I think it's coupled -- this is one of the issues that it's coupled with. Dosing is one the issues. Use in some populations such as blacks is another issue. You could raise the issue about if you really want to address use against background therapy of other anti-arrhythmics.

CHAIR HIATT: So you have a lot of other unanswered questions.

DR. MARCINIAK: There are a whole bunch of unanswered issues, which makes me, at least, lean to say okay, I'd be better off with another study to address all of these issues.

CHAIR HIATT: Okay.

DR. MARCINIAK: We'd really like to

see a simplified dosing regimen. We don't see how we can introduce that into practice unless it's actually tested fairly well in a clinical trial. They can argue whether that's necessary.

CHAIR HIATT: I think we fully appreciate your concerns. I'm only pressing you to better understand what the implication of that concern might mean.

DR. MASSIE: I find it a little bit hard to separate this issue from the one I brought up earlier, which is the lack of experience in the population that's going to receive it, in general, at least in North America. So we have -- I think they probably have the right dose. I don't know about the way of administering it or not, and I guess there would be errors. I'm no expert on medical errors, thank God, but what I want to see is actually our patients with our practice with this dose, if this is the dose the sponsor thinks is the right dose, or maybe

with this dose and a simplified dose in a real study.

I just don't think that we know enough to be talking about getting the rest of the information post marketing. So if you ask me the question you asked FDA, I think that you -- when you say you're going to get more information post marketing, you usually start with more information about -- it's true, you don't have blacks sometimes, you don't have other subgroups sometimes, but we have no North Americans almost in the pivotal trials. We do know that there are differences in practices between those, and I just don't think we'll find out all the answers we want later. And if we do, we may regret it.

CHAIR HIATT: Let me give you another one of my philosophical points on that. It's easy to sit on this Committee and ask sponsors to do all kinds of things. Let's go back to North America and find every African American we can, but the implication

of that request is resource-intensive. And I think we have to both sort of ask -- what I'm trying to get at here, what are the seminal issues that need to be resolved? And what of the things that you'd like to have, that you might be able to gather in ways that maybe with recent legislation might be more effectively gathered than previously. What are the things that might be deal-breakers now, or not?

Once again, I'm hitting it on the dose a little bit, because I think the sponsor has done a really good job showing dose response, and they've done a really good job in trying to defend a way to deploy that dose in the field. But the FDA has voiced concerns that they think that maybe there are unresolved issues around that particular thing. It's a nice example of what we're talking about here, because it truly gets at this compound in terms of safety and efficacy, because we see those relationships across the

dosing range.

DR. MASSIE: Well, I would say one word is what I don't think we know, and we need to find out, and that is safety in the population it's going to be used.

DR. HARRINGTON: Yes. I don't want to harp on this after Barry has already been harping on it, but lack of a representative patient population, to me, is really troubling, that there's a lot that we don't know, largely because we're ex-U.S. here. We don't have a good sense of the practice patent relative to our own practice patent. And I appreciate Peter Kowey's remarks that from the registry data, they look kind of similar. That's legitimate, but I would feel a lot better knowing that the way that it's going to be used in our population has actually been adequately studied.

I agree with you that I think they've done a nice job with understanding the dose. I think they've -- I applaud them for

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not ignoring the females when they saw there was a problem, but actually forging ahead to do rigorous trials in women, specifically, and acknowledging that there was potentially less of an effect there. But I think we need to tease this out more in a population that's representative of -- we're sitting here in the U.S. FDA, not the U.N. FDA, and we're trying to understand what's going to happen when we around the table are choosing to use this drug, or our colleagues.

CHAIR HIATT: I'm going to press you on that one, and now I'm going to actually bridge the two days, because the demographics are really similar, at least in terms of the racial demographic. Eastern Europe was included in the previous development program. We weren't as disturbed about that yesterday as we are today.

DR. HARRINGTON: I voted no yesterday, Bill.

PARTICIPANT: Well, yesterday, most

were Danish, yesterday.

CHAIR HIATT: Yes, we had more Western Europe than Eastern Europe.

PARTICIPANT: They were almost all Western Europe. They were largely Scandinavian.

PARTICIPANT: And they were -- when they counted the Canadian ER experience, which raises a different issue, but probably an important issue to understand better, was nearly 40 percent in North America.

CHAIR HIATT: Both populations aren't -- I mean -- okay.

DR. LINCOFF: I mean, since you're going to bridge, aside from the international differences, which I think are important, but may -- I don't think they're quite as important as some of the issues here, that we have no concomitant medications that are commonly given that have a real potential to interact with this medication, so it's not a theoretical, is this going to be a high-risk

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population, or the doctor is going to do something. This is the reality that these are all medications that affect risk. And this drug has a therapeutic margin which is not particularly wide. I mean, we've been talking about that all along, so if any of these shift that dose relationship and risk, we have no data at all. And that's not how these drugs are going to be used in practice, so I think that's a very real issue, not to diminish any other issue.

CHAIR HIATT: I appreciate that. So clarifying what might be different is really helpful. Thank you. Response?

DR. STRAUB: Yes, maybe a few comments. Going back to the 2107 Study, which was the dose finding study, that, indeed, was in a U.S. population, and we have been starting to do our dose finding efforts in the American population in the majority, so that one comment.

The second comment, and here's how

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we designed our infusion regimen, not to reiterate, but we have been coming a long way with this drug, so meaning we have tested virtually all regimens you ever can think of. I think our expectation was that the 10-minute infusion regimen is a regimen which you need to control in the first 10 minutes, rather than give a quick shot. If you would do that free from the hands in the EP lab, and you would over-shoot the dose, that would not be an ideal limitation of variability. So that's why we have chosen for a 10-minute controlled infusion regimen to get it up to plasma concentrations which are reasonable, and then maintain it throughout. That's the reason for the two-step.

Now a few words about dosing errors. The only two things which could happen once you, in our point of view, apply dosing errors, is that you have to adapt the infusion after 10 minutes, because the infusion speed after 10 minutes is a different

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one from the start of the infusion, where you have a different speed. So if you apply that with a one bag regimen, which is possible, then the nurse has to adapt that, or the physician. So if you forget to do that, of course, you could over-shoot the dose, so what to do about it?

We have heard from Dr. Sands how to do this. You can apply two bags, which would really for sure insure that you use two different bags that this doesn't occur. So that, we think, we can easily test in the post marketing observation study in order to put this right.

And the other thing is whether or not people would adhere to the label, and give a male dose to a male patient, and a female dose to a female patient. I think they're all my comments.

DR. KOWEY: I know how difficult this is, and I won't even for a minute try to over-simplify it, but this dosing regimen that

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you're seeing actually is -- what Matthias said is very true. It's a good deal of thought that went into this, and let me try to explain this electrophysiologically. We think that it isn't just peak concentrations that is the important principle in converting somebody to sinus rhythm, but it is the plateau, that is, the number of minutes that you can expose the membrane to the drug at a sufficient concentration. So the reason why this was put together this way is because we were able to optimize the amount of time the membrane saw the drug without having big over-shoots in QT. And you saw those data, it actually worked. And it was really worked out, I thought, pretty well.

Once that regimen was in effect, the numbers of torsade cases they saw, and they can probably show you the numbers, is very small, because they corrected the problem they had when they were giving it as a single infusion. That's my first comment.

My second comment is that we are kind of used to doing global studies in AF now. It's common for data sets to have high concentrations of people from Eastern Europe, for example. And I know the FDA knows this, that you're seeing lots of data sets like that. In fact, these countries have enrolled patients so rapidly, we've had to cap them - you know that, Bob - because we don't want them to be grossly over-represented. Unfortunately, in this particular data set, I think we're seeing more than we're used to seeing. But having said, the quality of the data from these centers is extraordinarily good, and their adherence to protocol, at least in the studies that I have had a lot to do with internationally, has been very, very good. And I don't have any a priori reason to believe that somebody from Poland is going to react to this drug for cardioversion than somebody from Canada. I just don't have any reason to believe that, so I'm a little

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surprised that I'm getting this reaction.

I mean, yes, in the best of all worlds, I agree with Barry, having some percentage of people in North America might be a nice thing, but I don't know what that percentage is. And it certainly hasn't been studied in any kind of rigorous way, so to put aside the data set, it's not relevant to the people I'm seeing, it may not be relevant to the people you're seeing purely because of the reasons we talked about earlier, but not because they're from Europe. I mean, I think that's a little disingenuous.

DR. HARRINGTON: So let me clarify my remark, because much of what you said I agree with, that our group certainly conducts many large international studies. And we have exceedingly good experience and relationships, and collaborations with our colleagues in not only in Central and Eastern Europe, but Southeast Asia, et cetera, outstanding investigators, high-quality research. You're

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absolutely right. But we've got a little bit of a different situation here, is that we've got virtually no patients from the U.S. in the pivotal studies. And I think that the issue that I think needs to be addressed, Peter, is, do I think that the patients fundamentally in Prague are different than the patients in Durham, probably not, in terms of, we're mongrels here in the United States. We're made up of people from all over the world, so I'm very comfortable with the genetic issues.

I'm more uncomfortable with the issues that Mike brings up. How certain are we that these patients are being treated the same way? I have the same concerns about AMI studies, ACS studies, PCI studies. Are they getting the same practice of care? And I think you're absolutely right, I don't think we know enough about this, and it's not been studied in a rigorous way. All we know is that there are international differences in clinical trials. Why there are, is very

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unclear.

DR. KOWEY: I guess I've taken some solace in the -- from the information, and Tom even said this earlier, that in looking at these numbers in the best way you can, it's really hard, because you don't have a lot of North American patients, that there doesn't appear to be any gross discrepancies in terms of either placebo rates of conversion, or in terms of drug -- or in terms of the dose response. All those things seem to be reasonably similar. And I'm sure that although the company isn't able to show it to you as quickly as maybe they'd like to, I'm sure we can go back and look at much more of the demographics, and medical histories of the patients that were enrolled in this trial. It doesn't have to be this very moment, but I think that probably can be done. And I'll be very surprised if there's a big discrepancy. But I under -- I don't think we're in gross disagreement. I just think that we have to be

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somewhat careful not to throw out the baby with the bath water, I guess.

DR. HARRINGTON: I would never throw out data.

CHAIR HIATT: And we actually said that a few hours ago, that maybe there's a country difference, maybe there's not. Certainly, the data are available to look at that. The groupings can be logically put together, and it's something you might want to do at a later date.

MR. SIMON: I'd like to make a comment from the patient standpoint. You mentioned that it's a complicated issue. If it's complicated for you, you can imagine how complicated it is for me.

From that standpoint, I think I'd like to ask you somewhat of a hypothetical situation so that I can understand. If I'm in Afib 24 hours, and I walk into my doctor's office, or I walk into the ER, and my doctor or the ER doctor has been out all night on

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work, whatever the case may be, and things are not exactly perfect. Okay? What do I do, if they're going to recommend using your drug, versus cardioversion, versus whatever? Can you talk me through the process, and what I'd have to do, what the doctor would have to do, what everybody else would have to do, so I can understand the logistics, I guess.

DR. KOWEY: Can I -- all right. Let me just clarify, so I answer your question as best I can. So you've come to the emergency department, so you're having atrial fibrillation of how long duration?

MR. SIMON: Say 24.

DR. KOWEY: Okay. So you've been in it for a day, and how are you feeling?

MR. SIMON: Lousy.

DR. KOWEY: Okay. You're feeling pretty bad. And you and I have made a decision together that it would be a good thing at this point in time to put you back into sinus rhythm. And the question you're

asking is, how would we together make the decision as to how we might want to do that.

Well, the first thing, if this drug were available, and I was considering using this drug, the first thing I would do is explain to you that that's an option. We have an option. If you had a laboratory screening, and an electrocardiogram, and your history and physical examination all looked like it was fine, so that we could do it, and you fulfilled all the reasons why I might want to use the drug, I would explain to you what the chances were that I was going to be able to convert you to sinus rhythm with the drug, and what were the chances that I might hurt you by giving you the drug, so I give you some kind of realistic appraisal of what the benefit and what the risk might be, judging what I know from the drug's development. And then we would make a decision, and you would decide whether you wanted to have that, or if you wanted me to have the anesthesiologist come and put you

to sleep, and do it electrically. And I'd explain those risks and benefits, as well.

MR. SIMON: Would I be the person that should make that decision, or should the physician, or should both of us?

DR. KOWEY: Well, this gets into a real complicated question of philosophy of care. You're a very intelligent guy, and the last thing I'm going to do is take a paternalistic view of your care. So, no, unfortunately, you're going to have to help. I'm not going to foist the entire decision on you, but I think that you and I have to work together on it.

MR. SIMON: From the time I get into the ER or the doctor's office, until the time conversion starts, what length of time are we talking about?

DR. KOWEY: Well, you'll have to ask Tom Marciniak how long he wants us to watch you. But I think it's somewhere around a decade. No, I'm just kidding. I'm sorry,

Tom, that was a low blow.

(Laughter.)

DR. KOWEY: No. I think -- I'm a person who's very comfortable with monitoring patients QT interval, so if I were to give you this drug and you converted to sinus rhythm, I have great confidence that I would be able to track your QT interval back to where I thought it was okay, and that's when I would let you go. So judging from what I've seen about the kinetics of the drug, if we gave you the compound and you converted to sinus rhythm, somewhere between two to three hours, in that range. That's for me. That's what I would answer. Now, obviously, there's lot of questions to be answered by the Committee, as well.

MR. SIMON: So you're saying two to three hours from the time I enter?

DR. KOWEY: The time I gave you the drug, to the time you were able to leave.

MR. SIMON: How long between the

time I get there, and the time I get the drug?

DR. KOWEY: In our emergency department, it shouldn't take very long. There are some places in Philadelphia that run it by calendar rather than by the clock, so it really depends on how fast we can get to you.

MR. SIMON: All right. And then after the drug, how long - about 24 hours before you leave?

DR. KOWEY: No, no, no, no. Once -- in the clinical trials, and in my practice, if I give an intravenous drug that's approved for the indication, and your QT interval is back to normal, and you feel okay, you go home right there from the emergency department.

CHAIR HIATT: The other thing your question implied is if your doctor had been on call all night, or the nursing staff, it's five in the morning before a shift change, would the medical error rate be a concern.

MR. SIMON: Right, the medical error. Yes, in fact, I skimmed over that.

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The medical error rate, what -- I don't know what the normal, if there is a normal medical error rate in the ER room.

DR. KOWEY: Well, this gets down to something that Barry brought up yesterday, and has been discussed, it was discussed - and, again, not crossing over - but it was an issue, and that is, who's going to use the drug, and under what circumstances? And I think one of the things that happens with these kinds of drugs when they get approved is that there's clearly a trickle-down effect. The first people who begin to use a drug like this are electrophysiologists, and people who have a very strong interest in cardiac arrhythmia. They're the people in the hospital that generally start using it, and it's only after a period of time, in my experience, where people have become comfortable with it, that it sort of trickles down, and other people in the hospital begin to use it. So I think in the very beginning

of its implementation, it's unlikely the ER doctor is going to do this. I suspect it will be a cardiologist, an electrophysiologist, and I think those people are able to do this without a high error rate. So I would say the error rate should be fairly low.

DR. HARRINGTON: But I think it's fair to say, let's not leave it on that note alone, I mean, we have a Institute of Medicine report that claims that medical errors are the fourth leading cause of death in this country, so I absolutely agree with Peter, that when drugs start in the hands of expert physicians, the error rates likely are lower. But as things trickle down, there's absolutely no question, I think that the FDA reviewer said this, errors will be made. That is the reality of our system, that it's not perfect, and systems are not geared up to deal with that.

DR. KOWEY: Or they cannot synchronize the cardioverter, and you put into

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ventricular fibrillation with electrical shock, so let's not assume that we know how to use procedures better than we know how to use drugs. We have error rates with lots of different things.

DR. HARRINGTON: And as reported in the news a few weeks ago, we could give you a logarithmic increased dose of Heparin by mistake, so there is all sorts of things that go wrong in American hospitals, and so this -- I agree with Peter, this is not necessarily different than others, except for that you're starting baseline with a more complex --

MR. SIMON: So if I can understand - well, let me ask you this, Peter, one more time. What's the worst thing that could happen to a patient if you follow the directions, but you made one error during that process?

DR. KOWEY: With this particular drug, and I agree with the panel completely, this drug does not have a very wide toxic to

therapeutic ratio, so if you were to -- if somebody were to make a mistake, Bill said this earlier, it's okay if it's lower, but what we're really worried about, if it's higher. So if you get a bigger dose of this drug, you could prolong your QT interval and develop torsade.

What you saw in the clinical trials when that happened, whether it was - and I'm not assuming it was a mistake - even when it happens without a mistake, patients are promptly cardioverted, and nobody in the clinical trial died of torsade. And that's the way it should be, by the way. If you have a drug that causes torsade, and this is true also in the Ibutilide experience back in 1996. There were torsade cases, but nobody died from torsade. And it should never happen that that happens, so what's the worst thing that will happen? You'll wake up in sinus rhythm, you will have saved the cost of anesthesia, because you would have become unconscious from

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torsade, so it's actually pretty good news.

DR. LINCOFF: I'd like to ask a somewhat related question to the general trend of questioning here. In one of your early slides you talked about unmet need, and which potentially of those characteristics this drug fulfills. So now that we've heard about the safety and the efficacy, and recognizing that there are two existing similar technologies. There's D/C cardioversion and there's Ibutilide, what's the incremental meeting of an unmet need that this drug provides? If these were all available to you, how would you choose? What would be your criteria? What unmet need advantage does this drug have?

DR. KOWEY: Well, I'm going to go out on a little bit of limb here without having comparator data, and I really hate doing this, because it's always -- somebody always saws me off, but what it looked like to me with the infusion rate that's used in the Tedisamil program, I think this drug will have

less torsade risk than Ibutilide. So if I were going to use a drug, and I wanted to use something on label, and I wanted to use something that I knew about its efficacy and safety, and I was afraid of the -- and I had a real concern about the Ibutilide torsade rate, then this is the drug that I would choose. Does that answer, Mike?

DR. LINCOFF: So it's certainly not ease of administration, or --

DR. KOWEY: No.

CHAIR HIATT: Other questions about Tom's presentation from the FDA? Other general thoughts you all want to get into before we turn to the questions? Anything from the sponsor side? Did you have any one, or any issues that you feel you'd like to step up and say anything about, what we've discussed so far?

DR. WALDO: Just one minor point. The notion about potential relationship of the drug to enhanced thrombosis, the data you

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showed from echo are correct, except they're also correct for spontaneous cardioversion. And, again, it gets down to basics, atrial fibrillation is a very rapid rate, they usually go about 350 beats per minute. They cause mechanical dysfunction, and depending on how long the Afib lasts, and is it variable, but if it's over 48 hours, for instance, one out of four people have stunting. It doesn't matter if they convert spontaneously, or you do it with a drug, or you do it with cardioversion, with external or internal cardioversion. Those studies have all been done.

So I know you were looking hard to find a mechanism for seven days out, and I think you have to assume that spontaneous is the same, this drug is the same as cardioversion. I think those are supported by data and studies.

CHAIR HIATT: I appreciate you saying that in one way, because

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mechanistically yes, maybe anything you do can disturb the milieu enough to create a thromboembolic event, and there's certainly drug effects that can induce greater cardio hypotension, et cetera. But I think what we've got from the summary, the information from both FDA, and now from the sponsor, just by my simple count, so my interpretation of that data is numerically a few extra thromboembolic cardiovascular events on the therapy, one, maybe two deaths can be attributed to the drug. I'm not sure that the bradycardia hypotension, I think it's relatively well balanced. That's how I would interpret those data. And, to me, it's a dosing strategy, so you start with the randomization, but then things happen after that. And what matters is where you are at the end of the day. That's what matters.

DR. LINCOFF: It matters where you are the end of the day for safety. If it mattered for efficacy, I mean, we already

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discussed today and yesterday that D/C cardioversion is probably better. We're all going to end up at the same place at the end of the day. It's how you got there. But that's, to me, the safety issue.

CHAIR HIATT: I totally agree. And then we've got the avoidance of harmful things, which we now have some information about the number of cardioversions at 24 hours, and you have this window. And I'm going to assume for today's discussion that out of atrial fibrillation means you've locked your symptoms, and that's a good thing.

DR. HARRINGTON: Yes. To me, that's what it all comes down to, is the avoiding electrical cardioversion being a good thing. And, again, I give Peter credit, he says from the beginning of the day that think about this as strategies, and as complementary therapies. We're going on this path towards normal sinus rhythm, and the sponsors show us that at 24 hours/seven days, in both groups

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people have a high likelihood of being in normal sinus rhythm. It's just how you got there.

CHAIR HIATT: And by the new strategy, what have you gained symptomatically that's advantageous to going that way? And is there any risk in choosing that strategy?

DR. LINCOFF: Avoiding bad things in Bob's paradigm of live longer, whatever - feel better, avoid bad things. Certainly, avoiding a cardioversion is good, but we've been unable in any of these discussions to really put numbers to true adverse events associated with cardioversion, so it's an unpleasant thing, but we can't quantify it being as a bad thing. So what we have to do is sort of weigh whatever risks are associated with the alternative against the unpleasantness, and the logistic difficulties of cardioversion. And we're doing that sort of an imputation here, or as --

CHAIR HIATT: We are sort of by

definition, aren't we, because we don't have a head-to-head comparison. And so, unfortunately, we can't -- it would be nice to have AE profiles specific to the therapy, and specifically related to their onset and offset for a comparison of active cardioversion versus drug.

DR. LINCOFF: Right. And the only way to have done that would have been to have done a trial which is controlled not by placebo, but controlled by just okay, we're going to electrically cardiovert from the get-go, and then at the end of the day, count up your adverse events. But that wouldn't have been able to quantify either the inconvenience, and the fear, and the anesthesia, and the time, and everything else associated with cardioversion.

CHAIR HIATT: I think if you prospectively cared enough, you could do that.

DR. HARRINGTON: But don't you think, Mike, that we're getting some of that

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