last two days, is that as patients convert to sinus rhythm, they probably lose their symptoms. I imagine that relationship is pretty strong. So with that as just an introduction to a couple of the global comments from the committee, I'll open that up for questions.

DR. HARRINGTON: Yesterday it was very helpful to see a histogram of the duration of symptoms plotted against the conversion to sinus rhythm. And given that you're asking for a label that would provide, you know, greater than three hours out to 45 days of duration inclusive in the labeling, I'd like to see the data. My read of the briefing book and the FDA analysis would be that like yesterday, the effect is highly concentrated in the folks who have very short durations of AFib, but I'd like to see the actual data. I don't know if you were here yesterday, but that histogram approach that they used was very visually understandable.

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DR. RACZKOWKSI: Yes, we understand. We've shown some data in the core presentations that do show that less than 48 hours and greater than 48 hours, there's an effect; and seven days and less, there's an effect. With women, however, going beyond eight days, we were not able to show a significant effect.

DR. HARRINGTON: Yes, but the greater than 48 hours and less than 48 hours is pretty big blocks. Forty-eight hours to 45 days is a big window. I'd like to see it broken up into 24-hour increments. I'm sure you have that.

DR. RACZKOWKSI: Okay. We'll see if we can provide that data.

CHAIR HIATT: In fact, my read of that data was the same, that the 48 hour threshold, as we discussed yesterday, when the clinically relevant decisions might be made seemed to provide fairly high response rates. It seemed that the response is both dose

dependent and highly time dependent in that the 48 hour cut point was kind of a critical cut pont in terms of the magnitude of the effect. So, you know, we don't want to give you too many assignments to try to pull off in the next few hours, but those are two kind of key concepts.

DR. MASSIE: Perhaps I could just give one more, which is the same as I presided over yesterday, and namely, the more about the types of patients and some idea, because it looks like the vast majority were enrolled in Eastern Europe. Maybe more about the what these people are like, what types of treatments they had, et cetera, how they could inform us about the patients that are going to be treated in North America. The other thing is I think, and maybe you can clarify this, that these people couldn't be on any anti-arrhythmic drug?

DR. RACZKOWKSI: They were not allowed to be on Class 1 or Class 3 anti

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arrhythmics at the time of entry into the study and --

DR. MASSIE: So for several days before -- I mean entry is -- in other words, there was no exposure of this agent with any other background anti-arrhythmic therapy?

DR. RACZKOWKSI: That's basically correct, yes.

DR. MASSIE: And no amiodarone for quite a long time?

DR. RACZKOWKSI: Well, and then after 24 hours -- other anti therapy was not allowed for the 24 hours during the infusion. But then afterwards, other anti-arrhythmics were allowed.

DR. MASSIE: Right. But what we don't know and what we've heard -- in fact, Dr. Kowey suggested that people want to have another anti-arrhythmic agent around to maintain these people -- is you have no information about safety when that strategy is being used?

DR. RACZKOWKSI: Okay. Let me ask Dr. Straub if he can address that issue.

DR. STRAUB: This slide shows you the concomitant medication taken by more than five percent of the subjects. As Dr. Raczkowski has said, the anti arrhythmics were forbidden, and we had to wash them out first before we brought tedisamil in. But after 24 hours, they were allowed to be brought back in. So this is the amount of concomitant medications taken. And you see there is a substantial amount of beta blocking agents, of course; more than 70 percent. You see cardiac therapy in more than 60, up to 70 percent; anti arrhythmic agents, of course, more 90 percent; anti-hypertensives, pretty rare; anesthetics, now and then. But RAS system agents in quite a high proportion of patients as reflective of the background cardiac disease.

DR. MASSIE: What is cardiac therapy?

DR. STRAUB: Cardiac therapy includes a variety of cardiac medications, preparations, digoxin, for instance. Is that answering the question?

DR. MASSIE: Well, it does but the answer is troublesome to me in terms of how we can judge the safety of this agent as it's likely to be used in practice.

DR. HARRINGTON: Yes. It seems hard to believe that in a trial where you're going to test an anti-arrhythmic agent that you wouldn't just have ticked the boxes for all the common cardiac medications that you could show us. I mean cardiac therapy, 67 percent, doesn't tell me anything.

DR. STRAUB: We would have -- if you want to know exactly what it was beyond cardiac therapy, yes, we can have that.

DR. MASSIE: The other thing that's a little surprising given the frequency of hypertension in this population is I actually think it's actually a

misclassification. When it says almost no anti-hypertensive therapy but, of course, angiotensin system blockers and the beta blockers and the calcium blockers may all be there for that reason as well.

DR. STRAUB: Yes, but that is not mutually exclusive, because the agents on the RAS system are also anti-hypertensive --

DR. MASSIE: That's what I'm saying --

DR. STRAUB: -- but it's -- so it's in principle. It's a sub -- it's a coding --

DR. MASSIE: It's other hypertensives --

DR. STRAUB: I's a coding. It's other anti-hypertensives, absolutely. On this slide, I can show you a little bit more on the concomitant medication of special interest here as exemplified for the female patients. I see here that you have separated the diuretics and drugs used in diabetics, so

these are classifications which are lumped together in today's modern medra terminology. That's how things are done.

CHAIR HIATT: We just sort of jumped from two topics. Could you go back to the time dependency in atrial fibrillation and what you were showing. And I think we've also -- I've seen data in the briefing packet about responses with the cut at 48 hours. Could we look at that?

DR. STRAUB: Yes. First, I'll show you the ZAP analysis in the less than 48 hours -- you see it here -- versus more than 48 hours. You see that in more than 48 hours, the point estimate of the effect is slightly diminished, although we were still effective in that patient cohort.

DR. HARRINGTON: Well, not slightly diminished. It's cut more in half here. I mean if your effect in less than 48 hours is -- I'm just trying to get the estimate there -- is roughly 30 percent, my

eyeball tells me that your point estimate on the greater than 48 hours is 15%. So when you show it as three hours to seven days, you're not telling us where the bulk of the effect is coming from. And so if you show us in 24 hour increments, for example, for the first week, we would have that data.

DR. STRAUB: Okay.

CHAIR HIATT: Well, yes, but I think we kind of know what's going on. And the other thing I'm struck with, if you go back one, is the absolute benefit. Statistical significance is clearly achieved even greater than 48 hours or greater than seven days, except in women. But the absolute reduction has to be taken into consideration as well, particularly when we get to where people land in 24 hours they look like.

DR. MASSIE: This is women only and as I remember, it looked a little different than men.

CHAIR HIATT: Yes. Let's look at

men, too, then if we could.

DR. STRAUB: You want to see the males?

DR. RACZKOWKSI: There was one other factor with the women in that they tended to be older and sicker than the men. They had more heart disease and worse creatine clearances, et cetera.

CHAIR HIATT: Yes. Women, in general, weren't as responsive as men, so -- but again, here you see the same kind of almost 50 percent reduction in response --

DR. RACZKOWKSI: Yes.

CHAIR HIATT: -- after 48 hours.

DR. HARRINGTON: And what's the statistical test of interaction for the greater than and less than 48 hours? I mean that's -- it's awfully -- I mean the point -- the boundaries of the confidence intervals barely overlapped here.

DR. STRAUB: Yes.

DR. HARRINGTON: I'm sure you did

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that.

DR. RACZKOWKSI: Let me ask Dr. Driessen, who's our statistician, to address that question.

DR. DRIESSEN: Stefan Driessen, Biometrics, Solvay. Unfortunately, we did not test the interaction for the subgroups, but if we would have done it, this would have been a quantitative interaction because it's still in the same direction.

CHAIR HIATT: Yes, exactly. I think interaction, you know, quantitatively, if they're going in different directions, then to me, that's an important qualitative interaction problem. But here it would just be a linear regression of time versus response, a really simple analysis maybe adjusted for any other things that might have been different between those patients longer versus shorter. And you're going to see a strong, probably not linear but parabolic relationship.

DR. HARRINGTON: Which is what we saw yesterday.

CHAIR HIATT: Yes, exactly. You're going to see probably the same thing. Did you do that kind of figure relationship with confidence intervals around it?

DR. DRIESSEN: No. Unfortunately, we did not do, let's say, the graph that was shown yesterday, the conversion rate as function of the days of atrial fibrillation.

CHAIR HIATT: Yes, because you know, ultimately, what you're asking for is a very long window on the label for approval here --

CHAIR HIATT: Yes.

CHAIR HIATT: -- and where clearly, overall, you've got a positive signal, and the you've got these fairly distinct subgroup effects. And then you have to look at the absolute benefit.

CHAIR HIATT: Well, surely. I mean let's say this is for the whole window,

and the less than 48 hours is, of course, coming out of that which is not unexpectedly, the larger than 48 hours is still quite relevant. It's almost 20 percent. And that's placebo corrected, so this is the difference versus placebo.

DR. LINCOFF: But is that all at 72 hours or is that all at --

DR. DRIESSEN: Well --

DR. LINCOFF: I mean to say beyond 48 hours is just a huge window. Just show us the data for a month, I think, would be the best approach.

DR. DRIESSEN: We will do our best.

CHAIR HIATT: Okay. So is -- we've asked for a lot of analyses to occur in a very short period of time, but I am sensible to whether that's a feasible request. But is -- what Dr. Lincoff was suggesting, you know, is that effect greater than 48 hours bundled up in the sort of still early time frame and

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is that possible to show us today or not?

DR. DRIESSEN: Well, again, we are certainly not able, let's say, to come up with a graph as shown yesterday, and I don't know if we will be able to show what you are asking for split up by day of the atrial fibrillation. We would have to look into that. But again, I mean basically, the data, as shown from the, let's say, three hours to seven days window versus the 24 hours, as such, subtracted those out gives you, of course, the indication where the majority of the conversion has taken place, and both of that data has been given. Does that answer it? Thank you.

DR. STRAUB: Maybe, again, as an attempt to bring further clarity to that in slide number 56 in the core presentation, I have shown the three hours to seven days window. What we also, of course, have there is the data for the 48 hours. So what you can see here there is still 46 percent in the

three hours to seven days and that is going then between eight and 45 days. It's significantly diminished. And you see the same in females. So that gives you assurance of a indirect curve.

CHAIR HIATT: You know, it does, actually. It does suggest that some of that effect is retained out to seven days which would suggest that maybe that curve doesn't look the same as it might have looked yesterday.

DR. HARRINGTON: But it would be nice to see.

CHAIR HIATT: Yes, sure.

DR. MASSIE: But this certainly gives you the impression that the absolute benefit is pretty small after seven days. It's eight versus zero for the males, but --

DR. STRAUB: Thirteen versus --

DR. MASSIE: -- 13 versus -- I mean -- yes, okay. I was giving the absolute numbers, but -- and for the women, it's not

significant. The contrast obviously that we're thinking of is that the previous sponsor with similar trends in the data only asked for approval for seven days.

CHAIR HIATT: I would like to comment on that comment. I really want to make sure that the deliberations today are taken on their own merits. And I think it's going to be easy to try to link one thing to another, and I think that's okay conceptually. But I just want the process to be absolutely rigorously, completely transparent around what we're seeing today. And obviously, our thoughts are sort of informed by what might have happened yesterday. But the sponsor absolutely deserves the best independent process today. I'm sure that's what will happen.

DR. HARRINGTON: So one of the things I'm trying to get at is that this 2-1/2 hour time-point, I think we'd all agree, is a little artificial. I mean what you're

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showing, and I think you do show, is you have a significant conversion to AFib with the drug relative to doing nothing at 2-1/2 hours, and then as Dr. Kowey and others have indicated, after 2-1/2 hours, a lot of other things happen.

But what I'm trying to understand is the -- for me, one of the key clinical outcomes would be the sparing of electrical cardioversion, and again, Dr. Kowey makes a compelling case that sparing electrical cardioversion as part of a strategy is a good thing for patients. Can you walk me through in the two groups what happened in the first 24 hours so that I have a sense of at the end 24 hours. I mean did the placebo patients start getting cardioverted at hour 2.5 and -

CHAIR HIATT: I requested that during the break.

DR. HARRINGTON: Oh, you did? I'm sorry.

CHAIR HIATT: And if you look at

the FDA briefing document on page 75, this is subjects d/c cardioverted and/or prohibited medication first 24 hours, 40 percent on placebo, 31 percent on .64, 37 percent on .48, 30 percent, roughly, on .32, so I think we'll -- these are critical questions. We're kind of -- we know a lot about during the formal treatment phase when the primary endpoint was assessed. And what we're asking is to get a kind of global summary of 2-1/2 hours to 24 hours and understand. And we kind of requested that for the safety side and this was to be part of the efficacy side, so just to clarify for the committee.

And I think the sponsor actually has quite a bit of that information already prepared. So we don't -- we'll come to that whenever you feel comfortable discussing that. And we've got plenty of time, so there's no rush here. I mean we could even come to it after lunch if we need to, please.

DR. HARRINGTON: The other

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question I have is a global question for a diagram. You described two populations -- the overall intention to treat and the so-called modified intention to treat, and I understand the modified intention to treat if you're only going to include the treated patients. But you had some other groups up there including patients for whom you did not have additional data on. And I know that you commented that, qualitatively, the ITT and the modified ITT were roughly the same.

But I'd like to see how many patients, sort of in a consort diagram like way, how many drop out of the analysis along the way. And if you could actually show me the ITT data and not just comment that it's qualitatively the same?

DR. RACZKOWKSI: That data was shown in the presentation.

DR. HARRINGTON: Maybe I missed it. Could you just point me to what page it's on.

DR. RACZKOWKSI: We're looking for the -- it was called a sensitivity analysis in the core deck, and we had excluded the patients who converted prior to receiving the medication. We also had excluded -- we'll wait for the slide to come up.

DR. HARRINGTON: That would be helpful. Thank you.

DR. RACZKOWKSI: And patients who received medication, yes. But then we subsequently did a very similar analysis to what you're describing.

DR. LINCOFF: You also excluded d/c cardioversions within the first 2-1/2 hours, right, even though that could be considered a treatment failure?

DR. RACZKOWKSI: No. I'm -- go ahead, Dr. Driessen.

DR. DRIESSEN: No. Absolutely. So let me try to walk you through what we did and how it was all done. So this is coming back to the presentation from Dr. Straub on

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the core slide deck -- primary efficacy sample, everything was pre-specified in the individual studies, and we did the modified AFib ITT sample. Basically, modified in a sense that all randomized were in except for those that did not get study treatment, so that were not infused, those that did convert just before the infusion, so they did get the infusion but just before they got converted, and those that did not have post baseline efficacy data.

So in summary, these are all cases for which you don't really have data on the primary efficacy variable being conversion into normal sinus rhythm, because all of those don't really have data so you would have to impute. That we, as a primary analysis, did not want to do.

And the other category, as mentioned by Dr. Lincoff, is the d/c cardioversions. And I'll show you what all happened with these. So a summary on the

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exclusions from the all randomized -- again, they were all pre-specified. They were all done without knowledge of the treatment assignment. We did indeed have four categories, and I'll give you the numbers in a minute

But let me point out that all of these exclusions were either balanced between the treatment groups or the numbers in categories were very low and, as such, we didn't expect any bias. And then, of course, the next step is to also -- the data show that and that is kind of sensitivity analyses that were performed.

We had one in the dossier. We did an additional analysis which is also very much mimicking the additional analysis from the FDA. And the results at the end is there is no impact on the efficacy findings. So now -- I'll get back to this one.

So first, the four categories I mentioned -- excluded were those that were not

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treated. In total we have 42 cases that were not treated. There were three cases in total that just before the infusion, converted. And we could only see that on the Holters. And there was one case that simply did not have any post baseline Holter or ECG, so we could not assess whether or not that patient converted. So that makes up a total of 46 cases.

And then there were an additional six cases excluded from the analysis, so not so much from the sample but from the analysis because they got a d/c cardioversion within 2-1/2 hours, and we felt that that was such an intervention that we excluded that for the analysis, from the primary analysis. But, of course, we did a sensitivity analysis including them and there were no differences.

So now I go back to the previous slides, coming back to the reasons why subjects were randomized but not treated in order to indicate that the reasons for not

including them could not really have led to any bias as such.

So, again, we have these 42 cases nicely spread across the treatment group, so that's important, of course, in terms of assessing whether or not there was any bias creeping in. There were 28 conversions out of the 42, and all of those that did not convert had following reasons -- three cases in total with a QTc too high; two with an AE before treatment; 3 with other safety exclusion criteria, things like creatinine too high and other block measures; three withdrew consent; and three we just don't know.

So this is the kind of, let's say, scale of reasons that these subjects were not treated and we just excluded from the analysis, at least from our primary analysis. But then again, we did a sensitivity analysis as indicated. So we included all of them and just assessed them based on conversion whether or not they even were d/c cardioverted or not.

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And these were all counted as successes as well as those that did not get treatment but spontaneously converted. So it's really all in the bank.

DR. MASSIE: I have to say that's troublesome given the distribution of five getting electrically cardioverted on the active drug and one on the placebo. And in fact, why were they converted electrically in that period of time? Because that may have reflected an adverse event related to the drug. It could have been some sort of --

CHAIR HIATT: Right.

DR. MASSIE: -- v-tach that made the doctors worry. But to call them successes is not the way I would analyze it.

CHAIR HIATT: But I don't think how they're going to handle the data is going to change our interpretation of the data.

DR. MASSIE: Maybe not but I think it's important to understand why they were converted before 2-1/2 hours against the

protocol and whether that reflected some safety concern on the part of the investigator or just they were getting anxious.

DR. HARRINGTON: There is a group in the Safety Tables where who had sustained ventricular tachycardia, right, who got cardioverted. Are these those patients? So it would be interesting that you'd v-tach and then and then cardioverted and you sound it as success. Is that --

CHAIR HIATT: So it might affect your safety interpretation but probably not the efficacy interpretation.

DR. HARRINGTON: Well, unless you're thinking of sparing electrical cardioversion is what you're really getting at here.

DR. LINCOFF: Or did they get tachycardic in their atrial fibrillation, not counting the VT lines of the adverse event reporting but had some other reason why the investigator thought they needed to be

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cardioverted?

DR. DRIESSEN: Well, I think there are several questions and maybe remarks that I can respond to. I think success may not have been the most appropriate term in this situation, but it's just indicating that there was a conversion be it through d/c cardioversion or spontaneous conversion or drug treatment conversion. It just -- we took also, in this sensitivity analysis, a very broad approach in the sense of intent to treat. So you take all the randomized and no matter what the treatment is, if they did convert, you'd count them as a conversion.

You can debate about that I'm sure. I can sympathize that you might say that that's maybe not the best thing to do. But, you know, face value, I intend to treat -- that's also what you could do. Then again, like the Chairperson is saying, there are so few cases that it doesn't really make a difference at the end of the day. And in

fact, that's also been confirmed by the analysis as conducted by the FDA because they also took a bit of a different approach as at least our primary analysis.

So let me walk you through this one. I just only show -- we also have it for the other studies, of course -- for the 12 studies, the Fib males. So this is our dossier placebo corrected for the three doses, so placebo corrected versus placebo. This is the analysis as given in the review document from the FDA whereby they included also all randomized, and that's the only difference with our sensitivity analysis -- the d/c cardioversions were taken as failures. But you can see, of course, that those two analyses don't differ a lot and certainly also not as to the statistical significance and, again, also not with our dossier.

So in summary, there's all kinds of ways to deal with the data. We have to find that the primary one, there's good

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reasons maybe to also do it sometimes a bit different. We also did that. But at the end of the day, there's no difference.

DR. MASSIE: I think our Chair capsulized better what I wanted to know, which is why it happened and whether -- I guess you could search your SAEs and AEs for those patients to see if there's some reason that they were converted, because conversion in this situation could be because the investigator was concerned with safety or who knows. Maybe the patient just said I want to leave soon or something like that. But --

DR. DRIESSEN: You're absolutely right so I'm coming back to your second question, and that is the following -- that this is the list of seven d/c cardioversions within 2-1/2 hours. Though not allowed, it happened. But in fact, and you have to believe me on that, but four cases were d/c cardioversions because of adjudicated torsade-like events, so torsades.

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CHAIR HIATT: Wait. Just say that again? So this slide here, those first four cases, three on drug, one on placebo are all torsade --

DR. DRIESSEN: Absolute --

CHAIR HIATT: -- that led to the cardioversions?

DR. DRIESSEN: I think -- I have to go back maybe to my listings, but at least these three were torsades. These are the three males and I think one of those is also a torsade.

CHAIR HIATT: So you're absolutely right. I mean if there was sort of a drug induced, and particularly drug-dose relationship toward torsade, this may actually reflect a response to that arrhythmia which is directly drug related.

DR. RACZKOWKSI: And those torsades events were shown in the core presentation, so these were included.

DR. MASSIE: Right. But it does

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shed a little bit different light that the investigator felt that they required cardioversion.

DR. HARRINGTON: At least what I'm looking at from the packet on Slide 92 is that you actually don't call them torsades. You say they're torsade-like.

DR. RACZKOWKSI: That's the same --

DR. HARRINGTON: Same thing is that? So you add the torsade-like up as torsade in your overall assessment?

DR. RACZKOWKSI: Yes.

DR. HARRINGTON: Okay.

DR. DRIESSEN: I mean that's coming back to the differentiation between AEs terminology and the CT Holtering. You see adjudication and in order to make that separation, we have defined it as such.

DR. CANNON: (Off mic.)

THE COURT REPORTER: Turn your microphone on, please?

DR. CANNON: I just wanted to make

sure that that line of questioning was through, because I have a different line of questioning.

CHAIR HIATT: We'll probably come back to it, but that's okay because, again, there's --

DR. CANNON: Okay. In the briefing material, it stated that tedisamil is a potent to the sixth inhibitor and that it may cause -- it may effect the viability of several medications including type 1C anti arrhythmic drugs. And my question is if that's the case, how frequently were type 1C agents given after administration of tedisamil, presumably because tedisamil didn't work and maybe somebody thought of trying a pill in the pocket type approach? And was there any increased frequency of ventricular arrhythmias or torsade in those instances as opposed to instances in which type 1C agents were not administered after tedisamil?

DR. RACZKOWKSI: I'm not sure if we

have that data immediately available, but what I will say is that the tedisamil infusion was given for the first 30 minutes within a 24-hour interval. Patients had already been washed out from type one or type three anti-arrhythmics prior to entry into the study, and then there was a prohibition for subsequent treatment for the 24 hours of the study, at which time the plasma levels of tedisamil had decreased substantially.

But let me ask Dr. Straub if he has any additional information he could add.

DR. STRAUB: As you know, during the 24 hours, class 1Cs were definitely forbidden, were also not given. After 24 hours, class 1Cs were allowed to be added, and we have seen a variety of anti-arrhythmics given after 24 hours when the plasma concentrations are fully gone. We also have adverse events data in the submission on that particular subgroup of arrhythmias. I'm afraid I don't have the slide here, but the

incidence of ventricular tachycardia was not different.

CHAIR HIATT: Yes. So the design is kind of interesting, because there's not a lot of con. med. going on during this treatment window and the wash out helps you kind of maybe isolate a bit more on the drug effect and the drug safety. Although, again, I'll point out in the FDA document, Table 44, that they sort of bundled the cardioversions and the concomitant medications, and we might want to separate those two things that happened during the window to better understand if there's an interaction between either of those therapies and the drug.

DR. HARRINGTON: So, Bill, isn't that going to be an essential element of discussion? Because, again, Dr. Kowey, when he presented at the beginning, talked about the complementary nature of what we're doing here with drugs and electrical cardioversion and that one of the reasons that IV amio, for

example, has gained popularity is that there is the sense that, okay, you can transition over to oral drugs. We know that half the patients aren't going to convert with this strategy, and so they're going to need something else perhaps.

So not having knowledge of being able to tie something else in right away is a little limiting, isn't it?

CHAIR HIATT: Well, it's a design feature. It's interesting because, you know, for that reason, the durability of the treatment effect may have been minimized a bit by the absence of appropriate background therapy being implemented. And so what we are seeing -- you know, and you might be looking at the absolute benefit of the drug during this time, and that might influenced by that very fact, which in some ways helps you isolate the drug effect, but it doesn't tell you what's going to happen perhaps under conditions of clinical practice. Comments?

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DR. KOWEY: Bob, let me try to flesh this out for you, because you're right, it's extraordinarily important. So in the clinical trial program, there was an effort to sort of keep these patients off of drugs so that you could observe the treatment effect. In real life, what would happen? The fact that you gave a drug intravenous for conversion, what would likely happen is that sometime probably sooner than 24 hours, you'd start an anti-arrhythmic drug.

What you would probably do -- and 1Cs, by the way, would certainly be on the list as something you might consider. So what you would probably do is maybe after a few hours or when you're satisfied that you've seen the electrophysiological effect of tedisamil go away, you'd start the drug. It takes time to load, so your probably looking at about a two to three day period over which you'd be giving the drug, so it's unlikely that you would get to this. The problem you

point out, Dr. Cannon, is very important, which is overlapping electrophysiological effect and potentiation. It's unlikely that that would happen.

DR. CANNON: You think that would be true even for the sort of the pill in the pocket approach where you use a higher than a standard dose of drug?

DR. KOWEY: Well, no. That's correct. You're right about that. Fortunately, we don't use that very often, but if you were to load either because of what you're saying, which is period therapy or because you thought there was something good about loading, then you're bumping up against tedisamil. And the electrophysiological effect of the drug we're inferring is all explainable by the QT. There may be more effect there after the QT goes back.

So to be conservative about it, I think we'd want to have some kind of a honeymoon period. What that might be? It

hasn't been studied, frankly. I mean they just didn't do it because they couldn't within the context of this trial. But a number of other drugs, as Matthias said, were used post tedisamil, and they don't observe a higher rate of pro-arrhythmia in people who got drugs after tedisamil than the patients who didn't. So that's the best I think that we can do with that one. Does that help?

DR. MASSIE: But how long after treatment with tedisamil? I mean is it while they're pharmacologically --

CHAIR HIATT: It actually influences what you would recommend if the drug were approved for physicians to avoid other concomitant therapies during this time or not?

DR. KOWEY: No. I think based on the data, you have no choice.

CHAIR HIATT: Right.

DR. KOWEY: You can't tell people to do anything other than for 24 hours --

CHAIR HIATT: Right. Whatever the trial period.

DR. KOWEY: You're stuck. Yes. Now again, I think this is another reason why you need to get more experience with the drug as time goes by to learn these things. But as things stand right now? No, I think it's off the table. I don't think you -- you can't give other drugs for those 24 hours, because I don't really know what's going to happen.

CHAIR HIATT: But if that were to happen as things roll out, and I think the observational study you proposed, actually, would try to capture that. And it looks like a well thought out study, but that is a concern because we don't know about drug-drug interaction problems on the safety side that might occur in clinical practice.

DR. KOWEY: Yes, I know. The reason why, again, I don't find this to be a particularly large problem for me is because I'm not treating people who have very frequent

-- this is not a strategy for people who have very frequent paroxysms. These are people who have their arrhythmia in discreet episodes and then usually go several days before their next episode. So if there is a hiatus, if you say, look, 24 hours is off the table, wait, the chances that somebody's going to go back into atrial fibrillation within that short timeframe where you're loading after 24 hours is pretty small.

If it were a PAF where you were having very frequent occurrences, this is very problematic, but that's not the population that we're talking about.

DR. LINCOFF: I'd like to challenge that assertion a bit. You may not have as much of a risk of recurrence, but most of these drugs you want to start in-hospital, so you're mandating another day in the hospital. I mean your presentation early on emphasized the fact that you need to, in many cases, potentiate the effect -- not potentiate the

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effect on conversion but to maintain the conversion. And now to go back and say it's okay to just wait 24 hours or start a drug without loading, I think that is not a deviation, but it varies from clinical practice for a lot of people for a lot of these patients, and I think that needs to be recognized.

DR. KOWEY: Well, I'll just disagree a little tiny bit. We don't use 1C drugs in the hospital. In the vast majority of patients that we think are 1C candidates, they don't have coronary disease. They have relatively normal heart sweep. There's no labeling that says those drugs. Amiodarone, which is the most frequently used oral drug is never used in the hospital.

The two drugs that you're correct about, if we decided to use, would be sotalol and dofetilide. I got a lot of problems with sotalol and dofetilide on top of tedisamil, believe me. So I would like to see a lot of

data before somebody convinced me that I would ever put those drugs on top of tedisamil. So for the drug that Dr. Cannon brought up, the 1Cs or for amio, it's 24 hours; they go home; they start their drug as an outpatient like we do with everybody else. I don't really have a pretty big problem with that. And they're in sinus rhythm, Mike, so it's okay.

A A question or comments have circled around another large concept that I'd like the committee to discuss and question the sponsor, and that has to do with this spontaneous conversion rate. In our global discussion yesterday that Dr. Stockbridge kind of initiated over this -- sort of time dependency and the probability of spontaneous conversion randomized to placebo.

And once again, we sort of know what that short window of conversion rate looks like, and it's less than 10 percent. But it seemed to me that after 48 hours or after seven days, it wasn't that much

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different, maybe a little bit lower, maybe by half.

So what have learned about this population and it's probability of converting on their own that should help us inform whether the treatment effect, you know, potentiates that, how that might affect our thinking? So comments on the -- sorry I did not link things too directly -- but I think our sense was that the populations that we're talking about in these development programs aren't the ones that are going to, you know, in a very consistent way, convert fairly quickly when they first present. These are patients that maybe have a more prolonged propensity to stay in atrial fibrillation.

So my question is comments from the committee about the background probability of converting in this population.

DR. CANNON: Well, that's certainly my sense. I think the data that Chris Gallagher showed us yesterday might have

included a lot of younger, somewhat healthier people with PAF, sort of the lone atrial fibrillators where there is a fairly high spontaneous conversion rate. I mean my sense is most of the patients in these studies that we've reviewed with structural heart disease don't spontaneously convert as high as perhaps I would have thought prior to yesterday.

CHAIR HIATT: So I guess where I'm going with this, I'd like to maybe re-review those numbers with the sponsor a little bit on those placebo patients and those who had long duration versus short duration atrial fibrillation so we'd just kind of refresh our memory on what those conversation rates are on placebo and then to entertain comments from the committee about their thinking about, once again, this global problem of if you just wait a little bit longer, they might convert on their own.

DR. STOCKBRIDGE: You know that it's two to three percent who converted before

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you could even get the drug on board, okay, which is not much different from what you heard yesterday. You also know that it's three to 10 percent placebo conversion rates in the 2-1/2-hour window. That also doesn't sound very different from what you heard yesterday.

CHAIR HIATT: And then to continue that thinking, if you'd been in AF for a longer time, it was that spontaneous conversion rate was maybe half. It's still maybe around five percent, not closer to 10 percent, right?

DR. RACZKOWKSI: Let me ask Dr. Straub to address the question that you had asked.

DR. STRAUB: I show you here results of the primary efficacy parameter for the 3.112 study. You see the three hours to 45 days window with a the placebo response rate of 5.7 percent. You see less than 48 hours was 10.7 percent. You see more than 48

hour episodes were 0 percent. It's one study.

In the next study, you see 9.8 with three hours to 45 days, 26.3 percent, which is pretty high in the less than 48 hours, and again, zero in those episodes with more than 48 hours.

In the next study -- that's the first female study -- you see three hours to 45 days, 2.9 percent; 3.1 for less than 48 hours; 2.7 percent in more than 48 hours.

In the 17 study, again, 6.3 percent, 9.4 percent; again, zero. And finally, the last study, 4.5, 12.5, and two percent.

CHAIR HIATT: That's very helpful. And again, I just wanted the committee to kind of deliberate this a little bit, because it seems to me that when I read this material, it was watchful waiting. If you had AF for a long period of time, it was probably not going to result in very much, but then the treatment effect is a lot less. Watchful waiting if you

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have very short duration could be as high as a 25 percent conversion rate. You have a nicely demonstrated treatment effect over and above that. Thoughts on that?

DR. HARRINGTON: I mean I think you're summarizing what the dilemma here is in taking care of these patients is that if you get them early, that there's a reasonable chance that they're going to convert quickly. The longer you wait, that goes away if they're not a converter or it lessens if they're not a converter. And then you're ability to convert them with a drug also is less.

And then as you start weighing the -- you know, I thought Mike made a very good point yesterday is that he said, look, this is a group of patients that the doctors have selected or that he or she wants to convert and let's just accept that, that this is a group of patients that the doctor has decided he or she wants to convert.

What's interesting about these

studies is that they imposed upon the investigators, even though they presented themselves as these are patients that you want to convert but don't convert them outside of the study medication for a period of time. And so then there is a usefulness with that at the end of the 24 hours. And so I look forward to marching through all those details. I mean this last set of slides is helpful. It's informative.

DR. CANNON: Of course, there's always the uncertainty of really knowing how long they were in atrial fibrillation. Maybe they come to medical attention because they're ventricular response speeds up, but they could have been atrial fibrillation for much longer.

CHAIR HIATT: What about the population of, you know, sort of episodic versus sustained? I think there was also just some comments that came up about the sort of the demographics of these patients, their kind of AF. Can we characterize that a bit

further, too?

DR. RACZKOWKSI: Let me ask do we have a slide on that prepared, Dr. Straub?

DR. STRAUB: Demographics or the --

DR. RACZKOWKSI: No, no, the type of atrial fibrillation.

DR. STRAUB: Yes, let me see. Type of AF. These are recurrent or --

DR. RACZKOWKSI: Are you referring to recurrent versus first onset? Okay. Yes, we do have that information.

DR. STRAUB: So this slide shows you the history of AF and flutter. You have subjects with a first episode in about 50 percent of the cases, subjects with recurrent episodes about 50 percent, mean duration of AFib in years is about five years -- three to five years of duration.

CHAIR HIATT: Can you give us in response between those two populations?

DR. RACZKOWKSI: Okay. We'll have that slide up for you momentarily.

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CHAIR HIATT: Then I don't know if it's appropriate to ask, but the earlier request about summary data around safety and efficacy, is that something you're prepared to go to this morning still,, or is that something you prefer to wait on?

DR. STRAUB: Afternoon.

CHAIR HIATT: Afternoon. All right.

DR. MASSIE: In terms of safety, I really am concerned about one of the Tables in the FDA review and its implications.

CHAIR HIATT: Well, I'm sort of trying to maybe get the efficacy part and then we'll do the safety part. And then we're going to have the FDA review. And then we're going to have a bit of a global tabulation which we can get to very early in the afternoon. I think this will all start to come together. Michael?

DR. LINCOFF: Two questions. The first is it looks like from your indications

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on one of the first slides is that you are asking for a flutter. Can you show us the data, because as I recall, and I may be wrong here, but as I recall, much of it was just AFib. Can you differentiate the rate of conversion for us for atrial fibrillation and atrial flutter if that indeed is part of the -

DR. STRAUB: Yes, I can do that. May I just answer one of the earlier questions which was the first versus recurrent episode? The first episode seemed, in male patients, to have a little bit less of an effect than the recurrent episodes. If you see that in numbers, males and females, you see here at the dose of 0.32 in females, first episode 16.7, recurrent episode 19.6 success rate; first episode in males, 29.3 versus recurrent episode 41.7. So that answers that question.

Now the question about atrial fibrillation. Here is the primary efficacy parameter within 2.5 hours with respect to the

predominant rhythm. You see in females at a dose of 0.32 effects of 20.1 versus placebo 3.3. Atrial flutter -- this was not doing the trick, so we had less efficacy in this patient cohort, but we had for atrial fibrillation 30.2 in males on the dose of .48 and 14.8 versus zero. These results were both statistically significant as was the AFib cohort versus placebo with. The only one which was not was the female cohort versus placebo for flutter.

DR. LINCOFF: My other question related to QTc. Do you want to save that for a later safety thing? All right. We can tell from the background ahead of time there is some controversy regarding how long we should recommend in terms of monitoring. So as we had asked yesterday, can you provide some sort of estimate of the outliers in these QTc? You do have in your slide 100, the time trends with the point estimate for QTc returning to what looks like baseline within two hours.

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But again, with the size of the confidence intervals, etcetera, can you give us some feel for how many patients remain, and even longer than the two hours, with a prolonged QTc?

DR. RACZKOWKSI: Well, we based our monitoring recommendation on two things. First, it was the two hour window and second, when the QTc returned back to normal. So that is our recommendation for monitoring. So if a QTc is still abnormal, our recommendation is that we wait until that patient's QTc has normalized before the patients would be discharged.

CHAIR HIATT: And remember I think the committee's not convinced the clinicians in practice can actually do that.

DR. LINCOFF: I don't think that's a functional recommendation, so it would be better to have some information regarding what the distribution of returning to normal actually is. I think it would be better to

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actually prescribe a monitoring period.

CHAIR HIATT: Yes. Remember, you've got --

DR. RACZKOWKSI: Let me --

CHAIR HIATT: Sorry, go ahead.

DR. RACZKOWKSI: I'm sorry. Let me turn to our clinical pharmacologist, Dr. DeVries, and perhaps he can answer that question.

DR. DeVRIES: If you will decrease clinical pharmacology, on this slide you see the changes in QtcB, and we separate it into two groups, in groups with normal and mild renal impairment and simply if there's moderate renal impairment. And we have given the change from baseline, including the standard deviations, so what you see at the peak, for example, in the tedisamil groups, the maximum increase is about 30 milliseconds and also the standard deviations are comparable. So also in the renally impaired group, moderately renally impaired group,

there is almost the same distribution of Qtc.

CHAIR HIATT: Sorry to interrupt. The standard deviation is the standard deviation of the change or the population?

DR. DeVRIES: This is the standard deviation from the change.

CHAIR HIATT: I think it is and I think that's important, because that will help us understand the outliers of the difference, okay, so that even at 24 hours, you still have a 29 millisecond difference as an extreme?

DR. DeVRIES: Yes, 24 hours you'll see that the effect on QTc is gone both in the normal group and in the moderately renally impaired group. But you see the same standard deviations as in the placebo group. It's around 30 milliseconds.

CHAIR HIATT: But remember the concept in safety is it's not the point estimate or the mean that we care about. We care about the outliers, the 95 percent confidence interval of the worst case

scenario. Particularly when you go from very small numbers to the world at large, that's the outliers that we care about in terms of safety concern.

DR. DeVRIES: But what the data shows is there is a lot of variability in the change of QTc values, and you'll see that the standard deviations, both in the placebo group and the tedisamil group, are the same. So that's what these data show.

DR. STRAUB: There is one additional comment. All these QTc values are, of course, impaired by the fact whether or not patients are in normal sinus rhythm or in atrial fibrillation -- that's one. Point two is if they are converted, there is also an impact. So that's why in the beginning have shown the volunteer data which are very convincingly showing that after two hours, the QT effect is gone. In patients, it's not because it's confounded. That's our interpretation.

CHAIR HIATT: And I think the global commment was that, and we will come to the dosing regime, but that it's a complicated dosing regime and it's a complicated monitoring regime. And I think the question is going to come up whether it would simply be simpler to just define an outer limit of a monitoring window and not have the clinicians try to figure out the QT or not.

DR. HARRINGTON: And, Bill, that's going to be a critical thing to have some discussion around. I suspect we will when the FDA presents, because they're proposing a monitoring window that's many, many hours longer than what the sponsor has proposed. And so we need to understand that because some of the complexities, you know, monitoring someone for eight, nine hours is a lot different than two hours.

CHAIR HIATT: Yes, it sure is. And the feasibility of that and whether the patients might be let go prematurely and still

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be at risk is a concern.

DR. CANNON: So I'm struck with the number of deaths in women in this study, five deaths in women on drug versus one placebo, and I realize from Table 84 that you feel that most of these were relatively late and unrelated to the drug. But I'd like to review one of them, because it really bothers me, and that was shown on Slide 85 of your presentation, and it's subject 43001. I just want to get some idea of the relationship to the drug, because the investigator thought it was unlikely that the study drug was responsible for the patient's death which astonishes me, quite frankly.

DR. RACZKOWKSI: Well, let me just clarify. This was an 80-year-old woman who was a protocol violator in two ways. She had a history of v-tach and she also had rheumatic heart disease. The infusion was stopped and she became bradycardic and asystolic, and then she was successfully resuscitated. A few days

later --

DR. CANNON: Yes, but she was probably not the same person she was before the resuscitation.

DR. RACZKOWKSI: No. I understand. I'm not -- I'm just walking through the history here. A few days later, she received amiodarone which is another attempt to convert her, and we believe that that is the event that the investigator thought was unrelated. That's why the investigator thought that the ultimate death from the second episode was unrelated to the study drug, although there -- certainly, because the infusion was stopped, we can't exclude a drug effect on the initial critical --

DR. CANNON: Well, it's certainly fair to say that she had a near-death experience, I think --

DR. RACZKOWKSI: Yes, yes.

DR. CANNON: -- related to the drug. But my specific question was about the

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dose that she got. So at the top, it has .3 to .48. What dose did she get or was she started on before the infusion was stopped?

DR. RACZKOWKSI: Let me ask Dr. Straub to answer that question, please?

DR. STRAUB: In the beginning of this study development program, we not only had a 10 minute infusion regimen, but we also had a 30 minute, and we had a 50 minute infusion regimen, and all patients marked with 0.32 to 0.48 were receiving -- were randomized to a regiment which was planned to be 50 minutes -- 10 minutes the first half, then the remaining 30 minutes, the second half. So it was an additional infusion.

But in that 80 year old female patient, 10 minutes infusion were given, which have the same peak plasma concentrations as an 0.32 milligram per kilogram body weight infusion. And that infusion was stopped after 10 minutes.

CHAIR HIATT: You know, we're going

to have to have a fairly involved safety conversation, but since we got to the deaths, I think one of the challenges in a therapy that has, you know, a relatively short exposure window is really trying to wrestle with what events might be truly drug related and what might not be. And if you look at the sponsor's presentation on page 63, there is a pancreatic carcinoma on placebo. Well, we can easily dispense with that. But there are a lot of cardiovascular-related deaths.

In my read, trying to be more inclusive than exclusive and kind of writing off why people might have died -- they were protocol violators or they shouldn't have been dosed or some other drugs might have killed them -- you know, I think that case is an example where the drug was given, something bad happened and then things happened after that.

The other patient on my list was 61304, a pulmonary embolus that happened on

day one. Well, a PE that occurs in this context, you know, it's just hard for me to write that off. And then I think the more challenging thing are things that are cardiovascular in nature but they occur a few days out, so a CVA at day 16, acute MIs at days three and seven, you know, did something happen with the exposure that set the patient up for risk of a cardiovascular event?

And I just don't -- I think the uncertainty is always going to be there, but at the end of the day, you have to just take the numbers of people who died on drug and placebo and not over interpret whether that was or was not related and use that just to let it -- I mean so in my sense of trying to understand is there a safety issue, do we know? These are such small events. You have to assume there's some drug-relatedness here, particularly, well, since sort of mechanistically fit into a thromboembolic cardiovascular context around the time you're

doing something with an experimental drug.

And again, we'll see that tabulation after lunch, hopefully, and we can sort of just try to wrestle with the overall benefit risk relationship there.

DR. RACZKOWKSI: May I offer just one comment here?

CHAIR HIATT: Yes.

DR. RACZKOWKSI: Just to remind the panel that we, of course, did look at the deaths, and overall, the numbers were balanced between the placebo group and the tedisamil treatment group. And we can go into a greater discussion of specific instances if you'd like to.

CHAIR HIATT: And they are balanced numerically. I recognize that and I think the issue is what's the confidence interval around that? And how certain are we that we have, you know, one death in a thousand -- I mean how does that translate out? Are these truly things that the drug might have really

directly contributed to that are more on the drug side than the placebo side? That's all.

DR. MASSIE: Can I get back to one of the problems that I'd like to harp on, but it's pretty extreme in this. It looked to me like in the Phase III studies, that about 90 plus percent of patients were from Eastern European countries?

DR. RACZKOWKSI: That majority of the patients were from Eastern Europe, yes.

DR. MASSIE: Yes. I mean big majority, right? More than 90 percent?

DR. RACZKOWKSI: I don't believe it's that high.

DR. MASSIE: At least in several of the studies I calculated, it was about -- it may not be overall, because I didn't add it up. The other thing that makes me worried about the representative or applicability of this data is I'm looking at the list of exclusions that were listed in the FDA reviewers page on page 67.

Some of them are sort of obvious, but congestive heart failure, functional class 4; acute coronary syndromes at the time of randomization; but any history of rheumatic heart disease; history of life threatening arrhythmias ever before; previous ECG evidence of a second or third degree AV block -- that's I don't know how long before; sick sinus syndrome; myocardial infarction within 30 days; cardiac surgery within 3 months; stent placement or PTCA within 30 days; QTc greater than 470; creatinine greater than 1.8; and potassium less than 4.0, and concurrent treatment with anti arrhythmic drugs, we've already talked about; treatment with amiodarone within three months -- these are things that really are very common in the patient population I treat. In fact, some of them, particularly the cardiac surgery within three months, is often an indication for this type of intervention.

So I am just concerned about how we

can extrapolate this data a little bit for efficacy, because now that I see that the ones that are long or five years out, these are people, frankly, that I hardly ever bring in for cardioversion. And as I gather from somewhere else in the FDA review, a lot of them left the hospital without any attempt at cardioversion if they failed the therapy. So I mean somebody has to convince me that this information is relevant to the people who are likely to be pharmacologically cardioverted in North America.

CHAIR HIATT: So, Barry, two questions. And the first one, it is critical because they developed programs are truly international these days. Is there a treatment by country interaction? And the concern is that the background therapy and the standard of care may differ significantly between the U.S. and Eastern Europe for example.

DR. MASSIE: And systematically,

some of the things that characterize the patients we treat in the U.S. are, across the board, excluded.

CHAIR HIATT: So the other question then is is it a very exclusive population that's enrolled, not inclusive? And the representativeness of that is important. Now that, to me, is more of a kind of a conceptual issue. The first question is a data driven thing. I mean can you tell us if there is any differential response between - if you block countries, not by any specific country because there are a lot of countries, but you'd do Eastern Europe, Western Europe, U.S., North America, that kind of thing?

DR. HARRINGTON: Well, Bill, even more generally, can you just show us -- I mean I see it in the FDA review -- the countries of which these patients were enrolled in. I mean in the FDA overall analysis, around 10 percent are in the total safety pool. But in the Phase III, I'm not sure that there's anybody

from the U.S., at least in the Tables that I'm looking at. And the second part of the question, before you even get into the treatment interaction, is again, I'm going through both the FDA and the sponsor briefing book, can you just show us the demographics for the key things like percent ischemic heart disease, percent previous revascularization, percent hypertension to give me a sense of who they actually are? Percent hypertension.

DR. RACZKOWKSI: Dr. Straub?

DR. STRAUB: First, about the country distribution, you saw the number of randomized subjects by country. What you see here is that we had a variety of countries included, including the U.S., with 160 patients contributing to the overall dossier.

DR. HARRINGTON: Is this the Phase III studies or everything?

DR. STRAUB: This is everything what's in the U.S. dossier.

DR. HARRINGTON: And what's in the

Phase III efficacy and safety trials by country?

DR. STRAUB: There is only one study which is not contributing to that, and that is the proof of principle study, 2.107, which was a rather small study.

DR. HARRINGTON: so how many U.S. patients are in the Phase III studies?

DR. STRAUB: Okay. I'll show you this slide. It's a little bit busy with numbers. You see the United States contribution. So overall, 160. And here's the distribution over the various studies. The 2.107, which was the proof of principles study, had the majority of the patients. All the rest of them were the U.S. population, so 26 plus 16 plus 10 plus -- roughly 100 -- not 100, beyond -- 60 patients.

DR. HARRINGTON: Yes. My math was different. Okay.

CHAIR HIATT: Well, so the interaction question? So --

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DR. MASSIE: But all of the Canadians are also in that one study, so they're not in the Phase III either. You can see up there --

DR. STRAUB: No. The Canadian are in this study here, 27.

CHAIR HIATT: See, the problem with that long list of countries is to really ascertain everything that's going on, you have to group them. Did the statistical review look at that treatment by country interaction?

DR. RACZKOWKSI: Dr. Driessen?

DR. DRIESSEN: First, maybe the question back to the countries and the interaction with treatment. We did not specifically test that because, for instance, in the individual studies, we didn't stratify by country so it would, anyhow, be a post hoc. As you can see, though, there are various countries that have small sample sizes, so that's also making these kind of tests a bit more tricky.

But what we did do just the other day, so I cannot show you on the slide, but I can, of course, provide you with the details, is if I look at the data for the females, in the larger countries like Poland -- as you can see, that's a larger country contributing to the data; Russian Federation, that's also a larger one; and, of course, the Ukraine -- these are the larger countries that from the data that, let's say, placebo response in the females is 5.4 with .24, it's 12.5; with .32, it's 60.1, so there's an increase in the response; the same as for the Russian with, let's say, 10, 15, 20 percent consecutively; and with the Ukraine, zero, 13, 36, so with increasing dose, you get increasing responses in these larger countries.

CHAIR HIATT: So let me just understand what you just said. And the concern that I have that this creates is I've been involved in other development programs where the drug works really well in Russia but

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it doesn't work in the United States. So did I just hear those numbers to suggest that the Eastern Block countries, if grouped together, had a larger effect size in women than they would be in the non-Eastern Block countries? Is that how you'd interpret that?

DR. DRIESSEN: No. Well, I only listed Poland and Russian Federation and Ukraine, and that's, of course, not the whole list of countries --

CHAIR HIATT: But numerically, that dominates?

DR. DRIESSEN: Yes, sure, but it's like you said. I mean it's not the whole group.

CHAIR HIATT: We're just trying to get a sense if the -- because if the background therapies and the kind of the comorbidities of those patients are different -- maybe they're a bit more naive -- then perhaps the more Western countries where there may be a lot more medicines being used, are we

seeing a difference in responsiveness?

DR. DRIESSEN: Let me then indicate what the placebo response in all of those countries, and that's ranging from zero percent to nine percent, so that is fairly consistent with the overall picture.

CHAIR HIATT: So that's women, right?

DR. DRIESSEN: That's for the women, exactly.

CHAIR HIATT: That's not -- so if it was around less than 10 percent -- and then what was the best response women had that you just read off to us, 60 percent?

DR. DRIESSEN: Thirty-six percent in the Ukraine on the .32 dose for the females.

CHAIR HIATT: Thirty-six, which is better than the average, right?

DR. DRIESSEN: Which is better than the average, yes.

CHAIR HIATT: Okay. And then

correspondingly, can you kind of give us just an overview of what the men look like in those same countries?

DR. DRIESSEN: In the same countries, so placebo response in those countries was also below 10 percent; and then for the .48, we have, in Poland, 47 percent; in Russia, 50 percent; and the Ukraine 39 percent. So that is 39, 47, 50. That seems to be fairly consistent. And again, it's also increasing by dose, so there's --

CHAIR HIATT: Sure.

DR. DRIESSEN: -- coming back to the treatment by country interaction, you would then, without being, let's say, too scientifically into the third regimen, we could say that that's reasonably consistent.

CHAIR HIATT: I don't know, Norm. I mean I wouldn't want to pass judgment today on sort of unadjudicated data, but you might look at that. It might be worth sort of grouping these countries up in these logical

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blocks and seeing if there is any kind of sense of differential responsiveness based on -- and the demographics that --

DR. HARRINGTON: Yes, can we see that? Do we have that?

DR. DRIESSEN: Yes, I will transfer that to --

DR. MASSIE: Let me just --

DR. RACZKOWKSI: Dr. Hiatt, we do have a slide --

DR. MASSIE: I just wanted to make a comment before we lose that Table. I did calculations on what I think are the Phase III studies, and what I get is that, let's see, in North America, there were six, I think, because the rest were in the proof of concept-type of study; Western Europe, there were 26; Eastern Europe, 796. But I might not have classified them right, but I figured the 300's or the -- so I think that really tells us something, at least about the Phase III studies.

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DR. RACZKOWKSI: We do have the medical history. Some of the questions you're asking about history of heart failure or MI, we could share that with you if you'd like.

CHAIR HIATT: Just to try to summarize, I think, where we're going is that -- and again, I think Dr. Massie's helped us try to sort of crystallize the issue here -- that the populations, both under the demographics, background therapy, you know, standards of care may differ slightly between these different groups of countries. And we're hearing that it's possible that the responsiveness may differ slightly, that it looks like North America's under represented in the Phase III trials.

And if all that's true, it might be worthy of some further data evaluation by the FDA to better understand if there is sort of some signal that, based on the demographic profile, et cetera, that the drug might work differently in different countries. That's

all. I think that probably would be worth knowing.

DR. STRAUB: With respect to addressing the medical history, you have the slides here. This is the coronary artery disorder and 25 percent of the cases involved disorders; heart failure in about 20 percent; history of myocardial infarction older than 30 days, about 10 percent; age indeterminate myocardial infarction, .5 percent; acute myocardial infarction -- of course, these were then excluded if they were fresh acute myocardial infarctions; mitral valve disorders, 45 percent; central nervous system hemorrhages and cerebral vascular accidents, 2.9; and vascular hypertensive disorders in two cases only.

In females, that's the following picture; again, about 20 percent coronary artery disorder; heart failure not otherwise specified; myocardial infarction; mitral valve disorders slightly higher in incidents than in

the male patients cohort; about 5 percent nervous system disorders, and vascular hypertensive disorders.

DR. KOWEY: I'm sorry. I just want to respond to something else that Barry said that is very important, and that is you read off the exclusion criteria for the clinical trials, and I understand that that may not look like a totally typical population perhaps in the VA setting where people get cardioverted, but they have to understand two things.

Number one, this is a QT prolonging drug that was put into clinical trials in some relatively sick patients, and so it was really necessary not to have people on membrane active anti-arrhythmic drugs and to have an exclusion, for example, for recent use of amiodarone. They also didn't know a whole lot back then when they designed the trials about renal impairment and how much that might impact exposure. So the creatinine exclusion

-- I mean all the things that you listed make the population somewhat unusual in terms of perhaps the most usual population but there's reasons for all of that, number one.

Number two, it still doesn't take me out of the ballpark and being able to say I can use this in some of my patients. But I think your -- the point you're making about the fact that there have to be very clear instructions to physicians about who can and who should not get the drug. That's very clear. And that's a burden that the company will have in terms of educating and the package insert. But I don't think that takes you necessarily out of the ballpark of saying that this is a drug that you can use.

DR. HARRINGTON: So, Peter, while you're up there -- yesterday you made reference to the fact that you're running a large AF registry. I'm presuming that's mostly U.S. based or --

DR. KOWEY: No, actually, there's

two. One's mostly North America but the other one's global.

DR. HARRINGTON: So let's take the North American one. Can you give me a sense of the population with AFib in North America? Is it 20 percent coronary disease? Is that -- does that fit?

DR. KOWEY: Yes. It's actually almost exactly that number; obviously, lots of hypertension; lots of people with not severe heart failure, with less than severe heart failure; people with valvular disease but not severe valvular disease; lots of MR; very little MS. This is in the United States in North America. It really is very much the population you saw yesterday, and I'm sorry to do that. It's the population you saw yesterday and the population you're seeing today. It really isn't that far off the track, at least so far. Again, this is -- know they're not completed.

CHAIR HIATT: Yes. Well, that's

interesting, though. I mean so you have U.S. compared with Eastern Europe?

DR. KOWEY: Oh, yes.

CHAIR HIATT: So do they look different?

DR. KOWEY: Only to the extent of -- one issue is there's probably more non-ischemic cardiomyopathy in Europe and more ischemic disease in the United States. But there's just as much hypertension and diabetes over there as there is here.

CHAIR HIATT: A little bit more.

DR. KOWEY: There's more paroxysmal atrial fibrillation that appears in the United States than in Europe, but these differences are pretty small, much smaller actually than I thought I would have seen.

MR. SIMON: Do I assume -- I think from the information that was -- I believe it was stated that more cardioversion takes place in Western and Eastern Europe via pharmacological as opposed to electrocardial?

Could that be -- as a result of this study. Is that why this study shows less U.S. and more --

DR. KOWEY: Well, actually, it's interesting. I think I probably would turn it the other way around. The reason why those countries are places where people like to take drugs to get some information about them is because doctors over there are much more facile with and receptive to the idea of pharmacologic conversion. If you go to an electrophysiologist in the United States that do a lot of electrical conversions, they're going to tell you, well, like, why do I want to look at that drug.

So I think it's the other way around. I think you're right about there being a bias to go Europe, but I think the bias is because that's where people study these things and are receptive to the idea more than the U.S. and North America.

CHAIR HIATT: I would like to

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explore another kind of global issue, or do you want to make a comment?

DR. DRIESSEN: Yes. Coming back to one thing, that's the Eastern European versus American. So what you see here is that the U.S. population was mainly in the 2.107 trial. So that's the Phase II trial and that has already been shown by Dr. Straub. This Phase II trial, this was mainly conducted in the U.S. was with these results which were the start for going into Phase III. So in terms of conversion rates, I think we do have some figures also from the U.S., of course.

CHAIR HIATT: You're showing us three to 48 hours obviously?

DR. DRIESSEN: Yes, that's true.

CHAIR HIATT: Okay. Maybe we're coming close to the end of this discussion, but there's one other key point I want the committee to kind of address with the sponsor. It seemed me that what you have shown, which is very nice, is a very clear dose response,

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mainly in men but clearly seen in woman. So higher doses have a significantly better response in terms of conversion.

They also seem to have a threshold maybe of safety concern, and torsade being the most obvious one to me and perhaps the -- so you have sort of a parallel relationship between dose effect and safety concerns. And so I understand you sort of created two dose levels and you separated them from men and women, and they kind of look, when you look at the data, like they logically fall there.

But first of all, I wanted to comment about your impression that there is this relationship. And if that's true, then if patients were to be given a slightly higher dose, the risk might increase not linearly but maybe exponentially. And so then finding the dose and making sure the dose is adhered to would be extremely important. How much do we know, really, about the risk relationship as the dose goes up? The question is to the

committee and to the sponsor. Comments on that?

DR. RACZKOWKSI: Well, I think you've seen the data that once we exceed those as of .32 in women or .48 in men, that the risk of torsade does go up substantially. I think it's in the neighborhood of about 5 percent for men and about nine or 10 percent for women. And so that worksheet one of the limiting factors in terms of us going higher.

We, of course, have a risk minimization action plan that has been described by Dr. Sands, and that is going to be a very key component of our risk minimization plan, to ensure that medication errors or mis-dosing either between men and women or giving the wrong dose to a patient could occur. That's a very significant component of --

CHAIR HIATT: And I think we all appreciate that. What I'm thinking is is that you're on the edge, that the toxic/therapeutic

ratio is quite narrow here, and if I go down to doses that are reliably safe, I'm not going to see a lot of benefit. If I push the doses to get half my patients get converted, I'm going to be pushing the safety window.

That's the concern I'm expressing, particularly, as you see, I wrote down in my notes here that the slope for women is particularly steep. The women, at that higher does -- what was the point estimate, nine percent for torsade with a confidence interval of three to 20, and it's a pretty steep slope of the curve. And somewhere in the FDA briefing document, they do talk about the narrow therapeutic window.

DR. HARRINGTON: And it's not just -- you can't solve this just by -- if everybody was 100 percent compliant with the complicated dosing regime, in my mind, that doesn't necessarily solve the problem. That's the other component of the deliberation for me. It looks good today but that's just in a

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small number of patients.

CHAIR HIATT: Let me just make sure I understand what you're saying. Assuming that it's a perfect world and everyone gets it right, you're still not convinced that there's enough information to provide information on the outliers?

DR. HARRINGTON: Correct.

DR. STRAUB: The point estimate of 9.1 and the confidence interval of three to 20 is, of course, based on a very low number of patients. You see that the confidence interval is also very large. We had to stop the studies because of these incidences. If we would have seen different data, if we would have continued, we cannot answer with certainty today.

DR. HARRINGTON: One of the -- I'd like to perhaps --

CHAIR HIATT: Let's just make sure we understand that and just so the point is really appreciated. There aren't -- you did

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the right thing and there aren't a lot of events, and so the fewer the events the wider the confidence interval. And so had you stayed at those higher doses and gathered more events, the confidence intervals could have shrunk to maybe a level that might have been less concerning.

DR. STRAUB: Three -- for instance --

CHAIR HIATT: Well, that's the -- well, no. that's the other side of the confidence interval.

DR. STRAUB: I know. But in theory, theoretically, it could have gone the other way around --

CHAIR HIATT: But it --

DR. STRAUB: -- so --

CHAIR HIATT: Sorry. The conceptual basis for looking at safety is the upper end, not the lower end.

DR. STRAUB: I understand.

CHAIR HIATT: It has to be --

DR. STRAUB: Yes.

CHAIR HIATT: -- because you can only assume the worse case for safety.

DR. STRAUB: Yes.

CHAIR HIATT: You can play with it the other way if you're trying to flip it and prove that your drug prevents something from happening. But in this case, you got to live with the 20 percent, and if I hit that margin, that's what I'm worried about. And if I'm below that margin, you know, maybe it's really okay. And my only point, again, is those numbers suggest that you're close.

DR. RACZKOWKSI: Dr. Hiatt, if I may?

CHAIR HIATT: Yes.

DR. RACZKOWKSI: One of the components in our post marketing plan that Dr. Sands referred to was an observational study, and I think one of the big issues here with low rate events is that you need larger numbers in order to be able to accurately

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assess the rates of those events. And so this certainly is something that we plan to and will evaluate in that observational study in real world use.

CHAIR HIATT: And not to go off track, but your observational studies seem to be relative well-designed. We might ant to look at it later in the day and kind of comment on it, but the idea was that you would gather a lot of clinical variables that you maybe would use propensity scores to adjust for treatment decisions because there are option and adjust for the outcomes. So a part of the model would be the propensity score added to the model to look at the outcome of bad things happening.

And I agree you. I mean that's exactly what you need is more events. Now the question is do you need those events acquired during randomized trials or do you need them as an observational format? I mean that is another philosophical discussion we might have

later. But I applaud you for your observational study as you've shown it.

DR. CANNON: So I, too, was struck with what appears to be a very narrow therapeutic window for women in particular, and to a somewhat lesser degree, men. My question is were the toxicity in women, because the drug was given on a per kilogram basis, looked at with respect to adiposity, so some women may have more kilograms of muscle mass and others have more kilogram of fat mass, and maybe that' more of a variable in women perhaps than in men, and maybe it's an issue in Eastern Europe? Perhaps it differs form the United States? I don't know. This might get to Barry's question about the relevance to a more Western population.

Did you look at either efficacy or toxicity data, particularly in women, looking at it on a BMI basis or some waist circumference or some measure adiposity to see if that was explaining part of this narrow

therapeutic window in women more so than men?

DR. RACZKOWKSI: Let me ask Dr. DeVries perhaps to first address why we are using the dosing recommendations that we are. Because it is distributed in body water, we do use a weight-based dosing regimen. And I think this could also shed some light on the issue.

DR. DeVRIES: Yes. Just to explain why we used this dosing regimen, we know that tedisamil is non-lipophilic, and initially, it's only distributed over the total body water. So we want to prevent especially those high Cmax concentrations in obese subjects, and that's why we defined and kind of adjusted body weight. We kept the dose on the maximum BMI of 28.

And the question is, and that's what you asked, does it work? And therefore, I have this slide. There you see the pharmacokinetics not only in obese, but also in normal subjects and they are split for

females and males at the recommended doses. And the most important parameter for safety and efficacy is Cmax. So you see that, in fact, this paradigm works, that indeed both in obese and in normal female and male subjects, the Cmax are in the same concentration. Does this address your question?

DR. CANNON: It's higher with obesity --

THE COURT REPORTER: Turn on your mic, please?

DR. CANNON: The Cmax is higher with greater obesity, right, both for men and women? I don't know whether that's of significance from a pharmacokinetic standpoint it is higher.

DR. DeVRIES: In females, the difference is two percent. It's 984 in non-obese and 1,014 in obese. In the male subjects, the difference is -- yes, it's a lot higher but especially in the females, the difference is small. So I think based on this

algorithm we have, I think it worked quite nice to achieve comparable Cmax levels in non-obese and obese subjects.

DR. HARRINGTON: I want to go in a little bit of a different direction, but there's overlap here. As I'm trying to with the amount of data you have for safety, I was very intrigued when I read the briefing book that you had had an oral development program. And I totally recognize that oral therapy is different than acute therapy, orally delivered drugs are different than intravenously delivered drugs. I understand all of that but you have several thousand patients who have been exposed to an oral formulation. What do you think of the oral data and do they provide us any information?

As I go through the briefing book, it's noted that the risk of SAEs is increased in women, risk of SAEs increased in patients who had had a prior myocardial infarction, and I'm particularly in that one. And then I'm

intrigued with the issue of SAEs increased with patients who had had a borderline QT. Is there something to learn here, or is it just out of bounds that the chronic therapy is so different than the IV therapy?

DR. RACZKOWKSI: Well, the primary reason for discontinuation of the oral program is actually significant diarrhea in the patients. But perhaps I can also have Dr. Straub add some additional clarity to the question that you asked.

DR. HARRINGTON: Because if you had no -- you know, if it was completely safe given orally, that, to me, would be very reassuring that a lot of people had been exposed to the drug. But that's not the case here. So I'm just -- I want to put it in context. Okay.

DR. STRAUB: I think the oral development program was, for the main part, done in chronic stable angina pectoris patients, so it's a different patient

population. And the adverse event profile is also slightly different with more diarrhea components in there, which is a local irritation at the gut level, which also leads to diarrhea and then electrolyte imbalances. So what you see here is also a result of that.

So we had to struggle with some events which were a result of diarrhea or in connection with diarrhea with the electrolyte losses which would then even propagate events like a dysbalance for cardiac repolarization, and you would actually be able to trigger torsades.

So we have been, then in this direction, taken a decision to go away from the angina population, because we are facing a drug with QTc prolongation.

CHAIR HIATT: I recall you did see torsade in the oral program, didn't you?

DR. STRAUB: We did, yes. So we didn't, and we can't deny that this is an inherent and drug mechanism of action. But if

you want to compare oral versus IV, you're hampered a little bit with, of course, the absorption, then the gut-related adverse events. But we have to say -- and we have submitted the oral safety information to the U.S. FDA to have them also have a look at it in order to make them a picture about the large exposure we so far had and the adverse event profile of the drug.

I think because we cannot make any claim about efficacy in angina pectoris patients, but this, for the safety matter, would help us to make a judgment call also on patients with previous myocardial infarction or patients with angina.

CHAIR HIATT: Before we go to Dr. Kaskel's question, I really was curious, what did you see with angina with the drug? Did it help?

DR. STRAUB: It helped, yes. But it's -- but we cannot make that part of the case.

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CHAIR HIATT: We're not -- just curious.

DR. STRAUB: Just as for curiosity, it was a dose-dependent effect. It has been published. It's out there, the data and if somebody's curious, it definitely prolonged time to angina and lowered the ST-segment preparation.

DR. KASKEL: Yes, as the sole nephrologist here, I'd like to just make a plea about the kidneys. I think there's a subgroup here that needs to be evaluated, especially if we consider that CKD in North American comprises somewhere between 20 and 30 million people who have a creatinine greater than 1.4, and in that group, there's a large percentage that are obese as well. So the studies you've showed so far looking at renal function and creatinine clearances are grouped above 60 mL's and below six mL's.

In North America, we looked at the K/DOQI guidelines which are five different

stages of chronic kidney disease. So we need to apply some of those criteria to your group. Most of the patients below 60 mL's would be in a Stage II and III CKD in our country.

And then also, I think we need to pay attention to the fact that although the area under the curve is increased in your studies and the data that you showed in the renal patients with creatinine clearances less than 60, the Cmax wasn't. But I think that that might become important, especially if the patients are obese, as you showed here in your extracellular volume distribution data that these patients will have a different response possibly to the drug.

Then I think you have to pay attention to other confounding factors that could affect toxicity. Obviously, potassium is limited in the initial studies. They have to have a potassium less than four. Many of these CKD patients will not have a potassium less than four. They'll also be acidotic.