have no data on at all. So you've used it. So I'm probably looking to you for some guidance.

DR. SLOTWINER: Yeah. Well, no, I bring the question up reluctantly because I would like to have all three available, but clinically only one is available which we've been using off-label. I know I have to be careful what I say.

So I think that it's hard to extrapolate beyond the one catheter that I've used and presented in this trial. The modification to make a catheter bidirectional is not significant, and I don't know what the precedent here for the FDA is, whether that would require a separate trial. I suspect that that's not a major difference.

The remote navigation I think is a very different question, and to extrapolate the data here to a catheter that has entirely different characteristics of movement and pressure I think may be more than we can really justify from the data.

DR. BORER: Okay. Dr. Somberg has a question, but before then it's very important, Mr. Swink, I want you to clarify for us, is Dr. Slotwiner protected here? Is there a waiver for self-incrimination for off-label use?

(No response.)

DR. BORER: Well, you're not answering. Dr. Somberg.

DR. SOMBERG: Well, you know, first off-label use is not a crime. In fact, the FDA doesn't run the practice of medicine and approves -- and devices for use, and that relates, you know, the question that's brought up, I don't have a question but I have a comment, and that is we have to be careful. It's a very difficult area because we're getting into the practice of medicine, and let's step back from a catheter to a valve and, you know, a surgeon puts in a valve, but he has different degrees of training, different degrees of experience. Some surgeons look at the angiography and the ventriculography, the cardiologist does, and they get CTs, and others are more intuitive, let's say. When they open it up, they feel around, and I remember a very noted surgeon said I didn't look at your angiograms. I just feel where the bumps are and go distal to them. So you make that face, but he was extremely successful and quite famous in a northeastern city.

So suffice that to say that I don't know the answer to that, but the real question is that the label that you're going to give with particular

guidance really should be based on the study. So I guess I turn to Bram. One is the availability of these things. The other one is the guidance. It's hard to provide a guidance outside of factual information, but than again if we have certain availability but we require a navigation system, which I would imagine would be several hundred thousand dollars, additional to the cost of the catheter, you know, that may be putting a high burden on some people who are very good with Lassos and looking at squiggly lines.

DR. ZUCKERMAN: Dr. Somberg, you were doing very good until you got into the economic argument. So let me try to --

DR. SOMBERG: I'm just saying --

DR. ZUCKERMAN: -- give you some guidance to the Panel. Essentially at the end of the day, you're being asked to make a risk-benefit decision for five separate catheters. For a variety of reasons, the prime one being that one device was used in this trial, that risk-benefit decision will be easiest for catheter number one. For the other four catheters, you'll have to continue with your Bayesian hat and really think about how much data can really be extrapolated from one catheter design to the four

others.

It's also important in that thinking process that you put into the equation, as Dr. Borer previously mentioned, that what are these catheters doing versus what are potential safety problems, and you'll need to vet that out among yourselves and give us a recommendation.

Let me just say in a general sense, there's been a lot of discussion about off-label use. While the Agency certainly does not regulate the practice of medicine and off-label uses in the purview of physician practice, what is most helpful to us at a Panel meeting like this is if you do believe that a -- end catheter is not approvable based on the data, tell us and the sponsor what type of additional data would be necessary to make a particular device approvable.

DR. BORER: Okay. Having said that -- yes, Dr. Jeevanandam.

DR. JEEVANANDAM: Now, getting back to these five different models, I think, you know, then applying kind of the surgeon's approach to it, you know, one has to do with mapping and visualization, and I think that would materially affect the actual ablation. It's like telling a surgeon to do

something thorascopically using a 2-D thorascope versus a 3-D. You do a trial with 3-D, and then you say, well, then 2-D should work as well. So I think there's one component of it that's actually visualization and where you're going to ablate, which I think is going to be important for efficacy of this.

The other one is whether, you know, a catheter can only move one direction or it can move both directions. I would think that if it could move both directions, you can certainly move one direction where the trial was done. So I think one's uni or bidirectional probably -- I've never used these catheters, but I think that would make a big difference. You could always lock it into a unidirectional positions.

DR. SLOTWINER: Yeah, I think that's an excellent point, and I agree entirely. The catheter used was a unidirectional catheter, but bidirectional catheters are almost always easier to use and to manipulate. So I think it's not a tremendous extrapolation to imagine that a bidirectional catheter with navigation capability would have similar results.

Sometimes when a catheter is made

bidirectional versus unidirectional, it becomes stiffer because of the mechanics of that. I haven't used the bidirectional catheter. I don't have the data on it, but that would be my only concern. How strictly do we stick to the information that's given here to us versus what we approve. I think it's probably hard to move beyond the data that we really are presented. I think it would be an easy thing to acquire the information, easy study, although I guess nothing's easy, but we were given data on one catheter, and we don't know how the bidirectional catheter handling would change other than maybe steering a little bit more easily, but it may be stiffer. It may be more likely of trauma. It may be more likely of perforation.

So, you know, I think being a purist here, we have this data. This data, the safety looks reasonable. The efficacy looks reasonable, but I don't know if I feel comfortable going beyond that. I think navigation is clearly a critical part of this trial, and approving a catheter that doesn't have navigation capability, I find, would be very difficult to extrapolate to.

Of course, there is another navigation system that could be used with that catheter that

doesn't have the sensor in it, but then it gets complicated, and so I think again sticking to the data we have is probably the safest way to go. We're talking about a non-life threatening rhythm here. We're talking about symptom relief, and I think that's always paramount to keep in mind.

DR. BORER: Yes, Mr. Halpin.

MR. HALPIN: Yes, I just wanted to sort of touch base on this from an industry perspective. I think both the sponsor and the FDA, I think, have done a good job in trying to work through a clinical trial on a product which is already used off-label, and I think that creates a somewhat interesting situation for both the FDA and the sponsor. I think the adaptive clinical trial design was a great approach to take for that.

I think one of the aspects of approaching an off-label trial is that you want to actually provide labeling support for that use, and I think that the sponsor is very willing to do that in terms of how to actually instruct people how to use this or provide more support maybe than they have now in the off-label setting, and I think what maybe value for the sponsor and for the FDA is to get some guidance on if you extend beyond this one catheter, what is

some of the information that physicians, cardiologists would need in order to use it appropriately so that they can actually work and maybe get a number of these catheters approved versus just one.

I think the data shows that the procedure works. There may be some intricacies in some of these catheters versus others, but I think that your input in how you might bridge that would be very valuable for I think the sponsor and the FDA.

DR. BORER: Okay. Let me ask the sponsor, we had -- I think you answered one of the two questions, but the one that seems to be most burning, no pun intended here, is why was the lesion made in OUS 1 in the right atrium?

DR. YAROSS: Sure. Prior to the lunch break, we were asked if those were, in fact, deviations? Were they indeed prophylactic?

We had confirmed during our monitoring of the trial that at the OUS 1 site, those lines were provided prophylactically. They were protocol deviations. We picked this up in our routine monitoring. We worked with the investigator and decreased the occurrence of those deviations during the trial.

We disclosed these as deviations in your clinical report in your Panel pack. So, yes, those were deviations, and they're so reported.

I'd like to ask Dr. Wilber to address the clinical aspects of that, but maybe I can just touch base on a couple of other minor clarifications from after lunch.

I did just want to point out, Dr. Slotwiner, thank you for the discussion of CARTO. In discussing the use of pre-acquired CT or MRI images and merging them in, I think it was suggested that that would have been used in all cases. In fact, the CARTOMerge module was not available until May of 2005, and we know that some sites used it in later cases; other did not. So that was not used uniformly throughout the trial.

There was also a question from Dr. Naftel about failures before 90 days, you know, how could they be counted at day 0. If you recall, in the one slide where we showed the breakout of the failures in the ThermoCool group, there were two subjects that failed because they had a repeat ablation between days 80 and 90. So that was prior to effectiveness day 0, but those, for example, would have been counted in the Kaplan-Meier curve as a failure at

day 0.

Randomization was stratified by site. There were randomization blocks used, and I'll let Dr. Berry speak to that.

And then before I bring up Dr. Wilber and Dr. Berry, in terms of the catheter variance, we were asked, I think there was a question about was there precedent to approving a non-nav version based on a nav only trial. In fact, there was. For our atrial flutter indication for both our ThermoCool catheter and our 8 millimeter dual sensor catheter, the indication for treatment of type 1 atrial flutter was provided for the Celsius non-nav version based solely on data from a nav trial.

In addition, in terms of the remote magnetic catheters, those have been approved currently for both flutter and VT indications based on the construct if you will that if you can show you get the same catheter tip to the same point and make the same burn, that that can be translated into effectiveness and those data have been provided previously to the Agency.

So with that, I'll ask Dr. Wilber to -- yes.

DR. KELLEY: I'm sorry. I have one

question that I may have just missed earlier, but when patients had a second ablation, if they had a second ablation at 79 days, did the clock for the 9 months start over?

DR. YAROSS: No.

DR. KELLEY: So they were then only followed seven months after their final ablation?

DR. YAROSS: They still had their 90 days, I'm sorry, their 9 month effectiveness evaluation window still started at day 91 per the index ablation.

DR. KELLEY: So their follow-up time was shorter?

DR. YAROSS: That's correct.

DR. KELLEY: And then just a quick comment, but as I'm sure you know, doing an atrial flutter ablation without advanced imaging is very, very different than doing atrial fibrillation ablation.

DR. YAROSS: I understand, and that's why I'll ask one of the clinicians to speak to that.

DR. SLOTWINER: And if I could just say one thing. While there is precedent for approval of the non-nav version and the nav for atrial flutter, for ventricular tachycardia, the recommendation was the opposite. The navigation system, correct me if I'm

wrong, is required because it was felt that the study was done with that navigation system, and I think that just needs to be considered since this ablation is more similar to a VT ablation probably than a flutter ablation.

DR. YAROSS: It's an important point, and VT, part of our own thinking was since we were seeking an indication for treatment of unmappable VTs, where there was the need to be able to map voltage using the CARTO system, that to us was also an important consideration which is different we think than in these cases.

With the Chair's permission, then I'll invite Dr. Wilber to speaker to the clinical issue on the cavotricuspid isthmus lines, and Dr. Berry to speak to the randomization blocks.

DR. BORER: While you're coming up to answer that, it sounds as if we're moving OUS 1 from the analysis which was done and which we saw, removed most of these protocol violations, but I wonder if while you're answering the immediate question, whether you can come up with the data showing us what the efficacy would be or telling us what the efficacy would be in the patients whose procedures were done according to protocol which would be some of the

OUS 1 plus most of the non-OUS, just so that I can know that the data is reasonably consistent.

DR. WILBER: I think to answer that question first, we haven't performed an analysis that would eliminate all of the prophylactic flutter lines. So I'm not sure I can give you an answer based on that. And I don't know that we can answer some of these issues from the trial.

There's certainly growing abundant literature about the relationship between atrial flutter and fibrillation. First of all, it's become very clear since flutter ablation has now been done for about 10 or 15 years, we have now come very long-term data. Our initial report suggested when there was only 2 or 3 years follow up, that even though you successfully ablate flutter, the risk of atrial fibrillation is about 20 or 30 percent in that 2 or 3 years. Then we had a 5-year follow-up that suggested it was 50 percent. And now we have recently had an 8-year follow-up after isolated atrial flutter ablation, what's the risk of atrial fibrillation, and the estimates are up to 80 percent.

So what this would suggest, in fact, is that atrial flutter ablation has very little impact on atrial fibrillation.

In addition to those long-term observational studies after atrial flutter ablation alone, there have been some single center studies looking at the effect of whether or not you do flutter ablation on the outcome of atrial fibrillation, and there was one moderate size randomized study that suggested that, in fact, there wasn't a strong effect of whether or not you did the flutter line on the long-term outcome of atrial fibrillation.

I think that the performance of the prophylactic flutter line is because that's how that institution has been doing the afib ablation procedures since 2000, and I suspect they were reluctant to change a pattern of what was clearly a successful procedure for them, but the guidance document among other things that was published about, as you know, a couple of years ago, most of the people that are atrial fibrillation have abandoned routine flutter lines because of the judgment that it's not particularly effective in altering the outcome for atrial fibrillation.

So we can't answer your question from data from the trial, but there's certainly a growing amount of literature that suggests that flutter

ablation, although the relationship is complicated, doesn't usually have a major impact on the outcome of an atrial fib ablation.

DR. BORER: Yes.

DR. JEEVANANDAM: I just want a little clarification. So this nav system doesn't require 3-D mapping, and because you said some patients had CT scans and some did not, and did we separate out? I mean the patients who had the CT scans guided ablation, did they have better results than patients who did not have CT guided ablation? That's one question. The other questions is the nav system, does that relate specifically to 3-D mapping and guidance or is the nav system something separate?

DR. YAROSS: Regarding the first question, can you state your first question again just for a moment?

DR. JEEVANANDAM: You said that --

DR. YAROSS: The CT scans.

DR. JEEVANANDAM: Yeah, the CT scans.

DR. YAROSS: Right. All subjects who underwent ablation had pre-procedural CT or MRI, but that was as the baseline for the measurement of pulmonary vein stenosis. It was not mandated for use in the mapping procedure. So they all received those

measurements, but some may have chosen to use the CARTOMerge module once it was released in 2005.

Regarding the effectiveness, I can, you know, we didn't do a formal stratification of that. However, my information is that that CARTOMerge is not typically used by the highest enrolling site. So I would say that there probably is not a strong correlation.

DR. JEEVANANDAM: And the nav portion of this catheter was for the CARTOMerge?

DR. YAROSS: No. When we were referring to the NaviStar catheter, those are catheters that have a location sensor. In Dr. Slotwiner's diagrams, he showed you a map and then said, you know, if this were live, you would see an icon for the catheter tip. That's basically a mini GPS system that's in the tip of the catheter. That's the major difference between the nav and the non-nav catheters. That mini GPS signal allows you to locate the catheter tip in real-time when you are using the CARTO mapping system, which is a hardware/software system that allows you to visualize in real-time in 3-D what's going on in the heart.

However, as was stated, some clinicians do procedures outside of this trial without that using

other forms of guidance, such as intracardiac echo, fluoroscopy, circular mapping catheters, and so therefore there are multiple ways of locating these targets.

Does that address your question?

DR. JEEVANANDAM: Yes. Thank you.

DR. BORER: Dr. Slotwiner, and then Dr. Somberg.

DR. SLOTWINER: Yeah, if I could say the same as Dr. Yaross. It's confusing, but I was referring to two entities that we use often in guiding our ablations. The first is the catheter that has a navigation chip at the tip of it is located in 3-dimensional space by three magnets that are placed below the patient, and if we can turn the computer back on, I can show you the slide again to show the difference. Using that navigation system, you can construct a 3-dimensional shell of the chamber of interest and the pulmonary veins, and you can keep track of where you've placed each ablation lesion. Actually this is probably not the best example because it uses the CAT scan, but the 3-dimensional shell is one way to keep track of where our catheter is.

In addition, we can get a CAT scan and use

that to recreate in 3-dimension that chamber, and we can merge that CAT scan with our shell that we've created with the navigation catheter to improve accuracy and use both together.

DR. JEEVANANDAM: But without the nav system, you don't have that 3-dimensional shell.

DR. SLOTWINER: Correct. Without the navigation system, we can't create the 3-dimensional shell.

DR. BORER: John.

DR. SOMBERG: Yes. I'd like to ask Dr. Wilber, maybe you can comment on your feeling and the investigator's feeling because you probably have investigator meetings here, and was this a critical, I mean you're all experienced ablaters, and was this felt to be a critical aspect, the navigational system or did some people feel that, oh, you put it in but I can do it using the loop or I can do it doing other things and I didn't need it. Because I think we're getting into an areas of technical expertise that, you know, you're asking the committee, and I'm making this general, but the committee is being asked to make, and members of it are being asked to make a judgment on the experience of different electrophysiology ablaters, and this is going to vary

from site to site. So maybe you can say what the investigators were feeling.

DR. WILBER: I think clearly there's a diversity of opinion in practice, and part of it depends on how your own ablation practice evolves.

A couple of comments in that respect. Currently, there's new technology that's 3-dimensional echo that is different from CARTO altogether. There will obviously be new evolving technologies. We don't make an electroanatomical map anymore, and we don't use CT merge anymore, and we just use the intracardiac echo.

So there will always be evolution of different technologies for imagining. There are laboratories that use only very experienced laboratories and some that weren't in this particular study that only use circular mapping catheters and fluoroscopy as their predominant mode.

So the answer is ask a different investigator and they'll give you a different opinion about how it important it is for them to have 3-dimensional mapping, and so I think that it's difficult to come to a single conclusion.

DR. YAROSS: If I could just add briefly to that. There were clinicians that we did approach

about the clinical trial who have experience in this field who declined to participate in the trial because that was not their routine way of performing the procedures.

I also thought perhaps Dr. Hugh Calkins who chaired the HRS consensus document could come forward and speak briefly to the HRS consensus view on this issue.

DR. CALKINS: Hugh Calkins from Johns Hopkins. I was an investigator in the study, and I'm a consultant for Biosense. So, you know, there are lots of ways to figure out where you're ablating, you know, during these procedures, and it is striking if you look around the country and around the world, that different centers are passionate about different approaches. One of the largest centers in the United States almost never uses one of these mapping systems, but relies on intracardiac ultrasound. I, on the other hand, can't stand intracardiac ultrasound, and I rely heavily on these systems. Other centers use a venography of each of the four pulmonary veins, and you showed a slide the -- group. Yeah, they never use navigation. They just use Lasso and venography. So there's lots of different approaches.

I know in the consensus document, we didn't say there was a consensus that this was essential for the procedure. It was that some centers use it, some centers don't use it. And what is essential is that the endpoint is, you know, electrical isolation of the pulmonary veins as being the cornerstone which was the main acute endpoint of the study.

DR. BORER: Thank you. Before we go into -- Dr. Berry, I'm sorry.

DR. BERRY: So to address Dr. Naftel's question about randomization, the randomization was indeed in blocks by site. It was a block size of 11, 7 versus 4. So it's not quite two to one, but the anticipation was that the control patients, some control patients would drop out when they found out how they had been randomized, and indeed that did happen but not to the extent that they anticipated. And hence the five to one is really not that unusual in view of the seven to four.

The other thing I want to mention is what we were talking about, Dr. Borer's question about the prophylactic right atrial CTI. There were 23 according to the FDA and the sponsor, 23 out of 31 at the site. So if you remove those, there was one other prophylactic in the other sites. So if you

remove that one, it doesn't matter whether it's a success or failure, the answer is still the same. It's really quite a compelling statistical conclusion.

DR. NAFTEL: May I just say that that's a little bizarre to me, that all over the document it says randomization was two to one when, in fact, it was not.

DR. BERRY: The anticipation was two to one. They anticipated that it would be 2 to 1, and they incorporated what they expected and, in fact, they ended up with 56 to 103, slightly different from 2 to 1. It probably should have said seven to four, with an anticipation of dropouts.

DR. NAFTEL: It absolutely should have said that.

DR. BERRY: Yeah, I agree.

DR. NAFTEL: There's no discussion on that point.

DR. BORER: Okay. Before we enter a more structured setting here and focus on the questions, I want to make sure that everybody around the table has asked what questions they have or given what opinions they may want to give. We haven't heard from you recently, Dr. Fleming. Do you have anything you want

to chime in with here?

DR. FLEMING: Not specifically. I think as a potential consumer of that service, myself, and on behalf of those who I represent here on the Panel, I think my concern certainly is the safety and efficacy of the device, which is what we're here to determine, whether this particular device offers reasonable assurance of safety and effectiveness. I believe that at this time, that criteria has been satisfied to my satisfaction. I think the issue for me is far more practical perhaps, being a potential consumer of that service.

One question I did have is technical in nature. Maybe one of the gentlemen on the Panel who does these can answer it for me. Does this particular device that's before us in any way shorten the procedural time over and above say other catheters that are on the market? Because this involves laying on the operating table for eight hours and being either consciously sedated or asleep for three and half at least of those. And so I would like to know as a consumer, does a product like this potentially shorten the time on the table?

DR. BORER: David.

DR. SLOTWINER: Yeah. I don't think that

we really know the answer to that. The duration of the procedure is very dependent on the particular laboratory and the details of how they perform it, but it's a lengthy procedure, and there's nothing in the data presented here to suggest that this would be shorter than an alternative approach.

DR. FLEMING: Does the CARTO system, the navigational system, in any way assist with that?

DR. SLOTWINER: In terms of duration of the procedure? I don't have an answer to that. I'm not sure. I don't think so.

DR. BORER: John.

DR. SOMBERG: Well, Jeff, if I'm asking, if I'm making a statement that you think will fit in someplace else, but I wasn't sure where to fit these three comments I have in.

After hearing a lot about the Bayesian statistical approach, I think we should move away from just worried about that consideration, which I think some of the fears have been allayed.

However, I am concerned about some other aspects of the trial design. One was the asymmetry of the blanking periods, and I do think there could be some bias there. I brought up before with Dr. Wilber, you know, that there was 14 days versus

90 days, and we were talking about that's all it takes to titrate one antiarrhythmic. But there's a period that if anything goes wrong with the ablation procedures, it's not counted for a long period of time, but it is counted very quickly for the antiarrhythmic agent you can stabilize a patient and that may have some effects on it.

So I think that's one of the quirks of this small study that concerns me.

The other is just the use of transtelephonic. If you had to do it all over, I would suggest having some periods of 24 hour monitoring because, you know, symptom actuated, there could be a bias as Dr. Thompson brought in, and so there was some fixed points of measurement, but were they enough, and could we have had more episodes of AF that people were ignoring and weren't picked up on some small ones. So I think that's a problem with the study design.

And the last thing is I think you brought this up, Dr. Borer, and that was, you know, I'm concerned about the benefit. I mean, you know, those curves are dramatic, especially when you're leaving 100 percent effectiveness. There's no question about that, but what is effectiveness? And I mean we're

not talking about, these are not Kaplan-Meier life table where we're saving lives here, 100 percent survival versus 18 or 19 percent. We're talking about recurrence of PAF, and what's the significance of the recurrence and what's the degree, and these people are, you know, there's a lot of potential morbidity lying on the table for eight hours, three of which is sedated.

So these are considerations, and I just would like to hear a little bit, you know, someplace along the line here, a little bit more about, you know, how were they benefited, you know, the quality of life, you know, what are we really measuring and what is the significance here because we're going to be asked to vote yea or nay on that basis alone because this was essentially a symptomatic benefit. The blanking periods, how much did that bias it?

Is there anyway to look at that statistically? And also how, if anyone wants to comment from the clinical standpoint, how well do you think those fixed transtelephonic periods measured that? I need to hear about the length of those transmissions and, you know, sometimes people only transmit when they're feeling well because, you know, it's arduous to transmit when you're not.

DR. BORER: Why don't we start with the asymmetry of the time 0 issue. Dr. Thompson, could you perhaps talk to us about that a little bit?

DR. THOMPSON: There was a question earlier about what would have happened if the, I think Dr. Naftel asked this, what would have happened if the control had actually had a three-month dosing period, and so let's just forget about what happened to them from two weeks to three months. And actually the statistical group at FDA did think about that question, but we ultimately realized it couldn't have been answered using the data given to us because if you remember, once a control patient had a failure, they went to the ablation group.

So that's all a preface to say that I don't think that there's an answer, a statistical answer to be able to know definitively about whether or not the different blanking periods had an effect on the results. I mean we could make up all sorts of reasons why it did and probably reasons why it didn't. So it's something that has to be open to discussion.

DR. BORER: Okay. How about the monitoring issues? Maybe somebody from the sponsor can tell us the interval during which the transtelephonic

information was transmitted. What was the sampling time total?

DR. YAROSS: The transtelephonic monitoring was using a standard external monitor. They were instructed to transmit on a monthly basis -- I'm sorry -- on a weekly basis for the first two months and then monthly thereafter, as well as whenever symptoms occurred. The protocol called for a minimum of 30 seconds and point of fact, you know, really any continuous episode that was -- was adjudicated as such.

I did just want to comment I think to Dr. Somberg's question, there was some concern that if something bad happened, you know, in the first 90 days in the ThermoCool arm, you know, the patient could be retreated. In fact, adverse events or recurrence, adverse events were counted from day 0 of the treatment. And so there were some repeat hospitalizations for arrhythmia recurrence, that while those did not count against the effectiveness endpoint because the trial was based on a strategy of up to 3 ablations within 80 days, but anything bad that happened was counted in the safety analysis in both arms.

DR. SOMBERG: I guess I got too involved in

your company's program. I mean bad by not being effective.

DR. YAROSS: Thank you. I appreciate that. And then in terms of the issue of bias, about whether or not the delay between time of randomization and initiation of therapy could have had an effect, I would like to ask Dr. Wilber to speak to that.

DR. WILBER: Well, it's probably helpful for many people on the Panel that haven't been exposed to catheter ablation, the concept of the blanking period is really something that's evolved in the clinical practice of catheter ablation over the last probably 5 to 10 years, and particularly for atrial fibrillation ablation, it's become very clear that the immediate effect of the procedure doesn't manifest itself necessarily in the first few days. There continues to be both lesion progression and lesion regression. Some of this may involved the microvasculature. So if that's involved, then, in fact, you can get secondary expansion of lesions in a larger area, becomes electrophysiologically inert than previously.

There are not great animal models to suggest how long this time period should be until you get sort of the final product that you're going to

have, and there's probably ongoing remodeling that happens over a long period of time, but this period of three months has been something that has evolved probably over at least the last several years and is actually reflected in the guidance document in terms of how to evaluate outcome for atrial fibrillation ablation.

And so having said that, that's why the three months is opposed to a different time period, and I think there was an allowance made for repeat ablation at the cost that you couldn't reset the blanking period no matter what, and because our concern was obviously you didn't want to continually extend that time period of follow-up.

DR. BORER: You know, for whatever it's worth, I deal much more commonly with surgical maze than with catheter based ablations, and the surgeons, because of empirical data, have hit on three months as the time that you begin to look for effectiveness, too. But I think Dr. Somberg's issue was the other one that Dr. Thompson referred to, that is what about giving a little bit more time for medication, and the answer is, can't do it with this study. That's all.

With regard, before we get onto Dr. Jeevanandam, there was a third issue that

Dr. Somberg raised, I wonder if we can wait until we deal with the questions for that one, and that is, what is benefit because that's going to be central to our consideration. So we'll go to Dr. Jeevanandam and then Dr. Bilazarian.

DR. YAROSS: Dr. Borer, on that point, would it be acceptable for us to just speak a little bit more. We were asked specifically about quality of life. Would that be acceptable?

DR. BORER: Oh, yes, absolutely.

DR. YAROSS: Great.

DR. BORER: Absolutely.

DR. YAROSS: Dr. Calkins.

DR. CALKINS: It's interesting when you think about what the benefit is of catheter ablation of atrial fibrillation, and I think they can tell you for someone performing these procedures, yeah, the patients that end up getting this procedure, it's a quality of life issue. It's like hip surgery or knee surgery, and I tell patients, you'll know when it's time to get your afib taken care of, but the quality of life improvements you see in this study is reflected not only in, sort of the world of AF ablation, and I think it's striking that catheter ablation of afib is now the most commonly performed

ablation procedure in the world of any of the things we do. So regardless of an approved catheter, people are doing it worldwide, and that's because it works and patients feel better, you know, and the ones that are getting it are not the ones that are asymptomatic but the ones like in the study that have a poor quality of life that are really bothered by this afib, and we all know that the most symptomatic patients are paroxysmal patients, and oftentimes, you know, sort of the young healthy patients that the quality of life really matters to.

So I think it is a useful procedure, you know, the practice of AF ablation is exploding out there regardless of approved products simply because it works, and I think this study really reflects what we see in our day-to-day practice, but I'm sure David can comment on this since he does a fair number of these procedures.

DR. BORER: Did you want to say something about that?

DR. SLOTWINER: Oh, well, no. I agree entirely with what Dr. Calkins mentioned, and I was speaking with some of the Panel members earlier, the quality of life improvement that we see, these patients tend to be the most thankful. The carefully

selected, symptomatic paroxysmal atrial fibrillation patients, the improvement in quality of life is dramatic but, you know, it's a small set of the 2.3 million.

DR. BORER: Dr. Jeevanandam and then Dr. Bilazarian.

DR. JEEVANANDAM: I just have a question about the monitoring. So when you have the transtelephonic monitoring which is done on a regular basis and those were scheduled every week, and then if somebody was symptomatic, then they called in and then I guess they downloaded. So what my question is to the sponsor I guess, you know, what percentage of the patients that we now say failed therapy were because of the routine transtelephonic monitoring, and what percentage were because they called in because they were symptomatic? And I'm wondering whether that percentage was different with the control arm and the therapy arm and whether that was different between OUS 1 versus everybody else. I mean it's possible that OUS 1, no one called in for symptomatic afib and they were just looking at the scheduled telephonic monitoring.

DR. YAROSS: We had two slides in our presentation this morning that showed blocked

diagrams of the reason for failure in the different arms of the trial. May I have the first of that for the ThermoCool group?

So if you look at the reasons for failure, again of the failures in the ThermoCool group, 23 percent of the total failed due to symptomatic AF recurrence, and the remaining 12 of the 36 failures were due to other protocol adjudicated reasons, and if you recall, none of these occurred at OUS 1 in either category.

If I could have the next slide then to compare that to the control group. In the control group, 40 of the 47 failures were due to symptomatic AF recurrence per the standard monitoring regimen we've discussed, and the 7 remaining were because of intolerance to the antiarrhythmic drug, which from an intention to treat standpoint means the drugs cannot be effective. Does that answer your question?

DR. JEEVANANDAM: Yes.

DR. BORER: Okay.

DR. WEINBERGER: Can I just ask one question? Do these two slides imply that in the protocol driven follow-up monitoring, there was never a case of AF discovered when the patient was asymptomatic?

DR. YAROSS: There were some asymptomatic recurrences. In fact, we showed you those non-primary analyses and showed that, in fact, that there was a substantially larger different between the control and test when you looked -- a very large difference also when we looked at the symptomatic recurrence. There was also a very small difference between the symptomatic and asymptomatic recurrence curves, and those reflect the asymptomatic events that were picked up in routine monitoring.

DR. BORER: Okay. Dr. Bilazarian.

DR. BILAZARIAN: I probably should have asked this question earlier, but after this morning's industry presentation, and you showed very nicely your slide 67, CP67, where you excluded OUS 1 and showed obviously the impact that that had on the Kaplan-Meier curves, but then later in the morning there was a discussion about how other European centers were high volume and experienced. And I wonder if there is available data on excluding the other European centers?

DR. YAROSS: We have -- first of all, the other OUS centers were not all European but we did present earlier -- we talked to an analysis that looked at discounting those centers, and I can ask

Dr. Berry to come up and speak to that, if that would be helpful.

DR. BERRY: So we address discounting both OUS 1 and the other OUS centers, and we, for example, and Dr. Wilber presented this, this morning. If you discount the OUS 1 and also the other OUS centers, all four of the centers, well, I'll show you with the risk of inundating you with numbers, if you focus on -- this is OUS 1. These are the other three sites. If you said I'm going to discount by a factor of .8, some I'm only going to count 20 percent of the data here, 20 percent of the data here, and this is the number he showed, there's a 99.1 percent probability of superiority based on that discount.

So what this would mean is of the 31 patients who were on ThermoCool in this site, we're counting them as though there were 6 successes out of 6 and similarly here.

So if you discount completely, so that you don't count any of them, then the probability is .89. So it doesn't achieve the bounds, but if you count a little bit, it does achieve the bounds.

DR. BILAZARIAN: So can I infer from that analysis that as a clinician, you know we go from OUS 1 which has 100 versus 11 to the overall study of 72

versus 21, to excluding OUS 1 to what we saw in the last slide, 47 versus 18, can I conclude by the 00 that that 47 versus 18 would be further narrowed? Is that a fair conclusion?

DR. BERRY: No. It's mainly driven by the sample size issue. So if we get rid of all of the OUS studies, it decreases the precision that we have in making a comparison. And so that's largely driven -- it's because of power. So you have a smaller trial, you have less power to be able to make the conclusion. So it's essentially exclusively driven by the sample size and not by changing the bounds.

DR. BORER: The nominal difference would be approximately the same. It's just that the confidence intervals would be wider, and you wouldn't have the same significance --

DR. BERRY: Yes.

DR. BORER: -- basically or whatever the Bayesian term is.

DR. BERRY: Yes.

DR. YAROSS: If I can just follow-up on that point. If we go ahead, I think the question that was being raised was what happened if you excluded all of the non-U.S. data, and we did present

this morning an analysis both of the primary endpoint and of the additional evaluations of the U.S. data, and if it would be helpful, we could show that again briefly.

DR. BORER: Sure. Just that everybody has it in mind.

DR. WILBER: Probably one other -- now this is I think U.S. only. There's a couple of things. Most of the differences in sites were really driven by OUS 1, and so although we have comparisons of U.S. and non-U.S., the differences in non-U.S. are really largely driven by OUS 1, and once you take that out, in fact, the differences in the remaining sites are really very small compared.

Obviously it's important in this analysis to think about what happens at U.S. sites only, and I just want to emphasize that when you talk about not protocol defined failures, but failures due to recurrent atrial fibrillation, you see, if you remember the analysis for all of the sites, including OUS 1 was 75 percent and the ThermoCool were free of atrial fibrillation. Well, if you exclude that site, and you exclude the rest of the outside United States sites, you still have about 61 percent. So that, in fact, when you talk not about protocol defined

failures, deviations, but you just talk about recurrent atrial fibrillation, in fact, the difference between the U.S. and other sites is really not that -- quite as striking as you might have taken home, and it's 72 percent to 61 percent. And so again, although clearly there was a superior ablation outcome that was statistically significant at OUS 1, in fact, the magnitude of the difference, when you're talking about clinically meeting endpoints like recurrent atrial fibrillation or any observed afib recurrence, there's still a very strong performance at U.S. sites that's somewhat less but not certainly 50 percent less than sites in the total trial.

DR. BORER: Okay. Dr. Karasik, we haven't heard from you lately. Before we go onto the questions, do you have any issues you want to raise or questions or what have you?

DR. KARASIK: Yeah, I do. Thank you for the opportunity. I guess my question, one for Dr. Wilber, so you told us that the patients, well, that the patients are similar between the OUS site 1 and the other sites, but I didn't really see any patient demographics separated. Were the patients in OUS 1 younger, healthier, different? We didn't see any of that information.

DR. WILBER: We actually -- I didn't show you the data although we talked about it briefly, so if we can bring up that slide, I'll show you --

DR. KARASIK: It was the overall picture of the patient population --

DR. WILBER: Yeah.

DR. KARASIK: -- but I didn't see a separation.

DR. WILBER: Yeah. Patients at OUS 1 were slightly different. The differences weren't striking. You'll be able to see those in a minute. They were slightly younger. They had slightly smaller left atrial sizes and a slightly lower incidence of structural heart disease, so more often had structurally normal hearts. And you can see that information here. In terms of age, 54 versus 56. Do we have another slide on -- next slide on the remaining demographics. You can see here for -- there you go. For most of these variables, they're similar. A little minor difference in atrial tachycardia, atrial flutter. Continue. Hypertension is a little bit different. It's 44 versus 51, although that particular one was not statistically significant. You have left atrial size. I don't have the left atrial size with us, but there was

again a slightly different incidence.

So in general they were matched, but there were a couple of things that were again slightly more favorable in OUS 1 compared to the remaining sites.

DR. KARASIK: Thank you.

DR. BORER: Okay. I think we've reached that magical moment where we discuss the FDA questions. We each have copies of them, and I'm going to ask first of all that everyone comment, every one of the Panelists comment on each question, and we'll have different Panelists begin the discussion.

The first one on design, number 1, David, if you can read it and then give a response to it, and then we'll to around the table.

DR. SLOTWINER: Okay. The question regards design and patient selection. For inclusion in the study, patients need to have demonstrated three episodes of AF within the six month --

DR. ZUCKERMAN: Dr. Slotwiner, open up your blue folder. The questions have slightly changed. That's not question 1.

DR. SLOTWINER: Okay. All right. So new question number 1. Design - comparison to standard of care and generalizability of results. Therapy in

the medical control arm was limited to drugs approved for treatment of atrial fibrillation. Per FDA's recommendation, the list did not include amiodarone which is commonly used off-label to treat atrial fibrillation. Please discuss the impact of excluding amiodarone as a treatment option in the medical control arm. How does this affect the generalizability of the control arm to medical practice in the United States?

Well, I think we certainly use amiodarone frequently for the treatment of atrial fibrillation, but for these younger patients, I think the mean age was 57, for these younger patients with paroxysmal atrial fibrillation and no structural heart disease, amiodarone would certainly not be a drug we would want to turn to, and I think that the long-term risks of amiodarone outweigh the risks of catheter ablation substantially.

So I think that that was an appropriate and reasonable design.

DR. BORER: Judah, what do you think of this?

DR. WEINBERGER: As a clinician who uses amiodarone, I would not be interested in using it in such a young patient population. I tend to restrict

it to people in their seventies and above, where the total length of time they're going to get an amio is likely to be relatively short.

DR. BORER: Dr. Kelley.

DR. KELLEY: I would agree with that. I think, you know, certainly people use it, but if you look at why people stop the drug, maybe it's a little more effective than the other agents, but it's stopped more frequently to side effects. So I think it's not considerably better than anything else.

DR. BORER: Dr. Bilazarian.

DR. BILAZARIAN: I agree completely. I use it frequently in AF, but not in this patient population, more commonly in the subsets, elderly and structural heart disease patients.

DR. BORER: Mr. Halpin.

MR. HALPIN: It sounds like the FDA made a good recommendation and the sponsor followed it.

DR. BORER: Dr. Fleming.

DR. FLEMING: Again, not being qualified certainly to prescribe a drug like this, but as a consumer, potentially of a drug like this, I do not see its applicability in this particular condition that we're considering today. So, no, I don't see it as a problem that it was not used in the clinical

trial.

DR. BORER: Dr. Jeevanandam.

DR. JEEVANANDAM: As a surgeon, I use it in the immediate post-operative period, but for a very controlled time period. So we don't use it for more than six weeks. So I don't think I'd use it in this patient population.

DR. BORER: Dr. Karasik.

DR. KARASIK: Well, working in a veterans' hospital, I see a somewhat different population, and we use quite a lot of amiodarone and we use it quite successfully. I think if there had been an amiodarone arm in the trial, we would see a very different set of Kaplan-Meier survival curves especially when you take the OUS site 1. So I do have a little bit of problem with not using the drug in this study, although I agree with the comments about wanting to avoid the drug in the younger population.

DR. ZUCKERMAN: Dr. Karasik, can you expand upon how you think the results would have been changed? That's the purpose of this question. Certainly there's no Medicare age cutoff for this type of trial. It did turn out that mean age was in the 50s, but in the 65 and older, are you implying --

how much do you think these results suggest a very liberal difference between treatment and control?

DR. KARASIK: Well, I think there's ample data in the literature that suggests that you can get about a 40 percent success rate with amiodarone in terms of freedom from atrial fibrillation within the first year of therapy. And that would compare to that 47 percent freedom in the group of patients if you remove the OUS 1 site. So I just think the results would look a bit different if amiodarone had been used in this trial.

DR. BILAZARIAN: I agree as well, but I would further add, and hopefully you would agree that not only would we get that kind of result 40, maybe even 50 percent reduction in atrial fibrillation in that one year, but the rate of symptomatic atrial fibrillation may be even higher than that. So the reduction in the amount of patients on amiodarone that may have atrial fibrillation but without symptoms may even be higher than 40 to 50 percent.

DR. BORER: Dr. Somberg.

DR. SOMBERG: Yeah, I think all that is true but there are two factors here. Number one is that you couldn't design a trial with amiodarone because of its pharmacogenetic effects, and the

second thing is, amiodarone has a terrible side effect profile. So while you might get reduction in symptoms, which I agree 100 percent and show high efficacy antiarrhythmic drug, it wouldn't be -- I mean you would have to then -- the other side of the coin is you would have a much higher incidence of adverse effects, even at nine months on the amiodarone group compared to the ablation. So then you would have a risk-benefit ratio that would still come out in favor in all likelihood of the ablation. So, you know, I mean there's a tremendous need for amiodarone without amiodarone's adversity, no question about it, and when that appears, maybe another set of studies in the literature will be needed, but that doesn't relate to the device itself.

The device I think has shown that it is potentially effective with these analyses curves when one compares it to the drug therapies that ought to be used given the similar side effect profiles.

DR. BORER: Dr. Naftel.

DR. NAFTEL: I agree with Dr. Somberg.

DR. SOMBERG: Oh, well, thank you so much. I'm greatly honored.

DR. BORER: I agree what's been said about the concern about amiodarone toxicity and the fact

that the toxicity is dose cumulative, so that with time you can expect more and more problems. You know, that may be less of a problem with people as they get older and get less of it. On the other hand, my understanding of the distribution of PAF is that it tends to be in relatively younger rather than relatively older people, and when they get older, people tend to have persistent AF, a totally different ballpark.

But I would look at this in another way that hasn't been mentioned, and I just want to say it so it's on the record. No matter what antiarrhythmic drug you use, and the protocol called for this, patients need to be anticoagulated, and that's true with amiodarone as well as with any other drug, and especially as they get older. And that is a little bit of a problem because now you've added some morbidity to the strategy, which if I understood correctly was not part of the issue for many of the patients who are in the catheter therapy arm. Now, maybe it should have been, but that's a different issue. It wasn't.

So I think, you know, we do have to consider that any drug therapy would mandate, unless there were some major contraindication, an

anticoagulant adjunct.

The other point is that I think we're being asked to judge here whether the catheter based therapy is effective and acceptably safe for the intended use. That means that the catheter based therapy has to be compared to something. It doesn't necessarily mean it has to be compared to the kitchen sink. It just has to be compared to something that we have a reasonable basis to expect to work, and that was done here, and without jumping the gun on these questions, the catheter based therapy looked like it worked better, which tells us something about effectiveness which is what we really needed to know, whether giving amiodarone in some strategy would have resulted in greater efficacy without unacceptable adversity. I don't know. You'd have to do the trial if it were even doable, but I don't think that's our primary concern. So I would accept the study as it was designed.

DR. SOMBERG: Dr. Borer.

DR. BORER: Yes.

DR. SOMBERG: You brought up an important point, and I just wanted to add one thing to that was the use of anticoagulation. I think we should as a group stay away from any mention, I should say this

now, you know, in the label or recommendations, that because the catheter ablation decreased symptomatic atrial fibrillation, we are any way recommending that they not receive anticoagulation because some of the point I was trying to make was if you monitored these people enough with Holter, you may be reducing symptomatic, but I think you would still have episodes of PAF and those things, you know, going in and out is what can give you the embolic phenomena. So I would not, because those curves are beautiful, they separate out so much, especially with OUS 1 in there, I still would think these people need anticoagulation therapy.

So if the clinicians from the company think otherwise, or anything, maybe I should be re-educated but that's my understanding, that the success of ablation does not preclude the need for anticoagulation therapy.

DR. BORER: Dr. Zuckerman, have we responded adequately here?

DR. ZUCKERMAN: Yes, you have. You've given us an idea that this was a reasonably designed trial, and the amio issue was not the major point here.

DR. BORER: Okay. Now, number 2, maybe I

can ask Dr. Naftel to read that one and give the first answer about poolability.

DR. NAFTEL: Please discuss -- do you want me to read the whole paragraph?

DR. BORER: Just the part about outside the U.S., poolability.

DR. NAFTEL: Okay. Outside of the U.S. sites enrolled 60 percent of all patients in the study. These sites generally performed better than the U.S. sites as evidenced by the chronic effectiveness result reported at the highest enrolling site. At this site, none of the 31 ThermoCool subjects failed during the nine-month period, whereas chronic success rate for ThermoCool subjects in the remaining sites was 47 percent. The respective control group success rates were 11 and 18 percent, for the highest enrolling site and remaining sites. In addition, there were some differences in patient treatment between the outside U.S. and U.S. subjects. However, the posterior probability that the ThermoCool ablation group is superior to the AAD group was .997 for the remaining sites alone.

So the question is, please discuss the impact of differences between outside U.S. and U.S. sites on generalizability of the reported results to

a solely U.S. population.

Do you want me to give it the first shot?

DR. BORER: Please.

DR. NAFTEL: So it seemed to me from all the discussion the impression I got was that it was an issue of experience. Certainly that was the feeling. I know when someone asked if there was an analysis of experience across time in the entire study, I think the answer was that we didn't have enough patients at individual sites. Perhaps you could have done something in some of the larger enrolling sites because I think that's the issue.

It's maybe encouraging that the U.S. sites still had a good result. The point was made that those are perhaps centers of excellence, centers that you think would do well.

To me, the whole study is fine like it is. For me, I think I'm personally happy to generalize the reports, the results to a U.S. population, and I totally understand we're judging everything on the basis of what's in front of us and happy to do that, but then the next step is that postmarket study that I think is just going to be critical and needs to be designed correctly, and I think one of the endpoints was look at five years at the patients. I hope we'll

look a whole lot sooner than that to see what's going on.

DR. BORER: Dr. Somberg.

DR. SOMBERG: I was impressed by the lack of differences in the patient population and the dramatic difference between OUS 1 and the other sites, and I agree with Dr. Naftel completely. It's an experience which should be mentioned in the product labeling that this is a technique, dependent technique.

DR. BORER: Dr. Karasik.

DR. KARASIK: I agree with everything that's been said so far. I mean I think we were all struck by the difference. I was reassured to hear that statistically the differences were not significant, and I do think that, understanding how the catheter is implemented in the future, if it's approved, is going to be really important to know that the effectiveness of the therapy stays high and doesn't drop off as more inexperienced people use it.

DR. BORER: Dr. Jeevanandam.

DR. JEEVANANDAM: Clearly I agree with everybody that the difference was striking. I mean you go down from 70 percent to 47 percent if you took out OUS 1, and I think there's some data that

suggests that the recipients had less atrial tachycardia and had a smaller left atrial size, which all are predictors, at least in the surgical literature, of the success of these procedures. So I think that perhaps there are patients who are less sick for a less period of time, and perhaps that was what some of their results were. I mean it's hard for me to imagine that with all the sites in the U.S., that I know that there could be such a dramatic difference just because of pure technique.

And perhaps I'm also tainted by some of the bad work because, you know, the European sites have totally dramatically different results than the American sites do.

Having said that, I mean, you know, it looks like even without the European sites or outside the U.S. sites, I don't know if they're European, we still show that this was a device that was effective.

So I am a little more leery about pooling the data, but I think even with that point, it stands by itself.

DR. BORER: Dr. Fleming.

DR. FLEMING: I'm in agreement with the rest of the comments. I do think it is a matter of experience. I do detect that there is a patient

selection issue which emphasizes the need to properly select patients for this procedure. So even though the data seems to wash out to some extent, the differences are dramatic, but nonetheless I still think that we can generalize to the general U.S. population here. I don't think that that's an error to do so.

DR. BORER: Mr. Halpin.

MR. HALPIN: As a sponsor who's had to defend and look at clinical trials, you often see results that are not easy to explain. I think the fact that if you look at the U.S. results alone, that the data still meets its requirements, shows that it's going to work in the U.S., and I think the fact that in Europe it's being used and the results are very good I think just adds to that picture. So I think the data looks good.

DR. BORER: Dr. Bilazarian.

DR. BILAZARIAN: I agree with the prior comments. I guess I would just ask the FDA in their further review to see whether there is a linkage as has been suggested, more clearly between the experience of both the center and the operators that can be explained in some other way and that might help define the future use.

DR. BORER: Dr. Kelley.

DR. KELLEY: I pretty much agree with everything. I mean I don't know how poolability is. It's so different, but I think we still have efficacy, and I think the biggest concern is what will happen. If we really think experience is so important, what's going to happen when we generalize it to fairly inexperienced operators and centers?

DR. BORER: Dr. Slotwiner.

DR. SLOTWINER: I mean I don't quite understand why the data is so different, but the U.S. data does stand on its own, whether it's experience or other factors in Europe I don't know outside the U.S., but I feel comfortable with the U.S. data.

DR. BORER: Dr. Weinberger.

DR. WEINBERGER: I don't really have much to add other than to say that clearly the statistics say that this is an effective therapy even excluding OUS 1. I think that our estimation of the magnitude of effectiveness, however, varies dramatically whether or not you include OUS 1, and I think that ultimately when we're asked to judge about safety versus efficacy, we have to take into account our estimation of the magnitude of effectiveness. So at that point, we'll have to worry about it.

DR. BORER: Okay. I agree. I think this is fine when you pool or you don't pool. There were so many analyses done, and they all went the same way.

I would point out with regard to the magnitude of effect, which I think is very important, this was a small trial. There just weren't many numbers there, you know. There were many endpoints; there weren't many patients. The precision with which a point estimate could be made, I think, is relatively modest compared to what we're accustomed to looking at now, 10,000 patient drug trials, so I'm not as troubled by the apparent difference in magnitude of effect between OUS 1 and the U.S. sites as I might have been if there were more precision.

I don't know why the difference, if it's real. I don't know if it's real, but if it's real, I don't know why it exists. It could be experience and that would be my intuition, but then there are the 23 patients who had the RA lesion put in prophylactically. Who knows what that means? And having said that, we've now defined some things that have to be, if we believe this should be approved, and the FDA chooses to do so, we've defined some issues beyond the approvability issues that would

need to be explored in phase 4, in postmarketing.

Okay. Now, we come to --

DR. ZUCKERMAN: Dr. Borer, could I ask you for a little bit more clarification because from the FDA perspective, this is an important issue as the Panel has appreciated it.

I've heard two hypotheses so far regarding the difference between U.S. and OUS. One is it's an experience issue. The other is it remains indeterminate. Is there consensus on the Panel as to which way the Panel is swaying?

DR. BORER: Between those two. Okay. Why don't we just ask? Dr. Bilazarian, do you want come down on one or the other?

DR. BILAZARIAN: (Off mic.)

DR. BORER: Dr. Kelley.

DR. KELLEY: You know, I don't think I know. One hundred percent for afib is pretty amazing, and it's hard to imagine human experience doing that, but I don't think the clinical differences were that significant. So if I had to pick, I'd pick experience.

DR. BORER: David.

DR. SLOTWINER: I don't know. When I came in, I was thinking that it was experience, but as I

look at the centers, the U.S. centers, they have a lot of experience, and certainly the OUS 1 site shows that there's more than just experience that's factored into the difference of the numbers. So I think that it's not just experience. I think that there's some other factor, whether it's style of reporting for patients or I don't know, but I think it's not just experience.

DR. BORER: Judah.

DR. WEINBERGER: I don't think we can tell from what information we have.

DR. NAFTEL: I'm leaning towards experience.

DR. BORER: John.

DR. SOMBERG: Well, I think it's experience because it's not that there was about -- it says from upstairs it's experience, you know, so let's go with the vote. It's not that this center has, you know, great, you know, testimonials and then but has the same number of patients. They have so many more patients and they were doing the study and they have the same pressures on them that, you know, people don't want to get randomized, et cetera, and they came for ablation and all that, but they still were able to put in. So I think they have so many more

patients and have been doing it for a lengthy time, that may be longer, and there maybe -- and, you know, it's not just experience of doing it more. It's also the technique is what I said and how they go about doing it.

I sort of felt when I came in that it may have been due to the other ablative procedure there, but Dr. Wilber convinced me that the atrial tachycardia is not necessarily or the atrial flutter I should say is not the trigger for the recurrent PAF. So that seems to speak against that, you know, that part of the literature doesn't go. So I think the hypothesis I would test would be experience, and that's a good one because as our centers get more and more experience as well with this catheter and technique, then hopefully everyone's 100 percent.

DR. BORER: Dr. Karasik.

DR. KARASIK: That's what we aim for. I think it's experience, exuberance, and it may be patient selection in a center that really has a very high volume normally. I don't think we can say any more than that with the data we have, small numbers.

DR. JEEVANANDAM: I mean I think clearly they're experienced, but I think there are other factors definitely in play here.

DR. FLEMING: Well, I would agree with Dr. Kelley, that it's hard to believe that 100 percent sometimes in anything is 100 percent, nor would I think it's 100 percent experience. I think it's probably a combination of experience, patient selection, and perhaps what's not been mentioned is post-operative management. I think the post-procedural management may have played into this dramatically in terms of recurrent afib.

MR. HALPIN: I would vote on experience just based having more exposure to the catheter combined with what the individual differences and practices and the person may have a lot more.

DR. BORER: For whatever it's worth, I don't know why there was the difference. I think there were several factors that may have been involved. Experience may be one, the lesions, the adherence to the protocol with drugs, you know, who knows. Patient selection. I don't think we can say for sure from this.

DR. ZUCKERMAN: Okay. Dr. Borer, your summary is helpful. The second thing that I'm going to ask you and other Panel members to think about when we do come to the hypothetical labeling question, which is question 5, is that the Agency has

an obligation to detail or write up this trial in the label in a truthful and accurate manner, and actually honing in and describing this particular point will be something that we're going to ask your advice on.

DR. BORER: Okay. Are we finished with this question for now?

DR. ZUCKERMAN: Yes.

DR. BORER: Okay. We'll move onto the next one. This is safety. Dr. Bilazarian, why don't you start with that one?

DR. BILAZARIAN: The seven-day primary adverse event rate in the pivotal study was 10.8 percent with a 95 percent upper confidence bound of 16.1. The adverse events included in the primary adverse event analysis are the following: and they're listed in the table. This study reported no occurrences of death, stroke, atrioesophageal fistula, myocardial infarction or thromboemboli within seven days of the ablation procedure. These serious adverse events have been reported in the literature for AF ablation procedures. The prespecified target upper confidence bound was 16.0 percent.

Please discuss whether the safety results demonstrate that there is a reasonable assurance that

the device is safe for the treatment of drug-refractory recurrent symptomatic paroxysmal atrial fibrillation.

DR. BORER: So what do you think?

DR. BILAZARIAN: I think that the summary statement of it exceeding its prespecified confidence bound is mitigated for me by the fact that this composite includes softer adverse events, like hospitalization and vascular complications, and there is very little in the more concerning permanent, disabling issues like death, stroke, fistula, myocardial infarction. So for me, although they missed that safety endpoint as a composite, I was reassured that the things that did occur were reversible or self-resolving. And again to harp on a repeated comment here, perhaps may be affected by a learning curve.

DR. BORER: Can I just add something here? Do you believe that these data suggest that there's not going to be any death, strokes, atrioesophageal fistulas, myocardial infarctions or thromboemboli within seven days of the procedure?

DR. BILAZARIAN: Yes, in OUS 1.

DR. BORER: Even there I might, if I were a betting person, bet against you. Okay. Dr. Kelley.

DR. KELLEY: Well, I mean I think the data support that it's safe. It's a small trial, and as you mentioned, there will be strokes. There will be deaths. The only other comment I have is about the drug-refractory because I'm still a little unclear if someone goes on a beta blocker for a little while and aggravated and tolerated or they went a little too fast, they could be in the trial. And I'm not certain that that's the spirit of what we usually consider drug-refractory atrial fibrillation.

DR. BORER: I think we're going to come to that next.

DR. ZUCKERMAN: Okay. Dr. Kelley, if I could ask you to expand a little bit further. I'm sorry for interrupting you, Dr. Borer. If we were to rewrite this question right now, we would ask about the concept of global device safety, which I think Dr. Bilazarian just mentioned as well as safety for each of the individual five devices. When you speak about safety, are you just speaking about the catheter that was used in the trial or all five devices that the sponsor potentially wants approved?

DR. KELLEY: Well, I'm speaking about the catheter used in the trial with a navigation system.

DR. ZUCKERMAN: Okay. And what would you

say about the four other devices?

DR. KELLEY: I don't think we have that information. I could guess that the bidirectional catheter would probably be equally safe, but I would -- I don't think I could guess that it would be without navigation. I don't think we have that information.

DR. BORER: David.

MR. SLOTWINER: Yeah, I agree fully with Dr. Kelley. I think the catheter tested looks safe with the navigation system as tested.

DR. BORER: Judah.

DR. WEINBERGER: I agree with what's been said.

DR. BORER: Dr. Naftel.

DR. NAFTEL: It's really nice to see that everybody's not hung up on that 16.1 percent, and so I appreciate that. And if you just had one less event, it would meet the requirement just fine, and the point that's made in the question, no occurrence of death, stroke, et cetera. So I vote that it's doing just fine.

DR. BORER: Dr. Somberg.

DR. SOMBERG: Well, I think everyone likes me because my dissenting voice is here. I don't

think we have safety information on a study this small, and I think anyone who says this device is safe on this small a number is, you know, we don't have the ability to do that.

Now, with that said, I think the way, and I was thinking about this earlier, the way the data should have been presented was these catheters have been use extensively, not in the atrial fibrillation ablation but, you know, the incidence of myocardial infarction, the incidence of AD fistulas, the incidence of a whole series of things. It's a generic problem. So the experience should have been and any company in this field should try to have a registry where they get very large experience for all these, I will use the word, generic adversities.

So I think what I would say is we're going to be able to make a judgment on risk-benefit for this particular indication for essentially one catheter, but I think it is generalizable for the FDA if they take into account the totality of the evidence they have, further information, and for the other uses from VT ablation to atrial flutter, et cetera, and I think that could be put in the label. So where we might say we saw no MI, no embolization, et cetera, et cetera, in this particular 150

something patient study, in compiling all the experience with these catheters, we see an incidence of this, this, this and this, and that's what, if I was a clinician talking with a patient, I would talk about because those are the overall incidences of the problem. You're smiling, Dr. Zuckerman.

DR. ZUCKERMAN: No.

DR. BORER: Can I just ask you, Dr. Somberg, in fact, although they didn't talk about it here, in the Panel pack, the sponsor did present the data on the other catheters from the studies that were pivotal for approval in the proposed label, and would you feel better if I told you that the numbers in those trials with approximately similar numbers of patients being studied were similar to what we saw here?

DR. SOMBERG: No, because I saw that. What I'm interested in is at the post-approval experience which is in the tens of thousands while the -- experience is maybe less than 500 or, you know, something in that nature. So I think -- I'm interested in post-approval surveillance data to be incorporated because, correct me if I'm wrong, some of these catheters have been out there since 2000, and there's also OUS experience which can be

commented on as well.

DR. BORER: Let me just ask so that maybe we can get some context here. From the numbers we have, from the numbers that are presented in this book and even in this trial, we can calculate what the upper bound of the 95 percent confidence interval is for adversity. It's going to be a lot higher than the point estimate, but we could calculate it. I couldn't. You could calculate it, you know, Dr. Thompson could calculate it. Did the FDA assess this? I mean you've got a whole set of data here. You have a point estimate for adversity, you have an upper bound of the confidence interval. In fact, you gave it to us, 16.1 percent for all the events, is the upper bound of the 95 percent confidence interval, I think that constitutes data. If you want to look at the terrible events, the tragedies which were far fewer, you can calculate the upper bound of the 95 percent confidence interval there, but, you know, am I incorrect here? I mean we do have a context within which we can judge the worst-case scenario, I think. Is that correct? Give us some wisdom.

DR. ELOFF: In the context of today's Panel meeting, FDA is asking the distinguished members of

the Panel for your recommendations as to whether or not the data presented in this package and that you've seen today, presented both by FDA and the sponsor, provides a reasonable assurance of safety and effectiveness for this device when used to treat symptomatic paroxysmal atrial fibrillation.

As much as I think Dr. Somberg has a very good point on the lack of events, like the serious events being observed in this group, I think that may speak to the potential true incidence of these events being seen in practice. We have no way of understanding that, of knowing that, based on the data in the trial presented. We have to work within the confines of the trial that was performed to come up with this information.

I will bring up a point that Ellen Pinnow made with regards to the postmarket evaluation when we get to that point. Postmarket data cannot and should not be used to answer the primary question of whether or not the data presented in the premarket phase constitutes valid scientific evidence showing a reasonable assurance of safety and effectiveness for this device.

DR. BORER: Yeah, I appreciate that, and we all do. My only point was and, you know, I'm not a

statistician, but I think I'm right here, that when you have data, you can define a point estimate, and you can define confidence intervals around it which provide a worst-case scenario, the upper bound of the confidence interval. And so we can make -- you want us to make a judgment and we will. I promise you we will, and I think we can, even if we can't accept that there were -- even if we know there weren't many events and the precision of the point estimate may not be what we wish it were, we can say what the worst-case scenario is, and we can therefore make a judgment of benefit versus of apparent benefit within the limits of precision that we have with that parameter, versus risk. I think we can do it. It's not that we have no data. We do have data and we can make a determination of worst-case risk or something like risk-based, I think. So I would suggest that maybe it's not right to say we have no data. We do have data.

But having said that, out of turn, let me go onto Dr. Karasik.

DR. KARASIK: I think that the safety results from this trial are in keeping and in line with the data that we have from many other trials of ablative therapy. But we touched on this one thing

only briefly, which is that what makes this catheter unique is that it's an open irrigation catheter, and so the patients receive a fair amount of volume during the procedures when they are lengthy, as atrial fibrillation ablations typically are with a mean time in this study of 211 minutes, I think. And so patients received upwards the average of 2, 2.2 liters of saline during the procedure.

Now, these patients all had normal ejection fractions. There was one patient who had an EF of less than 40 by echo but -- suggested the EF was over 50. But this was a very specific set of patients with normal ejection fractions. And I think we have to be very careful in thinking about a more general or a larger population of patients who might then be offered a procedure where they could get 2.5 liters of normal saline in 2 or 3 hours.

And, you know, the catheter has been used and approved for the use in ventricular tachycardia, but there I think the risk-benefit analysis would be different because you're dealing with a life threatening illness, and here we're treating symptomatic PAF, which although miserable is not usually life threatening.

And so I would just want us to consider

that as we go forward, and if we were considering any labelings or indications for use, that this is in a patient population with an EF greater than 60 percent which is different.

DR. JEEVANANDAM: I agree. I have nothing. I agree with what everybody's said. I think Dr. Karasik's points are very important, that this is a particular patient population, and the 16.1 versus 16 doesn't bother me. If you look at the actual complications, a lot of them are just prolonged hospitalization, which is not a big issue.

DR. FLEMING: I'm very satisfied about the device, and I would extend it actually to the other four catheters because they've been in use a long period of time as well. Again, I'm not an expert in that area, but it seems to me that the data does support safety beyond -- it's reasonable. That's the word we need to use, I think.

DR. BORER: Mr. Halpin.

MR. HALPIN: Yes, as an approved catheter that's being studied for a new indication, PAF, the data looks good. I didn't see anything and I didn't hear anything that would lead me to be concerned that there's something particular to applying this already approved device to PAF as an indication of treatment

of ablation.

DR. BORER: Okay. I don't see any major safety issue that would preclude me from judging that this device is acceptably safe for the intended use, but you asked about all five catheters, and there I have to demur a little bit.

I'm impressed with what David said earlier about the possibility that the bidirectional catheter may be just a little bit stiffer and what Dr. Karasik said about the risk-benefit relationship in this particular population. This catheter has to go across the intra-atrial septum with the potential to wreak havoc, and if it were a little bit stiffer, it could do that. Having done a lot of catheterizations, I'm quite familiar with that possibility. So I would be a little concerned about that, and I would be very concerned about extrapolating from a system that was used in a certain way with mapping in a study, 100 percent used that way, extrapolating from that to the risk-benefit relationship of using something that doesn't have mapping associated with it. I'm not suggesting that the other catheters are necessarily less safe. Maybe they're more safe. I don't know.

But, you know, in line with Dr. Somberg's

point, these numbers are small. I can't compare one to another. I can't compare a study done several years ago for one indication with a study done today for this indication with a different catheter. I don't think there's any way to do that. So I would feel very comfortable with the acceptability of the safety of this device for this indication. I don't think I can go any further than that.

Have you heard enough from everybody about this?

DR. ZUCKERMAN: Yes, that's very helpful. To give you a ballpark estimate of what the safety is right now in terms of what we know, because I think this may be critical for figure out how a post-approval study might be able to make things more precise or give us a better picture, I think there are 139 patients in this study. So for events where there are 0 adverse events, like stroke, Dave, can you help us here? If you use the rule of 3, would that be a good approximation; 3 over 139 is about 2.2 percent. So we're still in that wide region that Dr. Somberg is telling us about. David.

DR. NAFTEL: I agree totally.

DR. ZUCKERMAN: Okay.

DR. NAFTEL: Yes.

DR. BORER: That's the worst-case scenario issue that I was trying, not very well, to raise earlier. I think you've just done it for us and, you know, we know what we know and we don't know any more, and we'll learn more with more data, but I think what we've told you is that we feel comfortable that we have enough information now to make a risk-benefit relationship assessment for this device today, and then the FDA will do what it will do.

The next issue is effectiveness. Why don't we start with Dr. Kelley. You want to take that one.

DR. KELLEY: Effectiveness Results - General. The results of the study demonstrate freedom from symptomatic AF in the 9-month evaluation period in 53 out of 103 patients enrolled in the ablation arm, not including 14 censored patients compared with 9 out of 56 in the medical control arm.

Using available data only, the posterior probability of increased effectiveness, i.e. superiority, of ablation over control for freedom from symptomatic AF at 9 months was greater than .999, which exceeded the prespecified criterion of .98. In addition, the predictive probability of concluding superiority of ablation over control, had the full 230 subjects been enrolled and have

outcomes, is greater than .999.

Please discuss whether the chronic effectiveness results demonstrate that there is a reasonable assurance that the device is effective for the treatment of drug-refractory recurrent symptomatic paroxysmal atrial fibrillation.

So I would agree that it is effective with a few caveats. Again, the patient population is somewhat not representative of a larger population with atrial fibrillation. The mean atrial size here was 4, which is certainly not what I see in most afib patient. There are very few with structural heart disease. In addition, they all used CARTO, which I think is important, and I would echo my earlier comment about the drug-refractory characterization.

DR. BORER: Dr. Bilazarian.

DR. BILAZARIAN: I certainly agree that it seems effective, but it's of marginal clinical significance, thinking as a clinician, the 47 versus 18 percent difference that we see when we exclude OUS 1 is relatively disappointing as a clinician, to refer a patient for a procedure with this catheter in this setting and be able to quote a likelihood of being AF free even at 90 days, since the curve seems to be flat up to 90 days of less than 1 and 2. It's

disappointing from a clinically effective standpoint.

So I think I'm being asked whether it's effective based on statistical criteria, and I would say that I can't refute that it is, but from a clinician's viewpoint, to refer someone to very experienced operators at very experienced sites, with mapping, state of the art sort of approach, and end up with a likelihood of being AF free at 90 days of less than 50 percent is a disappointing result.

DR. ZUCKERMAN: If I could just ask subsequent Panel members when they're talking about this important question, as with the prior one, to make clear for the record whether you're talking about all five catheters or the catheters individually.

DR. BILAZARIAN: Thank you. So I haven't commented on the five catheter question, and I would say that from my understanding of what has been explained here, that the two catheters, that they would be relatively equivalent but I certainly agree with others' comments that I would not include the guidance catheters in that since they have not been investigated at all and may be as suggested, more or less safe. We certainly have no data on that. So I would feel comfortable extrapolating -- certainly

comfortable with my comments for this one catheter that's presented, and I would be comfortable extrapolating it to the bidirectional catheter. So that's two catheters, but I would not be willing to extrapolate it beyond that.

DR. BORER: David.

DR. SLOTWINER: I think the catheter studied in the patient population study, with the mapping system study, is clearly effective.

DR. BORER: Judah.

DR. WEINBERGER: I think that statistical effectiveness has been demonstrated. I think clinical utility is a different question. I don't know if we're being asked to comment on that. Within the other question that was raised about generalizability to non-study catheters, again I would say that we don't have enough information to generalize.

DR. ZUCKERMAN: Okay. Dr. Weinberger, you're always asked to put on your clinician's hat. So can you be a little bit more specific?

DR. WEINBERGER: Okay. I think there is a subset of patients who will drive me crazy enough that I'm willing to send them for a catheter ablation procedure which has a 50/50 chance of working after 8

hours in the EP lab. There is a subset of such patients. They don't constitute the run of the mill patients with atrial fibrillation. So there exists a set of patients, I'm not an electrophysiologist, for whom I would be willing to send them for a procedure based upon this study with this catheter. I think it's a relatively small fraction of patients who have atrial fibrillation.

That being said, I think that in the absence of anything else that works for those patients, we need an option. So there is an option that will treat half those patients after they've been exposed to it.

So I think that, you know, like you've got to try to consider the role of the therapy. This therapy has a role for patients who have not just met the criteria here of the study, but I don't think if I had a 38-year-old patient who, you know, who hadn't had a very extensive drug trial, I'd be willing to send him for this procedure, notwithstanding the fact that there's a 50/50 chance that this will cure him for 9 months and keep him away from me.

DR. BORER: That's pretty clear.

DR. WEINBERGER: I don't know if I've been sufficiently clear. I think that the clinical use of

this will be in the truly drug-refractory patients.

DR. BORER: Dr. Naftel.

DR. NAFTEL: So I think this will be the last time to comment at least from me on the statistical part of this unless I'm asked a question. But I am extremely encouraged with the effectiveness. It was enlightening to me to see that the Bayesian analysis and the frequentist analyses essentially came up with identical answers for the effectiveness, and I think it might have been lost on some of us for a moment that, Dr. Berry, when you said that you would have designed this trial exactly the same way, sample size and analysis, if they had come to you originally, I found that very comforting and very believable.

So what I'm trying to say is I think the whole analysis is good and points totally towards effectiveness, and I'm the guy that goes for the statistical effectiveness, and I certainly bow to others on the clinical utility and if the difference is big enough to make you send that patient for the procedure.

As far as the catheters, I just have to totally bow out of that and listen to the other experts on the Panel.

DR. BORER: Dr. Somberg.

DR. SOMBERG: Well, given the stipulation of some of the flaws in the study design, I still think that the study did show that this ablative procedure for PAF is effective.

I also believe that the point of where you make the ablation, or burns, is what's critical and how you might go about doing that might differ is certainly, you know, a valid point, and I also want to underscore for the other Panelists, Dr. Wilber's statement that he doesn't even use a navigation system anymore because they use 3-D echo. So it's a problem with the devices in general. It's not like a drug. There's so many competing and evolving other aspects. So I tie this all into the technique, and I don't think the technique is, but some part of the enthusiasm, but it has a lot to with procedural aspects, and therefore I think all the catheters, unless they make the ablation lesions differently, may be interchangeable if you can make that array of ablation lesions, and some people will need a robot. I would probably need a robot that would tell me exactly what to do. I press the button, it goes, the procedure's finished, and the robot tells me it's good and it's good by frequency or the Bayesian

approach. But otherwise, some people might just use a ring catheter and look at things as well.

So I think we can get on, you know, where it's slippery slope and, you know, we need to have everything put in a study might be excessive here.

DR. BORER: Dr. Karasik.

DR. KARASIK: I think as an electrophysiologist, we're always looking for tools, new tools that will help us manage our patients and hopefully make them feel better if not live better, not necessarily live longer. And although I agree with the statement that 47 percent success rate doesn't seem very robust when compared to the sorts of drugs we normally use, it is a significant improvement, and there are clearly patients who would take up that option, you know, they say if you give me better than a 50/50 or a 50/50 chance, I'll take it.

So I think that this study, given all it's flaws and reservations that you heard me express, I think at least this catheter, and only this catheter, appears to be effective for what its use is intended, although I would like to see a bidirectional catheter approved just because it would be a useful tool to have in the lab.

DR. BORER: Dr. Jeevanandam.

DR. JEEVANANDAM: I guess there's two questions. One question is the number of devices versus this device, and I think this device in this trial is shown to be effective, but I wouldn't automatically predict that for all the other devices that the sponsor wants to get approved.

In terms of efficacy, I also concur with everybody else, but it's very interesting. Everybody's talking about 47 percent. So people are starting to discount the OUS 1, and even at 47 percent, statistically it's effective, which is okay with me but, you know, it's going to be how, and I don't know if that comes to labeling or marketing, but it's going to be interesting, how this thing is projected out there in the market. Are people going to say, well, this is 75 percent effective or are they going to say it's 47 percent effective and take out the OUS 1 data?

DR. BORER: Dr. Fleming.

DR. FLEMING: I believe that the study indicates to my satisfaction that it's an effective device for which it's intended to used.

MR. HALPIN: I think the study met its predefined endpoint and showed that it was

statistically effective. I think it also scored on qualify of life endpoints and other secondary endpoints. So I think it was shown that it was effective.

With regard to five catheters versus one catheter, I think having enrolled 5500 patients and screened them to get 160 patients is a pretty high burden. So I think if there's any way that you can extend this data to the other catheters by logic versus having to reproduce the study over and over again, I think that would be a prudent thing to do, if it makes sense from a safety point of view.

DR. BILAZARIAN: So the only thing I'd like to just mention is a question that hasn't been raised is that blends the three concepts, the experience issue, the safety issue, and the efficacy issue. If this device is approved and rolled out, will the frequency or the number of second ablations be increased? And will a greater number of second ablations raise risk as we would expect more ablations would require, would result in greater risks without a significant increase in effectiveness. So might that safety/efficacy balance change again as it's rolled out because of the greater need for additional second ablations?

DR. BORER: It sounds like a question to put into that phase 4 study or post-approval study if it's approved.

Okay. I think in general everybody has agreed that this is an effective therapy. Personally, I'm not as concerned about the absolute magnitude of the effect from this study. First of all, I'm not sure what it really is. I mean I know what the point estimate is in the United States and outside the United States, and there are factors why those seem to be different, but my guess is that over time, they're going to come closer together and go up probably. That's my guess, my intuition.

My concerns just to put them on the table about my understanding of the true effectiveness are primarily based on the design flaws, the symptomatic endpoint, the whole list that Dr. Thompson gave. Those make it hard for me to be, you know, as certain as I might want to be about the absolute outcome, but as sort of a general statement, it looks to me as if this therapy is three times as effective as giving drugs, and I would echo exactly what Judah said. Most patients don't have -- when they have paroxysmal atrial fibrillation, it's not sufficiently symptomatic so that they absolutely require to be

sent to an EP lab for a pulmonary vein isolation procedure. On the other hand, there is that segment of patients who are, for whatever reason, psychological debility, physical debility, whatever it is, there is that segment of patients who really can't tolerate recurrent AF and who are refractory to drug therapy, you know, have adverse severe, et cetera, and I think it's important to have this modality available for them, and I think it's three times as likely to be successful as whatever they were on, and so I think that's pretty good, and we'll see what the absolute effectiveness is as more data come in, but I don't think that's the dispositive issue in defining approvability.

Have we given you enough information on that one, Dr. Zuckerman?

DR. ZUCKERMAN: Yes.

DR. BORER: Thank you. Then we will go onto the next question which has to do with the device labeling. Dr. Karasik, why don't you, if you would please, start out on that one.

DR. KARASIK: One aspect of the premarket evaluation of a new product is the review of its labeling. The labeling must indicate which patients are appropriate for treatment, identify the product's

potential adverse events, and explain how the product should be used to maximize benefits and minimize adverse effects. Please discuss whether the proposed indications identify the appropriate patient population for treatment with the device.

Well, I think this gets to the question Dr. Kelley raised which is drug refractoriness --

DR. ZUCKERMAN: Excuse me, Dr. Karasik. Before we hear your comments, could I ask everyone to open up their Panel pack to Tab 6, where the labeling is, and that particular question refers to the current indications which is on page 3 of that label. And it's Section 2.

DR. KARASIK: So drug refractory, symptomatic paroxysmal atrial fibrillation.

DR. ZUCKERMAN: Yes.

DR. KARASIK: So what is drug refractory? And I guess I have the same concerns that have been voiced before, which is that if you look at the HRS guidelines and the ACC guidelines, drug refractory implies that you've failed a class I or class III antiarrhythmic agent, and I think that should be specified. I don't think class II and class IV belong in that mix. I also think there should be something about patients with heart failure, you

know, perhaps not class III -- let's say not class IV heart failure patients, but I have concerns about that population receiving the catheter for AF.

DR. BORER: Dr. Jeevanandam.

DR. JEEVANANDAM: Where are you looking at because the one that I have over here looks at VT.

DR. ZUCKERMAN: Open Tab 6, page 3 of the label. You're right. And do you see Section 2 is the indications and usage.

DR. JEEVANANDAM: Okay.

DR. ZUCKERMAN: Okay. So Part A refers to just the IFU statement. To give some clarity, certainly the comments that Dr. Karasik just made are extremely useful in terms of what warnings and precautions this Panel might recommend for heart failure patients and patients on certain class II and IV agents, but there's a fundamental question as to whether that last statement drug-refractory symptomatic paroxysmal atrial fibrillation is specific enough to indicate what this device is doing.

DR. JEEVANANDAM: Well, it seems pretty general to me, and I would concur with her question about what exactly -- I mean do you have to define what is drug-refractory afib?

DR. ZUCKERMAN: No, that would be described in the clinical indication section, but you can add more specificity. For example, you can recommend that drug-refractory paroxysmal afib for treatment of all AF episodes, symptomatic episodes, asymptomatic episodes, for cure of the disease, et cetera. I mean you can describe what the device is doing.

DR. JEEVANANDAM: Well, I think this study was on symptomatic paroxysmal atrial fibrillation in patients with normal ejection fractions. So I would probably say it's not indicated for somebody in heart failure with an EF of less than 35 percent, or hasn't been tested.

DR. BORER: Dr. Fleming.

DR. FLEMING: Is it possible to drug-refractory and intolerant to the medications because obviously -- does that include that?

DR. BORER: Yeah, I think what's -- the way the term has been used here, refractoriness includes the concept of intolerance.

DR. FLEMING: Okay. So I think this is a good reflection of what the study was designed to demonstrate. So --

DR. BORER: Mr. Halpin.

MR. HALPIN: I think that the indications

for use indicates the study and in general what was tested on the product. I think that one other thing I would mention is that if there are particulars, it doesn't necessarily have to be a change in the indication for use. You could use the precaution section if you felt very strongly about something.

DR. BORER: John Somberg.

DR. SOMBERG: I think it's appropriately written. Remember, for those who don't like class II and class IV, I tend to agree with them, but that was in the protocol. That's the way it was happening. So if you want to stick to the protocol and not count the other catheters, then you have to stick with the protocol. But I'm being complex here. I think this is reasonable. Many people define drug-refractory differently. Someone sends a patient to me. They know they're going to go through five, six drugs. Someone sends a patient to someone else. I think Dr. Wilber, they go through one or two, no offense but, you know, it's just a different approach, and --

DR. BORER: These people from Chicago, they just can't --

DR. SOMBERG: It's thin crust pizza versus deep dish, you know, things like that. But I think it's a reasonable thing, and I think that would work

in the community, and it's really what the protocol was addressing in their inclusion/exclusion criteria.

DR. NAFTEL: I agree. For me it's because it's the protocol. The protocol was written and it looks good to me.

DR. WEINBERGER: In the context of this IFU where you're putting it right next to cure of type 1 atrial flutter, I would prefer if this were, to somehow underline if this was a symptomatic treatment and not a curative treatment. So the indications might say something like for treatment of symptomatic patients who have drug-refractory symptomatic atrial fibrillation. So the instructions should underline that the treatment is really just a symptomatic treatment rather than an attempt to cure.

DR. BORER: David.

DR. SLOTWINER: I think it's fine the way it is, reasonably vague. I'd just leave it like that.

DR. BORER: Dr. Kelley.

DR. KELLEY: So, you know, I still have an issue with the drug-refractory thing but it may not be practical. I think there should be at least mention of the risk of heart failure patients, of the potential risk, and then can I ask a question about

the labeling that is under warnings and precautions or are we going to do that later?

DR. BORER: No, go ahead.

DR. KELLEY: Okay. Well, under warnings and precautions, it says the patient who's had a prior atrial flutter ablation procedure may be at greater risk for perforation and/or pericardial effusion with the use of this system, and I'm just unclear on where that came from since a lot of these patients had flutter ablations during the procedure.

DR. BORER: Do we have data from anywhere that anyone wants to provide for us?

DR. YAROSS: We'll have to check and confirm, but my immediate recollection is that that would have come from one of the prior indications for use, and it was not specific from this trial. We'll double-check that.

DR. SOMBERG: I don't think they're saying that if you had in the same sitting, but those people have had distant procedures, a repeat procedure, and I remember at an EP conference hearing that. I don't know what the data support is; maybe others can address that.

DR. KELLEY: Well, even so, I'm just puzzled as to where that came from.

DR. SOMBERG: Well, I've heard that, too, said that if you've had a prior ablation, there's a higher risk if you go in a year or two later and do another ablation but --

DR. YAROSS: Now, in our prior, in our atrial flutter study, there had been some incidence of tamponade, and those had been more likely in patients with prior failed atrial flutter procedures. So that's basically a holdover from that --

DR. KELLEY: But you were re-ablating in the same place presumably, and this would be --

DR. YAROSS: That's correct.

DR. KELLEY: -- a different place presumably.

DR. YAROSS: Yes.

DR. KELLEY: Okay.

DR. YAROSS: Our goal has been to have on integrated instructions for use document but we, of course, can break things out based on what the Panel and FDA recommends.

DR. JEEVANANDAM: I can give you -- from a surgical point of view, you know, we can do these -- we can do epicardial ablations, and if you do an epicardial ablation on somebody who has already had an endocardial ablation, that tissue is certainly

scarred and, you know, there's going to be some transmittal injury. So you can have scar tissue and the tissue is quite tough. So doing a surgical ablation on somebody who has already had a catheter-based ablation is actually much more difficult, and you can get into problems with the tissue characteristics right at the area of the ablation site can tear. So I think if you're going for repeat catheter-based ablation and somebody's already been ablated, that tissue is just not going to be normal. So that's probably they had a higher incidence of perforation.

DR. BORER: Dr. Bilazarian.

DR. BILAZARIAN: I would disagree with the suggestion that it be a vague indication and that it be a stricter indication listing, and the reason for that, from my clinical viewpoint, is that a frequent reason why patients in this age group that meet these clinical entry criteria seek ablation is the desire to not be on anticoagulation, and obviously patients have to be told that that's not an appropriate reason to have ablation, but having clarity around this, for patients seeking information about it, would be beneficial. So I agree that Dr. Weinberger's idea of having it say that this is for the symptom treatment

of drug-refractory atrial fibrillation, and I don't think it would be complex to add that the definition is as was defined by the study population, at least three episodes of atrial fibrillation in the last six months.

DR. BORER: Okay. So there seems to be general agreement that it really should be for people who have symptoms.

My own opinion is like Dr. Bilazarian's, that it should be a little more specific, but I think in a slight different way, and this just may represent my bias. I don't think it's good enough to say symptomatic atrial fibrillation. You know, people are going to use this the way they're going to use it, and people are going to define the words that I'm going to use in different ways, and that's okay. Judgment's appropriate. But I think that the issue here is that the people for whom this procedure at this moment in time with the data we have should be used are people who have unacceptably debilitating symptoms despite efforts with drug therapy.

So I would be very specific with that language. I don't think it's for symptomatic atrial fibrillation. You know, anyone who has a paroxysmal and feels palpitations is symptomatic. I don't know

that that's a reasonable basis for doing a catheter-based ablation with some degree of very real risk of major events, not high, but real, measurable, definable.

And secondly, I understand that the protocol, I agree, was written the way it was written, and it's probably not right to try to segregate sections of therapy, but the result, the number of patients who received rate control therapy alone was small, and the results were so disappointing that I would specify that this is really intended for people who have failed antiarrhythmic drug therapy that does not include just rate control therapy alone. So I would put those two concepts into the indications section.

In terms of the heart failure and left ventricular dysfunction, you know, we have no data. I think you just have to say that in the label. We have no information. We don't know what it will do in these patients and leave it at that.

Is that sufficient for this --

DR. ZUCKERMAN: Okay. This has been a very helpful discussion, but the points that Dr. Borer just brought out are critical to discuss a bit further. Dr. Borer suggested a more specific

indication statement. Can I hear from any other Panel members as to whether there's general agreement, disagreement?

DR. BORER: Let's don't all talk at once. David, why don't you say something.

DR. SLOTWINER: I don't know how detailed you want to go on that line, but I think we have indications that in patients with preserved left ventricular function, not significant valvular disease, paroxysmal symptomatic atrial fibrillation, refractory to antiarrhythmic drug therapy, I think there are some who will not tolerate. I wouldn't get too specific on that, but this patient population, I think we have data that shows it's safe and effective. I don't know if you want to go about specifically eliminating every other group, heart failure, valvular disease, you know. We don't have that information. I would say these lone paroxysmal symptomatic atrial fibrillation patients.

DR. BORER: I think the issue though that Dr. Zuckerman may be asking about is the adjectives I put in front of symptomatic.

DR. ZUCKERMAN: That's correct.

DR. BORER: Unacceptably debilitating symptoms.

DR. SLOTWINER: I missed that. Sorry. I would leave it vague because in day-to-day patient care, these AF patients, symptoms can vary tremendously from patient to patient, and their perception of what's acceptable can vary tremendously, and I think to try to be too specific here is probably not going to help.

DR. BORER: Just to clarify, before anybody else chimes in, I agree absolutely with you, but I'd like it for the patient to say, hey, I just don't want to live with this. I don't care what the level of debility is in some absolute sense. I think though that the patient has to say I'm not willing to accept this. I'll take that risk to get rid of this thing, whatever it is. That was the kind of thing that Judah was talking about before rather than telling people, gee, you have symptoms. Therefore, I'm going to give you this procedure. I'm going to make your symptoms go away when they didn't ask for it.

DR. SLOTWINER: I think that's incumbent on the physician to discuss with the patient, and I certainly insist on them saying that, but whether you can put that in the labeling, I don't know.

DR. BORER: Okay. Judah.

DR. WEINBERGER: I think that what you're doing is you're taking the art of medicine and you're legislating it here.

DR. BORER: John.

DR. SOMBERG: I'm the first one to say that the study was too small in size to get a good handle on adversity, but I saw no signal that warrants your concern for raising the level to this highly symptomatic population. So I think drug-refractory which to me means a couple of antiarrhythmics and a good considerable trial, others it would mean less, but that's as Judah says, the practice of medicine. So I think that's fair.

What I disagree with is the aspect of heart failure. I think it should be said up front that there's no data here because there is a potential problem. I mean it's very clear. It's giving 2 liters plus of saline, and that's, you know, you take people with class III, class IV heart failure and you put them in the hospital, and you give 100 people 2 liters of saline, and you're doing to have, you know, a good demonstration of codes and pulmonary edema all over the hospital. So I think this is an important thing, but I wouldn't want to, you know, once again legislate. There are people who, you know,

appropriate diuresis, appropriate catheter management, who are having intractable PAF that is bothersome, it would improve their quality of life. So I think one has to be warned, but, you know, it's up to the patient and the physician to make the decision.

DR. BORER: Okay. I think you've heard a reasonable spectrum.

DR. ZUCKERMAN: Yes. I think I've been outvoted here. Why don't we go to B and, Judah, why don't you take that one if you would.

DR. WEINBERGER: AF often occurs in patients with heart failure. At the September 2007 advisory committee meeting on the general topic of trial design issues for the study of devices intended to treat AF, Panel recommended that patients with structural heart disease be studied as a separate group. The clinical study specifically excluded patients with advanced heart failure, left ventricular ejection fraction of less than 40 percent, and New York Heart Association class III or IV.

Please comment on whether the labeling should include a warning that the safety and effectiveness has not been demonstrated in patients

with heart failure.

I think that we have discussed this, and I would volunteer that we have unanimity about such a statement being appropriate.

DR. BORER: Does anybody disagree with that?

(No response.)

DR. BORER: Okay. Can we, without going around the table, is that enough information on that one?

DR. ZUCKERMAN: Yes.

DR. BORER: Thank you. Okay. We have C. Mr. Halpin, why don't you grab that one.

MR. HALPIN: Okay. Number C, in the clinical study and protocol, the CARTO EP Navigation System was required to map the anatomical location of the pulmonary vein and the RF lesions. The PMA application requests approval for several catheters that do not include a location sensor capable of generating electroanatomic maps with the CARTO EP Navigation System.

Please comment on whether the data collected in the clinical study can be generalized to devices that are not capable of generating electroanatomic maps. If not, please discuss whether