

1 has to be commended for trying to be as
2 rigorous as they could, but then you have to
3 put it in perspective and that's -- I think
4 that's what this discussion is about.

5 CHAIRMAN MAISEL: Mike, did you
6 have a follow-up?

7 DR. DOMANSKI: Yes, that really,
8 Al, that actually answers the question exactly
9 as I would ask it to be answered. The OPC is
10 the wrong metric. I have one question because
11 it keeps coming up. Why did the company agree
12 to something that is the wrong metric? Maybe
13 it's just a tactical question but I'm kind of
14 curious what the thinking was because, you
15 know, that's what we're trying to get rid of
16 here, I guess.

17 DR. SOMBERG: Maybe they didn't
18 know it was the wrong metric.

19 DR. DOMANSKI: Well, yes,
20 apparently but I'd like to fully understand
21 the --

22 DR. BAROLD: I'm going to answer

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1 this simply by saying that we worked very
2 closely with the FDA to come up with an
3 appropriate study. I think there were many
4 discussions about many aspects of the trial,
5 many end points and I think it was a -- there
6 were many issues that were brought up and this
7 was the study design that was decided upon.

8 DR. DOMANSKI: So it was interacted
9 with the FDA and that's really the bottom
10 line.

11 DR. BAROLD: It was highly
12 interactive with --

13 DR. DOMANSKI: Okay, got it.

14 DR. CALKINS: I think one other
15 point that is relevant -- and it's our
16 evolving understanding of the interplay
17 between atrial fibrillation and atrial
18 flutter. And I'm just talking from my
19 perspective as a clinical electrophysiologist.

20 Five years ago I was of the mind set that
21 they were completely different arrhythmia,
22 atrial flutter and A-Fib is a different issue.

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1 Now, as Al points out, the more research
2 that's done, you go to -- everyone now sort of
3 realizes, well, of course, there's this
4 interplay between some A-Fib and a-flutter but
5 that wasn't recognized when they were
6 designing this study.

7 And in the study we did, we had a
8 30 percent rate of A-Fib and if you look at
9 those early studies, A-Fib is almost never
10 mentioned in the OPC studies. This is
11 something that's really been recognized very,
12 very recently and that, I think explains why
13 the study was designed the way it was. It was
14 felt to be much more black and white and not
15 this interplay, otherwise they would have
16 relied on you know, 12-lead EKGs or some other
17 more robust classification scheme.

18 CHAIRMAN MAISEL: Clyde?

19 DR. YANCY: This is just an open
20 question for all of the electrophysiologists
21 in the room. We obviously, are using dated
22 information for objective performance

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1 criteria. Are there not registry data that
2 capture the RF experience and report out the
3 early complication rates and then the long-
4 term effectiveness? That's the case with many
5 other interventions in the intervention world
6 and the heart failure world, other device
7 areas.

8 DR. SCHEINMMAN: We published the
9 results of a voluntary registry in the US and
10 then the same was done by Hedren Hendrix from
11 Europe. In terms of the efficacy at that
12 point, and again, we're talking about the
13 '90s, the efficacy was about 80 percent and
14 the acute adverse effect rate was about five
15 percent. So I think it was pretty much in the
16 ball game.

17 CHAIRMAN MAISEL: I mean, I think
18 we all acknowledge that those registries are
19 not going to have, you know, EKG telemetry
20 follow-up monitoring that these --

21 DR. SCHEINMMAN: Absolutely. This
22 is a voluntary registry, right.

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1 CHAIRMAN MAISEL: Yes. Please,
2 John.

3 DR. SOMBERG: Can you try to update
4 that to the 21st Century?

5 DR. SCHEINMMAN: The best update
6 probably comes from use data, where they used
7 eight millimeter tips which is standard now.
8 So I think you probably got the best data.
9 This was prospective data and the success rate
10 there is -- you'll notice about 87 percent and
11 is that really different from the 82 percent
12 that we were reporting?

13 DR. SOMBERG: And the other update
14 I was going to ask you is the -- and I don't
15 know the numbers offhand but I did see a
16 presentation about the implantable recorder, I
17 mean, speaking of frequency. That's the
18 ultimate, and the -- with RF ablation and
19 maybe someone, yourself or one of the other
20 experts here can comment on that, that it was
21 -- recurrence was seen with, you know, some
22 frequency and I can't remember what it was,

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1 but it's certainly not that, you know, you
2 have clinical success and therefore, if you
3 put in an event monitor, you never see
4 anything. You see a lot of sub-clinical.

5 DR. SCHEINMMAN: Yes, I think the
6 best data comes from the atrial fibrillation
7 literature, groups where they performed the
8 PBIs for example, and then the patient has an
9 implantable device and it's clearly evident
10 that you get a much higher incidence of
11 asymptomatic atrial fibrillation. That's
12 clear-cut. Now, I don't know of any data for
13 flutter. Maybe my colleagues can help me on
14 that.

15 There's two other points that I'd
16 like to make. I'm not associated with the
17 company. I have no links with them, but
18 looking at it as an outsider, my impression
19 is, is this is a no-brainer for two reasons.
20 Number one, the data that I reported leads to
21 a success rate that's a minimal success rate
22 because of the reasons we've gone over again

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1 and again. The other thing that we haven't
2 discussed is the benefits and these are not
3 trivial.

4 When someone like Hein Wellens says
5 that in Maastricht they use this procedure and
6 they don't use anesthesia, I mean, that's
7 fantastic. If I can use this for my patients
8 with COPD or severe heart failure, this is a
9 tremendous boon. So it's not just a matter of
10 haggling over what's the wiggle room. It's
11 the benefits to the patients that has been
12 brought up by some of the panel members. So
13 that would be my --

14 DR. SOMBERG: Bill, can I ask a
15 follow-up on that?

16 CHAIRMAN MAISEL: Yes, John.

17 DR. SOMBERG: I don't think anyone
18 here didn't notice that and maybe Dr. Wellens
19 would like to comment. The skepticism is that
20 it's such a small number and obviously, it
21 wasn't -- I mean, the FDA mentioned that it's
22 not a true protocolized investigation. So how

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1 would you respond to that? You know, it
2 sounds to me like a good working hypothesis,
3 but nothing something you would want to put in
4 a device insert.

5 DR. WELLENS: And I think I felt a
6 bit embarrassed by the critique of the FDA on
7 the pain study. First of all, how can you do
8 that blinded? The only person who is blinded
9 is the patient, because the patient does not
10 know what kind of ablative procedure, cryo or
11 RF is being done. Obviously, the operator
12 knows what he is doing, whether he is giving
13 cryo or RF.

14 So the patient did not know what
15 was going to be used, RF or cryo. Okay, so
16 that is one point. The second point is, pain,
17 the comment was the FOS score is a subjective
18 measurement. Yes, pain can only be measured
19 subjectively. And the FOS score is an
20 approach which is used by all the pain experts
21 so that's a well-accepted way to evaluate
22 pain.

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1 The third problem was there was no
2 P-value. Well, I showed you and I can maybe
3 show it again in that slide that when we
4 looked at the number of applications in the RF
5 group versus that were painful, 75 percent was
6 painful, but I think we should look at that
7 slide again because I think it's a very
8 important point.

9 There we are. So we have here on
10 the left, the percentage of painful
11 applications and as it is said, 75 percent of
12 the 94, 71 episodes were painful. In
13 contrast, when you look at the cryo, two out
14 of 125 were painful. So you can absolutely
15 make a P-value comparing the painful
16 applications in the RF group and in the cryo
17 group.

18 The other point is the number of
19 patients. We discussed this extensively with
20 the ethical committee in the hospital because
21 the RF people were going to have pain. So we
22 did not know whether the cryo people were

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1 going to have pain. And they said, "Well, you
2 have to limit the number of patients." So I
3 think that this study was done the way it
4 could only be done.

5 Now, another point, we are
6 discussing a clinical problem. The patient
7 comes to us with a symptomatic arrhythmia,
8 atrial flutter. As was pointed out, atrial
9 flutter can be difficult to treat. It can be
10 very annoying. So after a while, after you
11 have tried your pharmacological interventions,
12 you discuss ablation. Okay, ablation is
13 performed. The patient goes home and then in
14 clinical medicine, in clinical medicine, the
15 follow-up is that if the patient has a
16 symptomatic episode again, the patient comes
17 back.

18 Okay, that is clinical medicine.
19 We did -- if the patient did not come back
20 because of a symptomatic episode, look at the
21 patient again after one month, three months,
22 six months, 12 months. And at that time, we

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1 had a registration, a recording of the rhythm
2 of that particular patient. That is clinical
3 medicine. Ideally, you would love to have
4 continuous recording of the rhythm to know how
5 many asymptomatic episodes are there.

6 But that is not the real world. So
7 I very strongly feel that the way we did that
8 study in Maastricht is a clinical important
9 study to get clinical end points.

10 CHAIRMAN MAISEL: Thanks for those
11 comments. Other panel comments at this point?
12 Sharon?

13 DR. NORMAND: I just have one
14 comment and one question. The comment is that
15 you could have independent evaluators to
16 assess pain. That's what we typically do when
17 you can't blind. Just a comment. So I don't
18 need you to comment back on that.

19 I had a question that maybe I may
20 have misunderstood the readjudication of the
21 strips. And just a clarification, what I need
22 to know is the following; when those were

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1 readjudicated, it's my understanding it was
2 all the strips that were looked at. Because
3 you're looking at a time dependent outcome,
4 were the times changed as well?

5 In other words, as soon as you saw
6 something, if you disagreed with the
7 technician, that time, it could have happened
8 sooner. In other words, when you
9 readjudicated, you also looked at the timing
10 of the strip and then that was readjudicated
11 to say, yes, it actually happened earlier.

12 DR. WELLENS: I think that is
13 something that Mel better answer --

14 DR. NORMAND: Dr. Scheinman.

15 DR. WELLENS: -- in terms of the
16 investigation that he did.

17 DR. NORMAND: Yes, thank you.

18 DR. WELLENS: The thing is also
19 that now you're discussing atrial arrhythmias
20 and as was pointed out, atrial flutter and
21 atrial fibrillation often go hand in hand.
22 And atrial fibrillation is typically an

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1 arrhythmia that when you grow older becomes
2 more common. Each year above 51 percent of
3 your heart muscle is going to be replaced by
4 fibrous tissue. That is occurring in the
5 atrium, that is occurring in the conduction
6 system, occurring in the ventricle and that
7 means that more and more atrial fibrillation
8 come along.

9 CHAIRMAN MAISEL: Dr. Wellens, I'm
10 going to just interrupt you for a minute, if
11 we could have Dr. Scheinman answer Sharon's
12 question that would be very helpful, just
13 regarding the readjudication of the timing of
14 the end points.

15 DR. SCHEINMMAN: I would need to
16 have the help of someone from the company
17 because all I did was read it, give my opinion
18 and how the readjudication was made, was made
19 at a more senior level.

20 DR. NORMAND: So just for
21 clarification, every single stip was
22 readjudicated.

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1 DR. BAROLD: The strips that were -
2 - there were a few that were not readjudicated
3 and those were ones that patients went on to
4 have an atrial flutter ablation because those
5 were so obviously failures that we didn't send
6 those on.

7 DR. NORMAND: And so those timings
8 didn't change.

9 DR. BAROLD: No, the timings didn't
10 change and the times were always based on --
11 so the event recordings are sent in by the
12 patient at a specific time and date. And that
13 is the date that if there was a recurrence,
14 that time and date was always sustained.

15 DR. NORMAND: But just to be clear,
16 in theory, just to be clear in theory they
17 could have spotted that earlier if they had
18 been readjudicated.

19 DR. BAROLD: I don't think so
20 because I think the only time they could have
21 been spotted earlier is if there was
22 continuous event recordings. Then you could

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1 pick up the initiation of something but the
2 time of the event would never change.

3 DR. NORMAND: So, just so --
4 because maybe I'm not understanding you but I
5 suspect I'm not being very clear about my
6 question. So here's the concern I'm having;
7 is that you're using a time dependent analysis
8 here. And in theory, you'd want to
9 readjudicate everything. So pretend, just
10 pretend you've readjudicated everything and
11 you're saying, "Well, there's some that we
12 didn't have to readjudicate". It was clear
13 there was a problem.

14 And all I'm asking is the
15 following; if you had readjudicated
16 everything, even though there was a bad event,
17 obviously, it could have been sooner for --

18 DR. BAROLD: I think I get it.

19 DR. NORMAND: -- those people and
20 because you're doing a time dependent
21 analysis, the timing is critical to
22 readjudicate.

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1 DR. BAROLD: I think I understand
2 your point. I think that what you're -- if I
3 understand this correctly, is for example, a
4 failure, let's say somebody was brought back
5 to the EP lab on day 120, but, in fact, the
6 event recording occurred on day 100 --

7 DR. NORMAND: Right.

8 DR. BAROLD: -- the event would be
9 on day 100, not the day of the procedure, yes.

10 There were very, very few patients that were
11 not readjudicated. All right, there were some
12 of the reablations where there was some mile
13 inconsistencies just do to the shuffling of a
14 lot of papers, so here could potentially be a
15 small amount of error associated with that,
16 yes.

17 DR. NORMAND: And for the ones you
18 did readjudicate, as DR. Scheinman's lab said,
19 "Here's when it happened, I spot this as a
20 problem", then you take that date.

21 DR. BAROLD: Right, we take that
22 date and that time, correct.

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1 DR. NORMAND: Thank you.

2 CHAIRMAN MAISEL: John.

3 DR. SOMBERG: DR. Wellens, can we
4 come back to your study there and there were
5 three questions that were troubling to me and
6 that have come up and Sharon asked this again,
7 is was the pain assessment done -- it was done
8 by an individual who provided the pain score.

9 I think there's a mistranslation here. I
10 think that was independent.

11 DR. WELLENS: Sure.

12 DR. SOMBERG: The FDA made a
13 statement there was no -- okay, answer that
14 one and maybe I'll come back to the other.

15 DR. WELLENS: A psychologist who
16 has been doing this pain evaluation in the
17 Netherlands was actually the one who was
18 asking the questions.

19 DR. SOMBERG: And he was present
20 then. He was blinded.

21 DR. WELLENS: Excuse me?

22 DR. SOMBERG: The person who made

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1 the assessment was present and blinded.

2 DR. WELLENS: No. He can't be
3 blinded because you have a big console.

4 DR. SOMBERG: I see, he wasn't
5 blinded, okay.

6 DR. WELLENS: You can't --

7 DR. SOMBERG: Well, a psychologist
8 or psychiatrist may not know the difference
9 between an RF machine and -- but that's
10 another issue.

11 DR. WELLENS: Not in the
12 Netherlands.

13 DR. SOMBERG: Okay, they're well-
14 trained, I'm sorry about that. And the FDA
15 said there was no protocol. And you went to
16 an IRB and I can't believe an IRB met without
17 a protocol. So which is it? Was there a
18 protocol?

19 DR. WELLENS: Of course.

20 DR. SOMBERG: And why -- and they
21 also -- the FDA said they could not -- or the
22 company could not provide them with the

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1 tracings. You probably have more tracings
2 than anyone else in the world. Why could they
3 not be provided with the tracings just as a
4 curiosity?

5 DR. WELLENS: You're now talking
6 about the larger study. That's what you're
7 talking about.

8 DR. SOMBERG: You're right, I'm
9 comparing apples and oranges. I am not going
10 back to the other part of the study, the
11 larger one. Was there -- I mean, they said
12 they couldn't have tracings and there was no
13 protocol in that larger study also.

14 DR. WELLENS: Well, again, as I
15 said during my presentation, the protocol of
16 the ablative procedure or the protocol of
17 dealing with the creation of bidirectional
18 isthmus block is a very standard protocol.
19 And in fact, you can find the protocol, as I
20 pointed out, in the publication in circulation
21 2004, where you have the description of the
22 protocol.

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1 The other point is, that this pain
2 study was very critically evaluated by
3 circulation and accepted for publication.

4 CHAIRMAN MAISEL: I think at this
5 point, we'll take a break for lunch and
6 reconvene at 1:00 p.m.

7 (Whereupon at 11:59 a.m. a luncheon
8 recess was taken until 1:02 p.m.)

9 CHAIRMAN MAISEL: Good afternoon
10 and welcome back. I'd like to open this
11 afternoon session and invite Dr. Donna V.
12 Tillman to make some remarks on behalf of the
13 FDA to clarify some of the issues that came up
14 this morning.

15 DR. TILLMAN: Okay. I am Donna V.
16 Tillman. I'm the Director of the Office of
17 Device Evaluation, but that's not why I'm
18 standing here. I'm standing here because I
19 was the Branch Chief of what was the Pacing
20 and Electrophysiology Branch from 1997 to
21 2000. So I was actually at that mysterious
22 panel meeting of 1998. I wanted to just sort

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1 of clarify a few things that I think got
2 confused this morning and in order to do that
3 I think it's important that I go back just a
4 little bit further than 1998 and that is to
5 when FDA first started considering catheter
6 ablation.

7 As those of you who have been
8 involved with electrophysiology for awhile
9 know, catheter ablation actually started as
10 off-label use of electrophysiology and mapping
11 catheters and back in the early '90s, FDA got
12 concerned and there were actually a couple of
13 large clinical trials that were conducted that
14 eventually came in and supported PMAs for
15 ablation catheters to be used to ablate SVT
16 and these were four millimeter RF ablation
17 catheters. Based on these large single-arm
18 trials, FDA approved the first ablation
19 catheters for SVT. And based on those trials,
20 we went back and actually developed OPCs that
21 you're seeing today. Those OPCs were
22 developed for RF ablation, four millimeter

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1 catheters for SVT and they are the numbers
2 that you saw today.

3 I think it's important to note that
4 the safety endpoint was intended to be all
5 serious adverse events up to seven days. So
6 it was that OPC for SVT, at least, was
7 designed to include all adverse events, not
8 just device or procedure related and the
9 efficacy endpoint, the longer term one, was a
10 six month endpoint. So that was all SVT.

11 Well, then what happened is in the
12 mid to late 1990s people started taking these
13 four millimeter RF catheters that were
14 approved for SVT and using them to treat A-
15 Flutter and we got a lot of questions from
16 companies about what kinds of studies they
17 would need to do in order to support an A-
18 Flutter indication and that was why we held
19 that panel meeting in 1998.

20 At that panel meeting, one of the
21 questions we asked was whether a randomized
22 control trial or a single-arm trial was

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1 appropriate and the feedback we got, although
2 mixed, was by and large that a randomized
3 control trial was probably not feasible and
4 that we should be considering single-arm
5 trials with OPCs. And the OPCs that the panel
6 recommended, once again this was for RF
7 devices, this was what was being envisioned
8 back then, included a six month efficacy
9 endpoint and a safety endpoint that was very
10 similar to the one for SVT that was once again
11 based on serious adverse events up to seven
12 days on all of them. So that was where the
13 flutter OPCs sort of came from.

14 The other thing that was discussed
15 this morning that I think has muddied the
16 waters a little was in 2002 we published a
17 guidance document that actually Dr. Barold was
18 involved with that was about what a company
19 would need to do to take one of these four
20 millimeter RF ablation catheters and, once
21 again
22 RF four millimeter, and get it approved for

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1 what we call generic indications and that
2 guidance document which somebody mentioned had
3 the three month OPC in it. That was all about
4 what kind of data would be needed to support a
5 generic indication for a four millimeter RF
6 ablation catheter. It really doesn't pertain
7 even though the numbers look the same to the
8 question that we're dealing with today which
9 was A-Flutter.

10 So then that brings us sort of to
11 the part where I'm not an expert and I'm not
12 going to get into that, but that is what we
13 agreed with with this particular company and
14 the thing that our team, I think, was trying
15 to talk about this morning was we worked with
16 the company to design this study. I think
17 that although there were some questions about
18 what the most appropriate study design was at
19 the time we eventually agreed with the company
20 that a single-arm study with OPCs was a doable
21 study design and that study as the company has
22 acknowledged was designed with a six month

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1 efficacy endpoint and the OPCs, if you will,
2 that were designed were intended to be used at
3 six months and this adverse event endpoint as
4 has been said a couple of times was an
5 endpoint that included all adverse events up
6 to seven days.

7 So the reason you're here today is
8 that FDA doesn't consider OPCs as sort of
9 black and white in that if you make it you get
10 approved. If you don't make it, you don't get
11 approved. I mean, if that were the case
12 wouldn't have even bothered having this panel
13 meeting today.

14 The reason we're having this panel
15 meeting is although the company's results were
16 a little bit mixed, we think it's important to
17 bring together a bunch of experts like
18 yourselves and have you tell us based on the
19 totality of the data do we have enough to meet
20 the bar of reasonable assurance of safety and
21 effectiveness.

22 So as Bram said earlier this

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1 morning, I think it's important in your
2 deliberations. We want to hear from you about
3 what you think about the sponsor's data and
4 whether you think it meets the regulatory bar
5 and then if you think we need to go back and
6 change our OPCs, we're more than happy to hear
7 your input on that as well. But you shouldn't
8 feel like those OPCs are written in stone.
9 They were simply the best we had at the time
10 we developed them.

11 Anybody have any questions about
12 that? Does that clear it up or make it worse?

13 (No response.)

14 CHAIRMAN MAISEL: Thank you, Donna
15 V. I think that was excellent. So the two
16 major issues we had outstanding seemed to be
17 resolved which is a six month endpoint for the
18 OPC and the safety endpoint is all adverse
19 events within seven days of the procedure.

20 Does the sponsor want to respond
21 directly? Do you have issues with either of
22 those two things?

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1 DR. BAROLD: No. This was never in
2 question. This is what the study said we --

3 CHAIRMAN MAISEL: Right. I didn't
4 mean to imply that you questioned that.

5 DR. BAROLD: No.

6 CHAIRMAN MAISEL: It was more the
7 panel just looking for clarification. So
8 thank you. I think that resolves our
9 outstanding issues.

10 At this point, we'll move onto our
11 primary review from Dr. Slotwiner. After his
12 review, I'll give each of the panel members.
13 We'll go around the table. You'll each get an
14 opportunity to ask questions if you have any
15 and I will also let you know that some of the
16 sponsor's experts are only here until
17 approximately 3:00 p.m. So as you're going
18 around the table during your turn, if you have
19 any specific questions you'd like answered
20 from their experts, I would suggest you ask
21 them during that time.

22 So why don't we as DR. Slotwiner to

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1 inform us.

2 DR. SLOTWINER: Okay. Thank. It's
3 not going to be easy since we've been through
4 this in detail already. I was asked to create
5 a summary of the panel packet.

6 CHAIRMAN MAISEL: Could we put his
7 slides up please?

8 DR. SLOTWINER: I was asked to
9 summarize the contents of the panel packet
10 objectively and so summarize in about 10 to 15
11 minutes. So most of the information, actually
12 all of the information, we've seen earlier
13 today. So I'll skip over a lot of this
14 content so we can go onto the discussion. But
15 let me --

16 The device, I think, has been
17 described in great detail by the sponsor. I
18 don't think there is anything I can add to
19 that. The regulatory history was presented
20 very clearly by the FDA.

21 The reason we're here today is
22 because of the readjudication of strips

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1 evaluated initially by LifeWatch. The initial
2 submission estimated a lower chronic efficacy
3 rate based upon interpretation of strips by
4 technicians as opposed to physicians and Dr.
5 Simon in particular. So once those were
6 reexamined, the efficacy appeared much higher.

7 That was submitted in November of 2006 and a
8 statistical analysis completed in March of
9 this year and that's what we're evaluating
10 today.

11 And I wasn't sure beforehand if
12 everybody would be familiar with typical
13 atrial flutter but having Dr. Waldo here to
14 explain it certainly can do it better than I.

15 But I wanted to make sure that everybody
16 understood what we were discussing in terms of
17 the arrhythmia which is typically this circuit
18 here, counterclockwise circuit, of electrical
19 activity which is able to continue due to slow
20 conduction in this cavotricuspid isthmus
21 between the inferior vena cava and tricuspid
22 valve.

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1 In order to determine atrial
2 flutter, we have to demonstrate conduction
3 block along this line and bidirectional block
4 simply means conduction demonstrated from
5 pacing on the septal side versus the free
6 atrial side. So we demonstrate block in both
7 directions.

8 The radiofrequency data we already
9 know is used as the objective performance
10 criteria and the pivotal study design was
11 carried out at 24 U.S. sites primarily to
12 evaluate safety, acute and chronic efficacy.
13 And the FDA indicated to the sponsor
14 beforehand that the FDA considers there to be
15 a lack of evidence that cryoablation acute
16 efficacy predicts chronic effectiveness. So
17 the FDA indicated that the chronic efficacy
18 data would be very important for approval.

19 This is the objective performance
20 criteria that we just heard more about from
21 the FDA. I don't think I can really add
22 anything to what's already been said. But

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1 just to summarize, the acute efficacy target
2 was 2.5 percent, I'm sorry, 95 percent with
3 chronic efficacy greater than 90 percent and
4 the estimated serious adverse events should
5 have been less than 2.5 percent.

6 The study design is small here, but
7 again we've been through it in detail. Once
8 patients had met screening criteria, they were
9 brought to the EP laboratory and there they
10 were rigorously demonstrated by
11 electrophysiology criteria to have atrial
12 flutter as their arrhythmia. If not, they
13 were withdrawn from the study. Those who had
14 aflutter went on to receive cryoablation.
15 Once the line of bidirectional block was
16 achieved, they went into a waiting period
17 which was initially 60 minutes. But in the
18 study, that was reduced to 30 minutes with the
19 last protocol revision and if conduct would
20 have occurred, then the ablation was repeated
21 until bidirectional block was persistent or
22 the investigator could switch to

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1 radiofrequency. And the follow-up lasted six
2 months as we know and the monitoring strip
3 frequency I'll go through.

4 Specific points about the study
5 design. Again, there was initially a 60
6 minute waiting period observed after
7 bidirectional block was achieved. With the
8 final revision, Revision E, of the protocol,
9 this was reduced to 30 minutes and the follow-
10 up monitoring and compliance was quite strict
11 and we know it was performed by LifeWatch.
12 Each patient had to submit -- they were
13 supposed to submit at least one ECG
14 transmission per week for six months, but in
15 order to meet the minimum required, they had
16 to submit three ECGs per month for five out of
17 the six months.

18 Some more specific points about
19 today's meeting. The readjudication
20 originally in the original PMA, all the strips
21 were interpreted by technicians from
22 LifeWatch. That was determined to not be

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1 accurate. So Dr. Scheinman and his associates
2 have reviewed almost every tracing and that's
3 what's resulted in the reclassification of
4 several patients as chronic successes and
5 that's why we're here.

6 This is considered -- the FDA said
7 it considers this scientifically valid.

8 In terms of poolability of the
9 study data, they looked at each of the
10 protocol revisions, patients studied under
11 each of the protocol revisions, and again the
12 most significant revision was that change in
13 the waiting period. They look at gender,
14 different study sites and catheter model and
15 the P values were all insignificant except,
16 and this is a point I have questions on, the
17 reduced wait time. It was my impression that
18 that yielded a higher success rate and, if so,
19 that would be a question.

20 The results, serious adverse events
21 are shown in Table 7 which I didn't place on a
22 slide, but we've discussed already. One of

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1 those patients, I think, the FDA and the
2 sponsor have taken out of this group. So it's
3 now, I think, one less serious adverse event.

4 But anyway, the safety endpoint was not quite
5 met.

6 And these are the complications.
7 This is the patient, I think, who was removed
8 because it was atrial flutter after seven
9 days.

10 I'm going to skip over that.

11 And this slide doesn't show up well
12 but it's just the acute effectiveness study
13 group. We started with 189 patients. One
14 hundred and sixty had the catheter placed.
15 One hundred and forty were deemed acute
16 successes and of these, eight were removed,
17 censored, either due to lack of follow-up or
18 death. So the final group is 106 successes
19 and 28 failures.

20 Of those patients, I guess we can
21 disagree about what the study group is, but of
22 the 140 patients who had the catheter placed,

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1 87.5 percent had acute success demonstrated by
2 bidirectional block and this was deemed
3 effective based upon the radiofrequency
4 catheter ablation data.

5 Chronic effectiveness the sponsor
6 evaluated in two ways. Dr. Scheinman
7 evaluated objectively by reviewing the
8 transmission strips in a blinded fashion and
9 then we've heard in great detail about the
10 clinical determination made by one of the
11 treating physicians which judged some failures
12 to actually be clinical successes.

13 Based upon the core lab, Dr. Scheinman's
14 interpretation of the strips chronic efficacy
15 was estimated at 81.6 percent, a lower
16 boundary of 74.7 percent. The objective
17 criteria was 90 percent with a lower common
18 boundary of 80 percent. So chronic efficacy
19 was not met strictly by the core lab
20 interpretation.

21 This is the Kaplan-Meier survival
22 curve that we've already seen, event-free

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1 surveyor from atrial flutter over time, over
2 six months and you see how there's an early
3 drop of recurrence in arrhythmia then it stays
4 pretty steady after six months.

5 The chronic effectiveness clinical
6 determination was a post hoc analysis and some
7 patients deemed chronic failures by the core
8 lab were readjudicated by this investigator as
9 successes. Thirteen patients who were thought
10 to have atrial flutter by the core lab, Dr.
11 Scheinman, were readjudicated as chronic
12 successes regardless of the core lab tracing
13 interpretation. So this then yields the
14 number of a 90.5 percent chronic success with
15 a lower boundary of 85.7 percent.

16 The FDA considerations and concerns
17 with this are that it's a post hoc analysis.
18 The objective chronic failures were
19 reclassified as successes. It's an unblinded
20 analysis and it does reevaluate patients who
21 are already classified as a success by the
22 core lab.

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1 Two last slides. This is the
2 additional data from Dr. Wellens. I thought
3 it was just one person, but it's him and his
4 colleague. One hundred and eleven consecutive
5 patients studied. This is a peer review
6 publication from circulation and they took 111
7 consecutive patients with typical right atrial
8 flutter and performed ablation using the
9 CryoCor system and efficacy. Acutely, it was
10 estimated at 93 percent. Chronic at six
11 months 93 percent again and this was
12 determined by ECGs and we heard earlier today
13 25 were Holter monitors and clinical follow-
14 up.

15 The FDA concerns with this study
16 are that it's retrospective, single center,
17 not a single operator. The ECGs apparently
18 are not all available and the patients weren't
19 provided systematically with event recorders.

20 And lastly, the pain perception
21 study also from Dr. Wellens, published again
22 in circulation, peer reviewed, its title is "A

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1 Randomized Study Comparing Radiofrequency
2 Catheter Ablation with Cryoablation for the
3 Treatment of Atrial Flutter with Emphasis on
4 Pain Perception." Fourteen patients
5 randomized to receive radiofrequency versus
6 cryo and it's difficult, impossible, to blind
7 people in the room. There was no significant
8 in the success of the procedure, but using the
9 visual analog scale to perceive pain, all
10 seven of the patients with using
11 radiofrequency ablation perceived pain;
12 whereas, only one of the seven patients who
13 received cryo perceived pain. The FDA concern
14 was that this was not a blinded study.

15 So that slide is summarizing what
16 we've already discussed and I'm not sure if
17 this is the right time to raise further
18 questions or let me go back to you though.

19 CHAIRMAN MAISEL: Sure. You can
20 raise questions. You can question the sponsor
21 or the FDA if you have a couple of issues you
22 would like to address. That's fine.

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1 DR. SLOTWINER: I think that we've
2 had a very good discussion, but one topic we
3 haven't discussed is that change in the
4 protocol and I wanted to ask Sharon if she had
5 an opinion about the statistical --

6 CHAIRMAN MAISEL: Actually, David,
7 I would like to limit our discussion at this
8 time to questions or your observations. We'll
9 have some panel discussion about issues later.

10 DR. SLOTWINER: Okay.

11 CHAIRMAN MAISEL: So if you have
12 questions for the panel, we certainly can
13 raise those later. For now, if you have
14 observations or questions for the sponsor or
15 the FDA.

16 DR. SLOTWINER: Okay. Well, I
17 guess my question for whoever is allowed to
18 answer is was the statistical difference
19 between acute success different when the
20 waiting period was reduced from 60 to 30
21 minutes?

22 CHAIRMAN MAISEL: Dr. Barold, you

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1 commented a little bit on this earlier, but
2 why don't you address that issue please?

3 DR. BAROLD: The answer is --
4 sorry. Yes, there was a change in the acute
5 effectiveness, but again, because we and the
6 FDA agree this is a chronic effectiveness
7 issue we really tried to give as much
8 information on the chronic effectiveness,
9 whether or not it affected that, and I think
10 in the panel pack we gave you a fair amount of
11 statistics to show that it, in fact, did not.

12 We can -- if you could put up slide
13 54, that's the slide. Yes. This was not in
14 your panel pack, but this is the Kaplan-Meiers
15 curves for the 60 minute and the 30 minute
16 wait group. I think you can have a
17 statistical discussion which I'm not prepared
18 to do about the numbers that are involved
19 there. This was not statistically significant
20 by the test that we used and the test that we
21 provided you. Does that answer your question?

22 DR. SLOTWINER: Yes. Thank you.

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1 DR. BAROLD: Okay.

2 CHAIRMAN MAISEL: David, any other
3 comments or questions at this time?

4 DR. SLOTWINER: No, I don't think
5 so. Thanks.

6 CHAIRMAN MAISEL: Okay. At this
7 point, we will start going around the table
8 and give each panel member an opportunity to
9 ask questions. You're certainly not obligated
10 if you don't want to ask or make observations.

11 But if you do, I would ask you to limit your
12 comments to about five minutes please. Why
13 don't we start with Mike?

14 DR. DOMANSKI: I don't have any
15 questions right now.

16 CHAIRMAN MAISEL: Jeffrey.

17 DR. BRINKER: I would like to ask
18 Dr. Wellens a couple of questions. In the
19 animal study data, at least in the table, it
20 showed that the fluoroscopy time was about 50
21 percent greater in the animals that got the
22 CryoCor device. Absent in your data, the

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1 human data, was whether there was any
2 difference in fluoroscopy time or procedure
3 time. Could you help us understand that?

4 DR. WELLENS: Well, I think that's
5 a very important question. What I would like
6 to show is how we saw changes in the way cryo
7 was applied over the years. Originally, it
8 was started with at the same site twice five
9 minutes and then it was readily -- I really
10 should like to that. Do we have that backup
11 slide?

12 DR. BAROLD: Yes.

13 DR. WELLENS: Because I think it's
14 very relevant. Yes. This is from Maastricht.
15 These are data from Maastricht and as you can
16 see in 2001, then the procedure was at the
17 same site. You applied cryo twice for five
18 minutes and then you see over the years you
19 see a gradual diminishment in how many
20 applications you do per site and how long the
21 application lasts. So the fluoro-time has
22 been decreasing that light because it's

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1 obvious that you are shortening the procedure
2 and that also relates to the fluoro-time.

3 DR. BRINKER: So do you have a
4 comparison between your RF experience and your
5 present day cryo experience?

6 DR. WELLENS: No. We don't have a
7 randomized situation.

8 DR. BRINKER: Well, even a gut
9 feeling as to whether it takes any more --

10 DR. WELLENS: No. I don't think
11 so. We don't have that at this point in time
12 because I said earlier during the last three
13 years, all the actual fluoros were done using
14 cryo. So I can't tell you how over that
15 period if you would have been using RF the
16 fluoro-time would have been.

17 DR. BRINKER: All right.

18 DR. CALKINS: Jeff, could I just
19 make one comment and that is how fluoroscopy
20 is used during the ablation procedures, with
21 radiofrequency catheter ablation, typically we
22 fluoro the entire time of the burn in case the

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1 catheter moves and whatever. But with cryo
2 because it adheres to the tissue, you actually
3 -- although it may be a two minute burn or
4 freeze, you can turn off the fluoro because
5 the catheter stays put.

6 I think when Dr. Wellens started
7 his studies, he was fluoring the entire two or
8 five minute time because it was early in the
9 experience. We know you don't have to fluoro
10 at all once the temperature gets to -30. The
11 device is stuck and we never fluoro during the
12 application of cryo.

13 DR. BRINKER: Okay. So one of the
14 really background parts of the question, the
15 real reason for the question, is that this is
16 a 10 French catheter. It's bigger than the
17 other catheters you use. I know as an
18 interventional cardiologist the smaller the
19 catheter the better I feel. But I know EP
20 guys don't care about how many catheters and
21 how big they are.

22 (Laughter.)

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1 DR. BRINKER: So the one question
2 I'd have with the 10 French catheter is one
3 would assume that manipulation might be a
4 little bit different than a smaller catheter
5 and perhaps not quite as precise. So I would
6 like your feeling on whether there is a
7 material difference between the catheters that
8 changes any aspect of the positioning itself.

9 DR. CALKINS: Yes. My comments are
10 that the catheter actually handles remarkably
11 similar to a standard 7 or 8 French
12 radiofrequency catheter ablation in terms of
13 its deflectability and I think another thing
14 which has been learned over time is that
15 contact is important with a cryoablation so
16 that -- But the device has very good
17 deflection. You get very good contact during
18 that initial freeze and then it adheres to the
19 wall. But others in the panel may have some
20 comments.

21 DR. BRINKER: So you can answer
22 this. This is my final question and that is

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1 the issue about the heart block, the AV block.

2 One would assume that if you use cryo since
3 the injury is produced over a little bit
4 longer time that you would have some warning
5 and be able to stop before you got that. Is
6 that not true?

7 DR. CALKINS: No, that -- Yes, the
8 specific case that got heart block during this
9 procedure, the operator, the investigator
10 basically wasn't paying attention and he was
11 burring on the septal aspect of the isthmus in
12 atrial flutter and was unaware when the heart
13 rate abruptly fell. And it was only when he
14 finally terminated atrial flutter they figured
15 out it was heart block in that functional
16 block. So it was really an operator error.

17 Typically, with flutter ablations,
18 they try to stay off the septum because
19 anywhere on the septum in terms of the
20 potential with cryo of having reversibility of
21 heart block, that's a potential advantage.
22 Certainly, if you see heart block and you turn

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1 off right away, it can warm up and the heart
2 block can be reversible in most but not all
3 cases. But I think this was just a case of
4 operator error.

5 DR. BRINKER: Thank you.

6 CHAIRMAN MAISEL: John.

7 DR. DAUBERT: Can I speak to your
8 first question as well?

9 CHAIRMAN MAISEL: Sure. Please try
10 to keep it brief.

11 DR. DAUBERT: Sure. In terms of
12 the catheter handling, I have significant
13 experience both in this trial and in other
14 investigational trials and I would concur with
15 Dr. Calkins that despite it being a slightly
16 larger catheter it does indeed handle well, so
17 not a disadvantage there, I don't think.

18 CHAIRMAN MAISEL: Thank you. Dr.
19 Somberg.

20 DR. SOMBERG: I have two questions
21 for the panel of experts from the company and
22 you can decide who wants to answer each of

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1 them and I'm going to throw them both out.
2 One is the advantages that the -- I understand
3 the catheter will be adherent to the area that
4 you are ablating, but how is -- Is there a
5 contra or down side of that that to get an
6 uninherent there might be more of a problem?
7 Please answer that.

8 And the other issue is I'm still
9 trying to assess the best comparators in this
10 procedure because I think we've somehow
11 changed from the earlier guideline sec of what
12 is efficacious and by adding another layer of
13 assessment and that was the monitoring which
14 made it more precise and therefore introduce
15 more atrial flutters. So correct me if I'm
16 wrong, but what I think what I'm gleaning from
17 you gentlemen is that the appropriate
18 comparators for RF frequency ablation when
19 only clinical and electrocardiographic EKGs at
20 time of office visit was used you would see
21 about a 90 percent efficacy and with the
22 assessment made on the cryoablation system

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1 looking at clinical events, presentations and
2 electrocardiography excluding the monitoring,
3 you presented about an 87 percent efficacy in
4 the corrected clinical work and that would be
5 comparing best as I can see apples to apples.

6 Do people agree with that or they don't agree
7 with that and I think that's a pretty
8 important issue at this point.

9 DR. FELD: I'll address those. I
10 haven't had the opportunity to speak yet.
11 Thank you for the opportunity. The first
12 question, I've had extensive experience with
13 the system from early preclinical days to now
14 clinical days as well as for a background.
15 But the catheter does manipulate well.

16 The adherence to the tissue, I
17 think, is very valuable because you can
18 eliminate the need to fluoro during that time.

19 The catheter doesn't move. So when you find
20 the target and freeze, you know it's going to
21 stay there; whereas, with RF, it will move.
22 So you're not going to accidentally drift

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1 towards the septum if you're careful and run
2 into some of the problems that you might with
3 radiofrequency.

4 I really don't see any down sides
5 to that. You can, we call it, rewarming or
6 thawing, but you don't want to move the
7 catheter acutely. So you have to be a little
8 bit careful that you actually don't move the
9 catheter until it has clearly reached a
10 positive temperature above zero, usually
11 around 20 degrees. So that is one potential
12 concern, but we've not found that as a
13 disadvantage.

14 With respect to this issue, at the
15 end I got the impression this morning that the
16 panel is not going to consider the reanalysis
17 that we've done on the clinical side. But I
18 continue to feel the way you appear to and
19 that is that the clinical outcome is really
20 the important and that the OPCs may be more
21 comparable to that clinical outcome in
22 introducing the event monitoring as we've seen

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1 with the atrial fib trials. You can lower
2 your efficacy rates 10 to 20 percent below
3 what you might expect on a clinical outcome
4 which would bring that also in range with our
5 event recording data.

6 In addition, something that we
7 didn't mention this morning was there was a
8 question about these single episodes of atrial
9 flutter in a significant number of patients
10 where they were later determined to be a
11 chronic success. I think as you showed on the
12 slide a moment ago that most of the
13 recurrences were relatively early on the
14 Kaplan-Meier curve.

15 And we now know also from the
16 atrial fib trials that there's a period over
17 the first month or so and we call it a
18 blanking period where the recurrence may not
19 be considered clinically important because of
20 maturation of lesions and remodeling or
21 reverse remodeling of the atrium and I think
22 that it may actually occur to some extent with

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1 the atrial flutter as well so that maturation
2 of lesions or remodeling may be lead to a
3 clinical success where there might even have
4 been a single event early on.

5 So I would agree that the clinical
6 approach is really what we should be looking
7 at and that's my opinion. I understand your
8 constraints that it's necessary to follow your
9 strict guidelines and so the event recording
10 data may be used here. But it would put us in
11 a comparable range with that data.

12 CHAIRMAN MAISEL: Thank you. Pam.

13 DR. KARASIK: Thank you. I just
14 have a couple of comments and questions. I
15 just want to reiterate what Dr. Brinker said.

16 I have some concerns about the size of the
17 catheter and I'm glad to hear that it appears
18 to be easily manipulable, but I wonder about
19 groin complications with the 10 French sheath.

20 You know, we use 10 French for intracardiac
21 ultrasound, for transseptal ablations and
22 things like that, but we do a lot of flutter

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1 ablations, far more than AFib ablations and I
2 just wonder about the safety of regular use of
3 10 French catheters. So I wondered if Dr.
4 Wellens had seen any -- You have more
5 experience perhaps.

6 DR. WELLENS: No. I have not been
7 doing the catheterizations. Those were done
8 in the unit in Maastricht by Dr. Timmermans
9 and Dr. Rodriguez. So I think you should ask
10 the people who actually did that.

11 DR. DAUBERT: Of course, this is a
12 concern to all of us, the use of large
13 sheaths. But as you pointed out, we do use
14 the 9 French sheath routinely for the
15 ultrasound and catheter and a lot of time in
16 the left atrium for most of us and sometimes
17 the right. But I don't believe we've seen a
18 higher rate of complications from the use of
19 the 10 French sheath versus an 8 which we
20 would normally use for a standard RF. Now we
21 may have some data. I think, the table showed
22 there were very few hematomas.

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1 DR. KARASIK: Right. One.

2 DR. DAUBERT: One, in fact, in the
3 entire study. So that's very low and just
4 from a clinical perspective using it routinely
5 and in other studies, we have not seen a
6 higher risk with the 10 versus the 8 size.

7 DR. KARASIK: Okay. Thank you. I
8 had another question about the console in
9 reading the manual and how to work this. This
10 is not -- You can't adjust temperature. This
11 is a fixed parameter. The only thing that you
12 can adjust is the duration of the burn.

13 DR. BAROLD: The freeze.

14 DR. KARASIK: The freeze. Sorry.
15 New lingo. Okay. Freeze is burn. Right?
16 The freezer burn, right? We have that. And I
17 had a question about labeling and I don't know
18 if this is the correct time to ask it.

19 CHAIRMAN MAISEL: Sure.

20 DR. KARASIK: So in the labeling
21 information that's provided at the back of the
22 manual, there's a page I can barely read even

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1 with my glasses, but it does talk about
2 placing the catheter in the left atrium and I
3 wondered about that.

4 DR. BAROLD: Well, understand that
5 this is draft labeling and that should we get
6 to the point when we have formal labeling
7 things will be carefully reviewed by the FDA.

8 For anything like that, it would be my guess
9 that anything related to the left atrium would
10 be removed from the labeling.

11 DR. KARASIK: And it --

12 CHAIRMAN MAISEL: Pam.

13 DR. KARASIK: Well, let --

14 DR. SOMBERG: Why was it there?

15 CHAIRMAN MAISEL: I mean I think it

16 --

17 DR. BAROLD: I can talk -- I'll
18 tell you why it was there in the first place.

19 We basically took labeling from another
20 catheter that had been approved just as this
21 is the draft type of labeling. I don't think
22 it's appropriate to have something with left

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1 atrium in there. I think it's an oversight on
2 our part.

3 CHAIRMAN MAISEL: It would be
4 removed.

5 DR. BAROLD: Yes. I think it's an
6 oversight.

7 CHAIRMAN MAISEL: Pam. Other
8 questions?

9 DR. KARASIK: Last question is
10 whether or not you think you need to have any
11 specific physician training if you should
12 acquire marketing approval for the device.

13 DR. BAROLD: You know, we've
14 discussed this. We have not come up with a
15 formal plan. I can tell you that when we, for
16 example, set up a site for our clinical study
17 we do actually go through training with them.

18 We have not considered setting up,
19 for example, an animal lab. But there
20 certainly are things that we do need to go
21 through with a site on how to use the console,
22 how to set up, tips about the catheter. For

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1 example, it is very important not to move the
2 catheter in the middle of a freeze. So there
3 is that type of training that does occur we
4 haven't set up. Because we're still in
5 investigational use, we have a training
6 program for that, but we haven't set up
7 anything formal.

8 CHAIRMAN MAISEL: Thank you, Pam.
9 Norm.

10 DR. KATO: Thank you. A question
11 for the sponsor. In reading and re-reading
12 your inclusion/exclusion criteria for your
13 study, I would like you to comment about the
14 use of medical therapy. I also remember at
15 one of the presentations you said 35 percent
16 of patients were on some type of drug therapy
17 before they were ablated. Fifteen percent has
18 drug therapy afterwards. I mean, are you
19 advocating this, well, one comment on the use
20 of medical therapy and where your catheter
21 kind of falls into the scheme there and also -
22 - or are you advocating this as primary

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1 therapy?

2 DR. BAROLD: I'm not -- I think
3 that that is very dependent on who -- when the
4 physician chooses to use a catheter to ablate
5 atrial flutter I think it depends on how that
6 treating physician is going to manage that
7 patient. We are not advocating that -- The
8 study is not an advocate of atrial flutter
9 ablation over medications. We're saying that
10 if the physician chooses to use an ablation
11 for the patient that this is a tool for them
12 to use.

13 I don't think that it would be
14 appropriate for us to advise or dictate
15 medical therapy around the treatment of other
16 arrhythmia or even the additional treatment of
17 atrial flutter in a patient. Is that what
18 you're asking?

19 DR. KATO: I mean, for example,
20 even in other device studies many times the
21 inclusion criteria will say optimal medical
22 management or failure of -- optimal medical

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1 management exclusion will be or inclusion will
2 be failure of optimal medical management.

3 DR. BAROLD: Right.

4 DR. KATO: You're not saying
5 exactly what drugs you would use but at least,
6 say something that this is to be used when
7 medical therapy fails and the reason why I ask
8 about this is because in many situations that
9 we're seeing out in the field that, for
10 example, biventricular devices or, excuse me,
11 devices for heart failure may be used in
12 preference to, let's say, valve replacement
13 surgery.

14 DR. BAROLD: Right.

15 DR. KATO: We've seen certainly
16 debates about multi-vessel stenting versus
17 bypass surgery and then medical therapy on top
18 of that. So in terms of how this is going to
19 be promoted, how this is going to be utilized,
20 you just want to -- Your point is you just
21 want to leave it completely up to the
22 practicing physician?

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1 DR. BAROLD: It's the standard of
2 care for treatment of atrial flutter which I
3 will allow Dr. Calkins to elaborate on, the
4 standard of care is ablation and this is the
5 tool that people could use to do it. So there
6 is not really -- It's not comparable to the
7 heart failure situation where it's an adjunct
8 to optimal medical therapy. It's different
9 scenarios.

10 So I think Dr. Calkins can address
11 that issue of medications versus ablation.

12 DR. CALKINS: I think there are two
13 points worth taking. One is where does
14 catheter ablation fit in in the management of
15 atrial flutter and I think over the years it's
16 evolved from being a second line therapy after
17 antiarrhythmic drug therapy has failed to what
18 I think many centers around the country,
19 around the world, are performing catheter
20 ablation of atrial flutter as first line
21 therapy simply because lots of studies have
22 shown that antiarrhythmic drug therapy is

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1 highly ineffective with a 10 to 20 percent
2 long-term success rate and the risk of
3 proarrhythmia and atrial flutter is a
4 relatively straightforward procedure where you
5 ablate the isthmus and so forth.

6 The other, I think, point which is
7 worth mentioning is the one-third of the
8 patients who were on antiarrhythmic drug
9 therapy at the time of the procedure and that
10 is for this entity called Type I drug induced
11 atrial flutter. If you have patients with
12 atrial fibrillation and you put them on
13 particularly flecainide or propafanone, their
14 atrial fibrillation can evolve into atrial
15 flutter. You can then ablation the flutter
16 and then leave them on the antiarrhythmic
17 drug therapy to control the atrial
18 fibrillation and that's actually an approach
19 that was discovered by Dr. Wellens that many
20 people call it Type IC atrial flutter. So
21 it's an antiarrhythmic drug converting afib is
22 a very big ablation procedure or surgical

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1 procedure to atrial flutter which is a very
2 straightforward procedure and then continuing
3 antiarrhythmic drug therapy to control the
4 AFib in that patient group.

5 CHAIRMAN MAISEL: Norm, do you have
6 any other questions or comments?

7 DR. KATO: No. That's it. Thank
8 you.

9 CHAIRMAN MAISEL: Clyde.

10 DR. YANCY: I have kind of a broad
11 clinical question for the physician
12 investigators and for the advisory expertise
13 that the sponsor has with us. Looking at this
14 as best we can and using the objective
15 performance criteria as a reference point, we
16 don't see signals that Cryo is any more safe
17 and we don't see signals that it's any more
18 effective. We did get a very definitive
19 statement that there are benefits and the
20 benefit was defined in the context of less
21 sedation and less pain.

22 And so the query is to understand

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1 what the clinical utilization of Cryo would be
2 versus RF and so if you can give me a sense of
3 what the clinical circumstances are where this
4 technology would prevail over RF or how you
5 would make the decision which patient would be
6 treated with RF versus Cryo, that would help
7 me with context.

8 DR. SCHEINMAN: The -- in looking
9 at the benefits/risks equation which we do
10 every day of the year is we would focus on the
11 patients with pulmonary insufficiency for
12 example. We really don't want to give
13 anesthesia. Patients with morbid obesity, the
14 patient with severe heart failure where just
15 the anesthetic alone may tip them over, I
16 think in that group I would be inclined to go
17 with the Cryo first. If it doesn't work, I
18 can always fall back on RF. So that's the way
19 I would use the equations.

20 It reminds me of the kinds of
21 considerations we had CryoCath was being
22 introduced for --

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1 DR. BAROLD: I don't think we're
2 allowed to talk about another company.

3 DR. SCHEINMAN: Okay.

4 DR. YANCY: Before Dr. Scheinman
5 leaves, were there any patients -- What number
6 of patients fit that profile in the current
7 study?

8 DR. BAROLD: That was an exclusion
9 for --

10 DR. YANCY: Yes, I thought that
11 heart failure/low EF was an exclusion.

12 DR. BAROLD: Right.

13 DR. YANCY: So this is a
14 theoretical.

15 DR. BAROLD: Correct. It wouldn't
16 necessarily pertain to the study population.

17 DR. YANCY: Okay.

18 DR. BAROLD: Correct. But I think
19 that --

20 DR. CALKINS: In terms of the tools
21 we have to ablate atrial flutter, right now we
22 have 8 millimeter RF ablation catheters with

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1 either 60 or 100 watt generators. We have two
2 different types of irrigated catheters and
3 this would be a fourth year tool that's
4 available.

5 I think how it's used is like with
6 the three catheters we have now, the two
7 irrigated catheters and the one, the next
8 several 8 millimeter catheters is that
9 different institutions have different
10 preferences. So one institution may love the
11 8 millimeter catheter, use it for every
12 patient. There was a point that was made
13 earlier that they use it in every patient,
14 whereas another center likes irrigated
15 catheters and another center may say "I prefer
16 Cryo because the efficacy at least from the
17 data we've seen today appears to be
18 equivalent."

19 So you have the Maastricht
20 experience where they use it in 100 percent.
21 You have other centers where it might be more
22 of a niche item where they say, "This patient

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1 I don't want to sedate because of morbid
2 obesity. I would have to use general
3 anesthesia. So I'm going to use Cryo to make
4 it pain free." And then other centers may --
5 so I think there will be a wide range.

6 I mean, part of it is in order to
7 be doing cryoablation you need the console.
8 So there's an initial sort of only centers
9 that have the console will be doing it
10 initially and how they use it, I think, will
11 evolve a little bit over time based on their
12 own experience.

13 But certainly Dr. Wellens'
14 experience certainly speaks to the point that
15 in some centers it's the preferred energy
16 source because it's painless and then there's
17 these theoretical advantages of preserved
18 tissue architecture and no steam pop
19 information and other things like that. But I
20 think different centers will use different
21 tools and it's hard to predict exactly where
22 it will settle in.

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1 CHAIRMAN MAISEL: Adam.

2 DR. LOTTICK: I want to re-raise
3 the acute failure rate with regard to the 30
4 or 60 minute time frame. Because when I
5 looked at the statistically significant
6 reduction in efficacy when the 60 minute
7 waiting period is utilized, you go from a 70
8 percent rate of success to a 95 percent rate
9 of success roughly.

10 Then we use the chronic data to say
11 that that acute difference doesn't matter
12 which makes me if anything call into question
13 the chronic data because if we are going to a
14 modality -- what it looks like is that if you
15 had used -- if you wait an additional 30
16 minutes, you'd see a 25 percent reduction in
17 acute efficacy and yet that doesn't translate
18 into any change in the chronic outcome data.

19 DR. FELD: I'm concerned that this
20 may be a chance for statistical aberration.
21 If you think about it, it doesn't make a lot
22 of sense. If you wait longer to make sure

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1 there's block that you would have, I believe,
2 you said it was less efficacy. In other
3 words, if you wait longer, theoretically you
4 would have better efficacy.

5 DR. LOTTICK: But the problem is if
6 what's happening is that you're failing to
7 achieve block that is going to persist and
8 what you see at 30 minutes is that you have 95
9 percent of patients having block, but then you
10 wait out until 60 minutes and you've now got
11 only 70 percent of those patients having
12 persistent block, then if I would extend that
13 to long term outcomes it would seem to me that
14 what you should see is that there should be a
15 lower rate of -- or a higher rate of
16 recurrence of flutter if you're using a
17 shorter waiting period.

18 DR. FELD: I understand. But we
19 don't see that which make me worry about the
20 chronic data.

21 DR. BAROLD: I think it is a sample
22 size issue. I think it's a statistical issue.

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1 I think we've shown statistically there's no
2 difference. There is a small sample size for
3 60 minutes versus the 30 minutes. There is no
4 statistically significant difference between
5 the chronic effectiveness which is -- I
6 understand the difference in the acute
7 effectiveness. But one would expect a
8 different result in the chronic effectiveness.

9 So I think it's a statistical anomaly.

10 DR. LOTTICK: Yes. Although if the
11 populations had a low recurrence rate of
12 atrial flutter to start with, then you would
13 not see any significant difference in the
14 chronic outcome data.

15 DR. BAROLD: Yes. It's --

16 DR. LOTTICK: But it would --

17 DR. BAROLD: Yes, your point is
18 correct. It's difficult because one piece of
19 information that we don't have is the amount
20 of arrhythmia burden prior to.

21 DR. LOTTICK: Right.

22 DR. BAROLD: And so correct. Yes,

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1 there's really no way to assess that at this
2 point. I think we are left with the
3 statistical analysis that we have.

4 DR. LOTTICK: I don't have any
5 other.

6 DR. ZUCKERMAN: Dr. Maisel, can the
7 FDA respond to that?

8 CHAIRMAN MAISEL: Sure.

9 DR. GOMATAM: Actually, I just
10 wanted to show you some calculations that
11 I've done. We looked poolability and you have
12 that in your panel pack. So when we looked at
13 poolability for acute effectiveness and
14 chronic effectiveness core lab readjudication,
15 we saw no difference between protocols for
16 chronic effectiveness, but we did see a
17 difference for acute effectiveness.

18 But as Dr. Normand pointed out
19 earlier, chronic effectiveness is conditional
20 on acute effectiveness. So this is the
21 original. This is close to what you had in
22 your panel pack. You can see here that this

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1 is significant. It says that acute
2 effectiveness is significantly different
3 across protocols, whereas chronic
4 effectiveness is not and here is the break-up
5 table that I had corresponding to that. So
6 you can see what it looks like, go back up.
7 I'll handle it. You can see how it looks for
8 -- this is across both models for the two
9 protocols. This is A through D and this is E
10 and above.

11 But then I also did unconditional
12 six month analysis. Here you see acute
13 effectiveness is the same and here you see
14 that chronic unconditional six month
15 effectiveness is also different across
16 protocols. And if you look at this break-up
17 table here, you see the differences across.
18 So this is models A through D and that's
19 models E and above.

20 CHAIRMAN MAISEL: We're going to
21 move on. We can discuss this data later if
22 the panel wants to. Adam, did you have any

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1 other questions?

2 DR. LOTTICK: No.

3 CHAIRMAN MAISEL: Okay. Sharon.

4 DR. NORMAND: Thank you and that
5 just reinforces my statement about the need to
6 look at unconditional probabilities. So I'll
7 just say that again. I did have another
8 question of clarification. I think, Dr.
9 Slotwiner, in your summary you had indicated
10 and again I may have misunderstood. So I
11 would like to the sponsor to answer this
12 question. But in your presentation, I think
13 you said that the readjudication was not done
14 on evaluations that were deemed successes by
15 the core lab.

16 DR. SLOTWINER: I believe that was
17 only for the clinical assessments, not for the
18 --

19 DR. NORMAND: Okay. I just wanted
20 to make sure of that because you're getting
21 back and forth on that.

22 So I only have two comments that I

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1 think I would like to make. One is I am a
2 little -- Suppose we remain with the main
3 protocol analyses. I do want to get some
4 sense of the analyses that perhaps either the
5 FDA did or the sponsor did related to handling
6 the missing data and by that I mean that as I
7 mentioned earlier one would not censor missing
8 observations. So I want to get some sense of
9 what your results would be like if you had
10 treated the missing data like one would in a
11 statistically valid manner. In other words,
12 you do have some missing information and
13 either you should have imputed or you should
14 have done some analysis to say something about
15 the sensitivity.

16 Let me tell you what I'm talking
17 about. I'm talking about those that did not
18 hand in the recordings. I think you called
19 them noncompliant. In the language that I
20 use, not that it's right, but noncompliant
21 would really talk about treatment
22 noncompliance. Here we're talking about

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1 collecting outcome data and that's missing
2 data. So I want to get some sense of how that
3 was handled. It looked like you censored it
4 which would not be appropriate.

5 DR. BAROLD: Well, the analysis
6 plan was determined with the FDA and it was
7 felt that censoring was appropriate for the
8 survival analysis because you would censor
9 that patient at the time that they became
10 noncompliant. So this was an analysis plan
11 that we had come up with with them and we
12 haven't heard any issues that that is
13 inappropriate.

14 We did not substitute or impute
15 anything because I don't think that would be
16 an appropriate way for this type of data.

17 DR. NORMAND: Absolutely. You
18 would to go less value carried forward. So I
19 understand it was okay.

20 DR. BAROLD: Yes.

21 DR. NORMAND: But maybe the FDA
22 could answer that. Why would you? Typically,

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1 that's not how we would handle missing data.
2 In an analysis, one wouldn't censor that. So
3 I'm a little perplexed. Again, I'm not --

4 DR. GOMATAM: Well, let me clarify
5 the question first. There are two kinds of
6 censoring. There is the censoring of some
7 event recordings because they were
8 indeterminate and in those cases, those were
9 just dropped and the rest of the event
10 recordings of the patient were considered.
11 And we looked through the eight patients who
12 were censored in our chronic effectiveness
13 analysis.

14 DR. NORMAND: So let's not call
15 them censored just so I understand what we're
16 talking about. So let me tell you what I mean
17 and again, just so everybody is using the same
18 language because I think -- again, it may be
19 me using it wrong but I would rather be clear
20 than not clear.

21 So if you don't have outcome
22 information on somebody.

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1 DR. GOMATAM: Six month outcome you
2 mean.

3 DR. NORMAND: Well, anytime because
4 they use several readings.

5 DR. GOMATAM: Okay.

6 DR. NORMAND: So it's outcome
7 information. Now if somebody died, that's a
8 different animal altogether. One could call
9 it a failure, but maybe you just want to say
10 it's missing. So you censor them. But if you
11 didn't have outcome information in knowing
12 that they were alive, I would claim and I
13 think I'll go out on a limb and say many
14 people that I know would say that's missing
15 data. So --

16 DR. GOMATAM: Right. But there is
17 -- if you recall, patients were allowed to
18 have -- I mean, they were supposed to have a
19 certain number of recordings every week, but
20 they could have a lower number and still be
21 counted as compliant.

22 DR. NORMAND: Having complete data.

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1 DR. GOMATAM: Correct. And so for
2 -- It's my understanding that there were
3 patients for whom event recordings were
4 censored.

5 DR. NORMAND: Meaning that they
6 didn't have the data available.

7 DR. GOMATAM: Well, no. Meaning
8 that Dr. Scheinman looked at it and said it
9 was indeterminate.

10 DR. NORMAND: Oh. So he couldn't
11 make a reading.

12 DR. GOMATAM: Correct.

13 DR. NORMAND: Okay. That's
14 different. Okay.

15 DR. GOMATAM: Right. So those were
16 censored, but if the patient still had enough
17 to make them compliant, then they were in the
18 analysis.

19 DR. NORMAND: Okay. So in other
20 words, no one has done the analysis to look at
21 the real --

22 DR. GOMATAM: Right.

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1 DR. NORMAND: Okay.

2 DR. GOMATAM: And I'm not sure if -
3 - I mean -- As far as I'm aware there were
4 160 patients, 140 of whom had acute
5 effectiveness. As far as I'm aware, none of
6 them had less than the minimum number of event
7 recordings.

8 DR. NORMAND: Good. But I guess
9 it's the one -- Okay.

10 DR. BAROLD: I might be able to
11 clarify this a little bit. In your panel
12 pack, we did give you an outline of the
13 patients that were censored.

14 DR. NORMAND: Okay. And I have
15 that.

16 DR. BAROLD: Right. And so you can
17 see, three patients died, right?

18 DR. NORMAND: Yes.

19 DR. BAROLD: And you can see
20 exactly at the time of when we censored them
21 and if you look at these patients, for
22 example, there's a patient that got censored

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1 at day two because he was noncompliant for one
2 month because he met that noncompliance
3 definition, but then became compliant again.
4 We read those event recordings and he, in
5 fact, had no flutter, but we still censored
6 him at day two. So we took the hit for that.

7 DR. NORMAND: I understand.

8 DR. BAROLD: But we did -- For
9 clarification the censor patients are in
10 there.

11 DR. NORMAND: Yes. Thank you. So
12 from my colleagues on the panel, you probably
13 understand where I'm coming from. It's almost
14 like we have a repeated measure study where
15 we're collecting repeated measures from
16 everybody and not everybody handed in the
17 information that we're supposed to hand in.
18 It's not typical, I would argue, that you say
19 we'll only take six out of -- If they have at
20 least six of the seven measures, we'll include
21 them. That's a real problem at least from a
22 statistical standpoint.

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1 I mean, I'm aware of the
2 practicalities of the real world. I
3 understand that, but there are statistical
4 methods to deal with those types of problems.

5 So that's where my question is coming from.
6 So that would actually induce more uncertainty
7 in the estimate of your chronic effectiveness
8 endpoint which would make the confidence
9 intervals a little bit wider from my, at
10 least, statistical standpoint.

11 I think that's all I really had to
12 ask in terms of a question. The one other
13 point, I know we were talking a little bit
14 about other locations in the panel pack. I
15 just want again -- it's another point of
16 clarification and I think it's in the SSED
17 summary by the sponsor where they describe the
18 design. They say that each subject served as
19 his or her own control and you're not using
20 the data that way at all and it's just I would
21 tighten that up. You're just using an
22 observational study and it's not quasi-

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1 experimental and you sound like you have a
2 stronger design than you really do. You do.
3 You just didn't use it. So I don't have any
4 more.

5 CHAIRMAN MAISEL: Okay. Thanks,
6 Sharon. David.

7 DR. MILAN: No questions.

8 CHAIRMAN MAISEL: Linda.

9 MS. MOTTLE: No.

10 CHAIRMAN MAISEL: Marcia.

11 DR. YAROSS: Nothing at the time.

12 CHAIRMAN MAISEL: Okay. I just
13 have a couple of points of clarification.
14 Just as far as if we're trying to tell
15 physicians how to use this catheter, what do
16 you tell them regarding the duration of a
17 freeze? I realize they were somewhat variable
18 and you gave us means and ranges. But what
19 are the instructions for the physician who is
20 using the catheter?

21 DR. BAROLD: We currently recommend
22 two minutes at this time. We have some

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1 preclinical data of which we are also doing
2 some additional data to show that actually
3 your lesion size is created at 30 seconds.
4 But we're just a little uncomfortable with
5 that. So we prefer to have a little bit of a
6 bounds. So we do recommend two minutes at
7 this point and then we recommend that the
8 catheter then gets up to a certain level
9 before it's moved. So we have formal
10 recommendations for that.

11 CHAIRMAN MAISEL: Great. Thank
12 you. Nobody had asked about the one catheter
13 that had a defect during the procedure and I
14 think I noted somewhere that the OUS
15 experience that there was a device that was
16 recalled from the European market. Is that
17 accurate and, if so, what are the issues there
18 and how have they been resolved?

19 DR. BAROLD: So it turns out it
20 wasn't a catheter. I was mistaken. It was a
21 console problem. We did have a few issues
22 with something called nitrous plugging that

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1 has been resolved. In fact, we've had
2 numerous discussions with the FDA about this
3 to assure that it's been resolved. So it was
4 a console issue.

5 CHAIRMAN MAISEL: Can you enlighten
6 the panel a little bit more?

7 DR. BAROLD: Basically, what
8 happened was that the, I don't need a slide
9 for this, device was, the console was, unable
10 to power up. It would get device failures on
11 there and it was due to a plug of nitrogen,
12 nitrous oxide. So we were unable to deliver
13 nitrous oxide to and from the catheter.

14 This has been resolved with some
15 software changes. So it's no longer an issue.

16 But there were some issues with that
17 initially.

18 CHAIRMAN MAISEL: So meaning "no
19 longer an issue," you had a bunch and some
20 change was made and it hasn't been seen since.

21 DR. BAROLD: It hasn't happened.
22 We haven't had it --

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1 CHAIRMAN MAISEL: How much
2 experience do we have post change?

3 DR. BAROLD: A couple of years and
4 remember, we're running a second trial and we
5 haven't had problems with it.

6 CHAIRMAN MAISEL: Okay.

7 DR. BAROLD: And the FDA did go
8 through this with us and asked all the
9 appropriate questions and have resolved.
10 We've resolved it and fixed the problem. We
11 haven't seen it in a long time.

12 CHAIRMAN MAISEL: And was that the
13 same reason for the recall in Europe?

14 DR. BAROLD: I'm not sure what the
15 -- I can't answer that one.

16 MR. BRENNAN: The event that
17 occurred, we had changed manufacturing
18 processes for the catheter and made a subtle
19 design change in terms of how the connections
20 occurred between the catheter shaft and the
21 articulation section of the catheter. Around
22 that time, we had an adverse event where

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1 apparently the physician trapped the end of
2 the catheter in the sheath and applied too
3 much torque and actually tore the catheter at
4 the intersection of that piece. We could
5 never document that that wasn't related to
6 that particular connection and since we were
7 in the process of changing how that connection
8 was manufactured rather than trying to figure
9 out whether the -- I think we were down to
10 something like 70 catheters still in the
11 European market. Rather than trying to figure
12 out whether we should leave them on and
13 document this particular event, we just took
14 them off and replaced them so that was it.

15 CHAIRMAN MAISEL: So that was the
16 earlier model, the 1100, or equivalent?

17 MR. BRENNAN: No, it was actually a
18 particular model of the 1200 at the time.

19 CHAIRMAN MAISEL: And any bench
20 testing that you've done to evaluate that and
21 can you reproduce the problem and how have you
22 remedied?

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1 MR. BRENNAN: Yes. We have not
2 been able to reproduce the problem in terms of
3 that particular catheter. We can tell you
4 that when you torque the catheter and trap the
5 tip it will tear at that particular junction.

6 But we have provided all of that information
7 on the previous models and every change to
8 FDA.

9 CHAIRMAN MAISEL: Maybe I can ask
10 the FDA to comment. Do you have any
11 outstanding issues regarding the device or
12 catheter performance based on the changes that
13 have been made in the adverse event or device
14 problem history?

15 DR. ZUCKERMAN: Before we do, could
16 you just identify yourself for the record and
17 for the panel?

18 MR. BRENNAN: I am Ed Brennan. I'm
19 CEO and President of the company and I do have
20 a financial interest in the company.

21 (Laughter.)

22 CHAIRMAN MAISEL: Just for clarity.

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1 So Dr. Faris or someone can comment on that.

2 DR. FARIS: I'll speak for the
3 review team. With regard to the event in
4 Europe, that was conducted by an earlier group
5 at FDA but we do have any outstanding
6 engineering concerns. Regarding the nitrous
7 plug issue that Dr. Barold raised, we had
8 extensive fairly recent conversation with the
9 company. Our understanding from that
10 conversation was that that was largely due to
11 a nitrous oxide supplier issue and that they
12 have put, the company has installed, methods
13 for verifying that that will not occur again.

14 DR. LOTTICK: I'm sorry. A nitrous
15 oxide, how does nitrous oxide plug? An
16 impurity in the nitrous oxide?

17 DR. FARIS: I believe it was water.
18 Yes.

19 DR. LOTTICK: That's a common
20 issue.

21 DR. FARIS: Yes. That's right.

22 CHAIRMAN MAISEL: Thank you. I

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1 have no further comments at this time. What I
2 would like to do now is move onto the
3 questions for the panel. So maybe we can put
4 those up. You have questions in your packet.
5 You can pull those out. We'll go through
6 them one by one and discuss them.

7 I will try to summarize issues if
8 we've had extensive discussion about them
9 already so that we don't have to rehash a lot
10 of things. But some things we haven't really
11 discussed in detail such as the first question
12 which is safety. It says, "The seven-day
13 serious adverse event rate in the pivotal
14 study was 5.6 percent with a 95 percent upper
15 confidence bound of 9.6 percent. The pre-
16 specified was 2.5 percent with an upper
17 confidence bound of 7.0 percent. Please
18 discuss whether the safety results demonstrate
19 that there is a reasonable assurance that the
20 device is safe for the treatment of isthmus-
21 dependent atrial flutter.

22 We've heard clarification that the

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1 OPC relates to all safety events and not just
2 device and procedure related. So maybe we
3 could hear from the panel members about what
4 is the appropriate numbers that we should be
5 looking at. Does this device seem safe to you
6 even though it doesn't make the OPC? Who
7 would like to start that? Dr. Milan?

8 DR. MILAN: Well, I have to tell
9 you, I mean, just looking at the data that I'm
10 not overly concerned about the safety of this
11 device. I think that the majority of the
12 adverse events were not device or procedure
13 related and I think that probably that's a
14 more reliable measure of the device's safety.

15 So I don't personally have a lot of concerns
16 about the safety of this device.

17 CHAIRMAN MAISEL: Dr. Somberg.

18 DR. SOMBERG: I agree with that but
19 I would have concerns if the same level of
20 information provided to the investigators was
21 not applied to the general users, clinical
22 users, of this device and therefore, I think

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1 that the company really has to develop a
2 comprehensive, think it out, thought-out
3 training program, not necessarily one we have
4 to go to CryoRelation University, but one
5 where there is information from the supplier
6 to using this console to using this catheters,
7 to "don't get frustrated and get cord in a
8 sheath and pull it out because you can tear it
9 and will tear it at this point" because that's
10 what we just heard.

11 So I mean, there are certain --
12 Like everything else, there are certain tricks
13 to the trade and I think we're going to see or
14 you will see an exponential series of problems
15 if there's not some sort of training and
16 remember you're investigators. You're
17 usually at a much higher level than all comers
18 in terms of use.

19 CHAIRMAN MAISEL: Sharon.

20 DR. NORMAND: I just would like my
21 clinical colleagues to convince me as to why
22 we have a pre-specified value of 2.5. It's

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1 twice that. It's old data. That is the OPC.
2 Tell me where my thinking is wrong please.
3 But I would think that things should get safer
4 as time goes on. And so tell me why there's
5 no concern when I see a rate that is twice
6 that from the OPC and again extrapolating
7 which maybe we shouldn't do, but we're doing a
8 lot of making up things right now. But if I
9 was to extrapolate to today, I don't know if I
10 should say the OPC today would be one percent
11 and that we have 5.6. So I would like some
12 discussion as to why there is no concerns with
13 safety.

14 CHAIRMAN MAISEL: Dr. Yancy.

15 DR. YANCY: I actually would like
16 to support and second Dr. Lise Normand's
17 concern because the queries before lunch
18 demonstrated no new information to suggest
19 that the actual numbers are any better than
20 the existing objective performance criteria
21 and we do have issues of concern that are
22 twofold higher and if we're going to have a

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1 level playing field as we talked about before
2 to go this much beyond the upper bound of the
3 confidence interval I think is a concern. And
4 so practically speaking, I share the statement
5 that I don't have a great amount of clinical
6 discomfort with what I see when I look at the
7 events enumerated, but with respect to the
8 process, this is a concern.

9 CHAIRMAN MAISEL: Norm.

10 DR. KATO: I guess I have two
11 concerns. No. 1, and this is not in any
12 particular order, I do share Dr. Normand's
13 comment about the fact that the safety results
14 are twofold worse and along with Dr. Yancy. I
15 guess the problem is that already if we say
16 that we're not concerned about it, then we now
17 are basically throwing out the OPC comparison
18 completely and then we can make any other
19 determination we want as far as efficacy goes.

20 So I think that is kind of taking us down a
21 slippery slope that we don't want to go down.

22 Now one other comment based on, I

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1 forget who mentioned this today, but I think
2 most EP physicians would say that atrial
3 flutter is not a life-threatening -- under
4 certain circumstances is a life-threatening
5 event, but most of the time it isn't. So in
6 that situation, I would default to the device
7 if this is going to be primary therapy of
8 doing no harm. So to me two, two and a half
9 times complication rate in a situation where
10 the disease is not life-threatening is a
11 problem.

12 CHAIRMAN MAISEL: Just to comment
13 on your life-threatening comment, there are
14 life-threatening complications of the
15 medications we choose to treat atrial flutter
16 such as anti-arrhythmia drugs which have a
17 risk of life-threatening proarrhythmia and
18 anticoagulation that may be affected by
19 elimination of atrial flutter which we know
20 all about the bleeds and deaths associated
21 with that. So I'm not disagreeing with what
22 you say, but just adding a little clinical

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1 perspective.

2 DR. KATO: You know, and you're
3 absolutely right about those complications.
4 However, these are complications which occur
5 within a small time frame within seven days of
6 an index event. The other events that you're
7 talking which I don't deny are true, but those
8 happen. I mean, there's no real predictive
9 time when they will occur. You say, "Well,
10 they're going to randomly occur over some
11 future time frame." But these occur within
12 seven days of the event. So there is
13 definitely a cause and effect here.

14 CHAIRMAN MAISEL: Much like the
15 benefit of CABG may not be realized for many
16 weeks or months after an up front mortality
17 risk from the surgery. John.

18 DR. SOMBERG: Sharon, I'm the
19 person who concurred with my other colleague,
20 of course, seated next to you there that from
21 a clinical standpoint I did not see a problem
22 and I'll tell you why. Because one is that

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1 most of the, in fact, almost all of the
2 adversities are not related per se to the
3 device. If you just measure outcomes on
4 people bad things happen and unfortunately I
5 think that's what we see here and I don't
6 think setting some sort of performance
7 standard for a device on unrelated device
8 activities when we're dealing with terribly
9 small sample sizes is a very effective way of
10 going about doing it.

11 So if I saw where we had two high
12 perforations, two hemopericardiums, four
13 exsanguinations due to getting caught at the
14 introducer site and all that, then I would say
15 "Wow. This is something that's really a
16 problem here." But when you start counting
17 the things that are by any stretch of the
18 imagination can't relate to the procedure and
19 the device, you get into a very difficult
20 situation.

21 I'm not one who supports this idea
22 of performance standards and especially

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1 something that's developed in '98 and then
2 comparing to 2007. But I don't think it's
3 correct also to say "Hey, things should just
4 get better. So we should go from 2.5 to 1.0."

5 That would be true if there were
6 1,000 patients in this study and we saw a 5.7
7 percent serious adversity and before we had
8 1,000 patients and it was 2.5, then we would
9 have to start scratching our heads and say
10 "Maybe there's some sort of correlation here."

11 But based on 140 patients, very hard to --

12 DR. NORMAND: But I think that the
13 issue that we're facing right now is you're
14 looking at this data in isolation. Right?
15 There is no control group. We have no
16 concurrent control group. So let's remember
17 that. The only thing we can look at is the
18 2.5 percent. That is what we have right here
19 that these pre-specified number was 2.5 in
20 absence of a control group.

21 DR. SOMBERG: Bt the only thing you
22 can -- You said the only thing you can look is

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1 the 2.5 percent. No, I can look one step
2 beyond that. I look at what that 2.5 percent
3 is and that's what we have done and that's why
4 I'm telling you. My explanation of why I said
5 that is I looked at it and if it was possibly
6 related to the catheter then I would be
7 concerned. When it's really almost
8 improbable, then I'm not. That's the
9 difference. I mean, I can only tell you why I
10 said what I said.

11 DR. NORMAND: Thank you.

12 CHAIRMAN MAISEL: Dr. Zuckerman,
13 settle this argument.

14 DR. ZUCKERMAN: Yes. Let me try to
15 propose a pathway for it. The first thing is
16 I think throughout this discussion we've noted
17 some problems with the methodology associated
18 with the OPCs and there are problems with the
19 safety of OPC that we've noted for multiple
20 years because it is a composite safety
21 endpoint.

22 That being said, the agency never

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1 takes safety lightly and I don't want to give
2 that impression. Instead what we do is we
3 routinely look at each of the events for this
4 composite safety OPC and Dr. Normand has asked
5 a very good question. Convince her
6 electrophysiologist that some of these events
7 like hyperthyroidism are questionable. So
8 maybe if Dr. Milan can revisit that by
9 specifically looking at slide 32, we can quell
10 some of the confusion here, FDA slide 32.

11 DR. MILAN: On page 11. Right. So
12 going through these myself, I have to say
13 these serious adverse events like atrial
14 flutter, now there was something that came up
15 in the meeting. But when I was looking
16 through the packet, it wasn't clear to me why
17 atrial flutter should count as a failed
18 ablation procedure and as an adverse event if
19 I make myself clear about that. Is that
20 right?

21 So then sick sinus syndrome, I
22 mean, this is a disease of the sinus node that

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1 may be an apparent prior to ablation and then
2 after you get rid of the atrial flutter, there
3 seems to be that bradycardia requires
4 treatment. It doesn't matter how you get rid
5 of the flutter, you're going to have the same
6 disease in the sinus node.

7 The acute respiratory failure, I
8 think, is counted as a procedure related
9 event. At least, I would count it as a
10 procedure related event. Atrial fibrillation,
11 this is a puzzle to me. We've heard so much
12 today about how atrial fibrillation goes hand
13 and hand with atrial flutter. Yet there's
14 only one, I guess, within seven days. But
15 anyway, the atrial fibrillation going hand in
16 hand with atrial flutter, it's not a
17 surprising event and again I think you
18 wouldn't be surprised to see the atrial
19 fibrillation after a radiofrequency ablation
20 or even cardiac version of atrial flutter. Go
21 ahead.

22 DR. NORMAND: But I was going to

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1 say don't forget we have to say relative to.
2 You're saying that these -- I need the
3 comparison. So you're saying that you're not
4 surprised that you see it.

5 DR. MILAN: Yes.

6 DR. NORMAND: But I want to know
7 you're not surprised to see it relative to
8 something else.

9 DR. MILAN: Right. So what I'm
10 saying is atrial fibrillation/sick sinus
11 syndrome, I would even go as far as saying
12 this patient regardless of what type of
13 radiofrequency, what type of ablation, I mean,
14 my guess is they would have had it. I mean,
15 certainly the sick sinus syndrome/atrial
16 fibrillation you could debate about it.

17 DR. DOMANSKI: Yes. You know, it's
18 not entirely clear to me why you're so sure
19 that's true. Because I mean sick sinus
20 syndrome covers a fair number of different
21 things.

22 DR. MILAN: Sure.

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