

UNITED STATES OF AMERICA
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH
CIRCULATORY SYSTEM DEVICES ADVISORY PANEL

+ + + + +

MEETING

+ + + + +

WEDNESDAY,
JUNE 27, 2007

+ + + + +

The meeting came to order at 8:00 a.m., in the Hilton Washington, D.C., North, Perry Parkway, Gaithersburg, Maryland, Dr. William H. Maisel, Chairman, presiding.

PRESENT:

- WILLIAM H. MAISEL, MD, MPH, Chairman
- SHARON-LISE NORMAND, PHD, Member
- JOHN SOMBERG, MD, Member
- CLYDE YANCY, MD, Member
- JEFFREY A. BRINKER, MD, Consultant
- MICHAEL J. DOMANSKI, MD, Consultant
- PAMELA KARASIK, MD, Consultant
- NORMAN S. KATO, Consultant
- ADAM LOTTICK, MD, Consultant
- DAVID MILAN, MD, Consultant
- DAVID SLOTWINER, MD, Consultant
- MARCIA S. YAROSS, PHD, Industry Representative
- LINDA MOTTLE, MSM, R, Consumer Representative
- BRAM ZUCKERMAN, MD, FDA Representative
- JAMES P. SWINK, Executive Secretary

Formatted: French (France)

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A-G-E-N-D-A

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1 P-R-O-C-E-E-D-I-N-G-S

2 (8:03 a.m.)

3 CHAIRMAN MAISEL: Good morning. I
4 would like to call this meeting of the
5 Circulatory System Devices Panel to order.

6 I'm Dr. William Maisel. I have the
7 privilege of chairing this panel. If you
8 haven't already done so, please sign the
9 attendance sheets that are on the tables by
10 the doors. If you wish to address this panel
11 during one of the open sessions today, please
12 provide your name to Ms. Ann Marie Williams at
13 the registration table.

14 If you are presenting in any of the
15 open public sessions today, and have not
16 previously provided an electronic copy of your
17 presentation to FDA, please arrange to do so
18 with Ms. Williams.

19 I note for the record that the
20 voting members present constitute a quorum, as
21 required by 21 CFR Part 14. I would also like
22 to add that the panel participating in the

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1 meeting today has received training in FDA
2 device law and regulations.

3 I'd like to ask people in
4 attendance today to please put their cell
5 phones on vibrate or turn them off.

6 And at this point, I'd like to
7 introduce the Executive Secretary of the
8 Circulatory System Devices Panel, Mr. Swink,
9 who will make some introductory remarks.

10 EXECUTIVE SECRETARY SWINK: Before
11 I read the conflict of interest statement, I'd
12 like to turn the floor over to Bram Zuckerman
13 who has a few announcements.

14 DR. ZUCKERMAN: Good morning, panel
15 members. I'm Bram Zuckerman, Director,
16 Division of Cardiovascular Devices. Before we
17 get into the review of this morning's PMA,
18 we'd like to do some housekeeping work to
19 honor two extremely valued panel members.

20 As you know, the work that you do
21 on this panel is extremely important to the
22 FDA and the public at large. Today we have

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1 several key voting members whose panel this
2 will be the last.

3 While Commissioner Von Eschenbach
4 was not able to personally congratulate you on
5 your distinguished public service, he has
6 enclosed two letters that I'd like to read
7 into the public record recognizing your
8 extremely valuable public service.

9 The first letter is addressed to
10 our panel statistician, Dr. Sharon-Lise
11 Normand. "Dear Dr. Normand: I would like to
12 express my deepest appreciation for your
13 efforts and guidance during your term as a
14 member of the Circulatory System Devices Panel
15 of the Medical Devices Advisory Committee.

16 "The success of this committee's
17 work reinforces our conviction that
18 responsible regulation of consumer products
19 depends greatly on the experience, knowledge,
20 and varied backgrounds and viewpoints that are
21 represented on the committee.

22 "In recognition of your

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1 distinguished service to the Food and Drug
2 Administration, I am pleased to present you
3 with the enclosed plaque."

4 And as Dr. Von Eschenbach's
5 surrogate -- a term appropriate for
6 statisticians --

7 (Laughter.)

8 -- I give you your plaque.
9 Congratulations.

10 (Applause.)

11 Also, today will be Dr. William
12 Maisel's last appearance as our panel chair.
13 It's hard to imagine that five years has gone
14 by so quickly with Dr. Maisel's distinguished
15 service, and it has really been a pleasure to
16 work with him.

17 Dr. Von Eschenbach writes the
18 following. "Dear Dr. Maisel: I would like to
19 express my deepest appreciation for your
20 efforts and guidance during your term as a
21 member and chair of the Circulatory System
22 Devices Panel of the Medical Devices Advisory

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1 Committee.

2 "The success of this committee's
3 work reinforces our conviction that
4 responsible regulation of consumer products
5 depends greatly on the experience, knowledge,
6 and varied backgrounds and viewpoints that are
7 represented on the committee.

8 "In recognition of your
9 distinguished service to the Food and Drug
10 Administration, I am pleased to present you
11 with the enclosed plaque."

12 And, again, as Dr. Von Eschenbach's
13 representative, I'm pleased to congratulate
14 Dr. Maisel.

15 (Applause.)

16 Okay. And now we'll proceed with
17 the regular panel meeting.

18 CHAIRMAN MAISEL: Thanks, Dr.
19 Zuckerman.

20 Mr. Swink?

21 EXECUTIVE SECRETARY SWINK: I note
22 for the record that our press contact today is

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1 Kris Mejia.

2 I will now read into the record the
3 conflict of interest statement. "The Food and
4 Drug Administration is convening today's
5 meeting of the Circulatory System Devices
6 Panel of the Medical Devices Advisory
7 Committee of the Center for Devices and
8 Radiological Health under the authority of the
9 Federal Advisory Committee Act of 1972.

10 "With the exception of the industry
11 representative, all members and consultants of
12 the panel are special government employees or
13 regular federal employees from other agencies
14 and are subject to federal conflict of
15 interest laws and regulations.

16 "The following information on the
17 status of the panel's compliance with federal
18 ethics and conflict of interest laws covered
19 by, but not limited to, those found at 18
20 U.S.C. Section 208 are being provided to
21 participants in today's meeting and to the
22 public.

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1 "FDA has determined that the
2 members and consultants of this panel are in
3 compliance with the federal ethics and
4 conflict of interest laws under 18 U.S.C.
5 Section 208. Congress has authorized FDA to
6 grant waivers to special government employees
7 who have financial conflicts when it is
8 determined that the agency's need for that
9 particular individual's services outweighs his
10 or her potential financial conflict of
11 interest.

12 "Related to the discussions of
13 today's meetings, members and consultants of
14 this panel who are SGEs have been screened for
15 potential financial conflicts of interest of
16 their own, as well as those imputed to them,
17 including those of their employer, spouse, or
18 minor child. These interests may include
19 investments, consulting, expert witness
20 testimony, contracts, grants, CRADAs,
21 teaching, speaking, writing, patents and
22 royalties, and primary employment.

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1 "Today's agenda involves the review
2 and discussion of the premarket approval
3 application sponsored by CryoCor Incorporated
4 for the CryoCor Cryoablation System, which is
5 intended for the treatment of isthmus-
6 dependent atrial flutter in patients 18 years
7 of age or older.

8 "Based on the agenda for today's
9 meeting and all financial interests reported
10 by the panel members and consultants, no
11 conflict of interest waivers have been issued
12 in connection with this meeting.

13 "A copy of this statement will be
14 available for review at the registration table
15 during this meeting and will be included as
16 part of the official transcript.

17 "Marcia S. Yaross, Ph.D., is
18 serving as the industry representative, acting
19 on behalf of all related industry and is
20 employed by Biosense Webster, a Johnson &
21 Johnson company.

22 "We would like to remind members

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1 and consultants that if the discussions
2 involve any other products or firms not
3 already on the agenda, or if an FDA
4 participant has a personal or imputed
5 financial interest, the participants need to
6 exclude themselves from such involvement and
7 their exclusions will be noted for the record.

8 "FDA encourages all other
9 participants to advise the panel of any
10 financial relationships that they may have
11 with any firms at issue."

12 I will now read the appointment of
13 temporary voting member statement. "Pursuant
14 to the authority granted under the Medical
15 Devices Advisory Committee charter dated
16 October 27, 1990, and amended August 18, 2006,
17 I appoint the following as voting members of
18 the Circulatory System Devices Panel for the
19 duration of this meeting on June 27, 2007.
20 Dr. David J. Milan, Cardiac Electrophysiology;
21 Dr. Pamela Karasik, Cardiac Electrophysiology;
22 Dr. Norman Kato, Cardiovascular Disease,

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1 Surgery, and Valve Replacements; Dr. Adam
2 Lottick, Clinical Electrophysiology; Dr.
3 Jeffrey A. Brinker, Interventional Cardiology;
4 Dr. Michael Domanski, Clinical Cardiology; Dr.
5 David Slotwiner, Cardiac Electrophysiology.

6 "For the record, these people are
7 special government employees and are
8 consultants to this panel or another panel
9 under the Medical Device Advisory Committee.
10 They have undergone the customary conflict of
11 interest review and have reviewed material to
12 be considered at this meeting."

13 This was signed by Daniel G.
14 Schultz, M.D., Director, Center for Devices
15 and Radiological Health, and dated June 4,
16 2007.

17 CHAIRMAN MAISEL: Thank you.

18 Today this panel will be making a
19 recommendation to the Food and Drug
20 Administration on the premarket approval
21 application P050024 for the CryoCor
22 Cryoablation System. The CryoCor Cryoablation

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1 System is intended for ablation of isthmus-
2 dependent atrial flutter in patients 18 years
3 of age or older.

4 Before we begin our presentations
5 today, I'd like to ask our panel members to
6 introduce themselves. Once again, my name is
7 William Maisel. I'm a Cardiac
8 Electrophysiologist from Beth Israel Deaconess
9 Medical Center. And we'll start on my left.

10 Before we go around, I'll remind
11 the panel members, or tell the panel members,
12 we can only have four microphones on at a
13 time. So don't turn your microphone on until
14 you're speaking, and please turn it off when
15 you're done.

16 DR. ZUCKERMAN: Bram Zuckerman,
17 Director, FDA, Division of Cardiovascular
18 Devices.

19 DR. DOMANSKI: I'm Mike Domanski.
20 I'm Chief of the Atherothrombosis and Coronary
21 Artery Disease Branch at the National Heart,
22 Lung, and Blood Institute.

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1 DR. BRINKER: Jeff Brinker,
2 Professor of Medicine and Radiology, Johns
3 Hopkins University.

4 DR. SOMBERG: John Somberg,
5 Professor of Medicine and Pharmacology, Rush
6 University.

7 DR. KARASIK: Pamela Karasik,
8 Assistant Chief of Cardiology at the VA
9 Medical Center in Washington.

10 DR. KATO: Norman Kato,
11 Cardiothoracic Surgery, private practice, Los
12 Angeles, California.

13 EXECUTIVE SECRETARY SWINK: James
14 Swink, Executive Secretary.

15 DR. YANCY: Clyde Yancy, Medical
16 Director, Baylor Heart and Vascular Institute,
17 Baylor University Medical Center in Dallas,
18 Texas. Area of expertise is heart failure.

19 DR. LOTTICK: Adam Lottick,
20 Clinical Electrophysiology, St. Vincent's
21 Hospital, Connecticut.

22 DR. SLOTWINER: David Slotwiner,

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1 Clinical Electrophysiologist, Assistant
2 Professor, Albert Einstein College of
3 Medicine.

4 DR. NORMAND: I'm Sharon-Lise
5 Normand, and I'm a Professor of Health Care
6 Policy and Professor of Biostatistics in
7 Harvard Medical School and Harvard School of
8 Public Health.

9 DR. MILAN: David Milan, Cardiac
10 Electrophysiologist from Massachusetts General
11 Hospital.

12 MS. MOTTLE: Linda Mottle, Director
13 of the Center for Health Care Innovation and
14 Clinical Trials, and Director of the Graduate
15 Clinical Research Programs at Arizona State.

16 DR. YAROSS: Marcia Yaross, Vice
17 President, Clinical Quality Regulatory and
18 Health Policy at Biosense Webster in Diamond
19 Bar, California.

20 CHAIRMAN MAISEL: Thank you.

21 We'll now proceed with the open
22 public hearing portion of the meeting. Prior

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1 to the meeting, no one requested to speak in
2 the open public hearing. Is there anyone who
3 would like to approach and address the panel
4 this morning? There will be a second session
5 this afternoon.

6 (No response.)

7 Seeing no one, we will close the
8 open public hearing and proceed with the
9 business portion of our meeting. At this
10 point, we'll proceed with the sponsor
11 presentation from the CryoCor -- for the
12 CryoCor Cryoablation System.

13 Once again, I'd like to remind
14 public observers that, while the meeting is
15 open, public attendees may not participate
16 except at the specific request of the panel.
17 The sponsor will have 90 minutes. We don't
18 have a timer, but I'll give you a warning when
19 there's about 10 minutes left.

20 DR. BAROLD: Thank you. Good
21 morning, ladies and gentlemen. First of all,
22 I would like to thank all of the panel members

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1 for coming today and helping us with this. My
2 name is Helen Barold, and I am the Chief
3 Medical Officer for CryoCor and an employee of
4 the company.

5 At this time, I'd also like to
6 thank the FDA review team for taking the time
7 to help us with the panel presentation and
8 this whole process.

9 The device that we'll be talking
10 about today is the CryoCor Cryoablator --
11 Cryoablation catheter and its console. The
12 intended use for the CryoCor Cryoablation
13 System is in the treatment of isthmus-
14 dependent atrial flutter in patients 18 years
15 of age or older.

16 This file has -- this slide
17 illustrates the file's regulatory history.
18 Dr. Faris from the FDA will be presenting the
19 history in detail.

20 Today our experts will be providing
21 you with data to support approval of this
22 file. We will be going through some

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1 preclinical data that will establish that the
2 lesions made by the CryoCor catheter are as
3 large as radio frequency, so, therefore,
4 should be able to adequately treat atrial
5 flutter.

6 We will demonstrate the results of
7 our U.S. pivotal trial. We will provide you
8 with a second clinical trial to confirm the
9 results of our pivotal trial. And in addition
10 to that, we will provide you with some
11 published literature which demonstrates the
12 unique clinical advantage of cryoablation over
13 radio frequency.

14 As you know today, all we need to
15 do is establish a reasonable level of safety
16 and effectiveness. And I believe that the
17 data that we will provide today will provide a
18 reasonable assurance of safety and
19 effectiveness for the CryoCor device.

20 Thank you.

21 MR. RYBA: Good morning. My name
22 is Eric Ryba. I am the Director of

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1 Intellectual Property for CryoCor and a
2 stockholder in the company. I will be
3 providing a brief overview of the CryoCor
4 system.

5 This slide shows the CryoCor
6 system, both the console and the catheter.
7 Cryoablation is the use of extreme cold to
8 ablate tissue and is performed through the
9 controlled delivery of nitrous oxide to the
10 tip of a catheter to produce temperatures of
11 minus 85 to 90 degrees Celsius in a reliable
12 and consistent manner.

13 In the system shown here, the
14 console houses the nitrous oxide supply in
15 addition to the microprocessor-controlled
16 nitrous delivery, precooling, and vacuum
17 subsystems.

18 A key to the system's performance
19 is in the patented precooler, which cools the
20 gaseous nitrous oxide to approximately minus
21 30 degrees Celsius -- a temperature that
22 condenses the gas to a liquid just prior to

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1 its entering a catheter.

2 A patented capillary tube at the
3 end of the nitrous supply line in the tip of
4 the catheter impedes fluid flow, ensuring
5 delivery of a liquid nitrous oxide. As the
6 liquid enters the tip, it results in a
7 pressure drop to approximately one atmosphere,
8 and at this pressure the nitrous oxide
9 immediately boils, achieving a temperature of
10 minus 85 to 90 degrees Celsius.

11 The catheter manipulates by
12 commercially-available radio frequency
13 catheters with a similar handling tip. It is
14 10 French and has a 6.5 millimeter tip
15 electrode. This slide shows the element of
16 the catheter in greater detail.

17 Shown here are the basic elements
18 at the catheter tip. The nitrous travels to
19 the tip through the high pressure supply tube
20 which ends within the larger volume of the tip
21 boiling chamber where it expands and rapidly
22 cools. The cryo-lesion will be formed where

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1 the tip is in contact with tissue.

2 In order to control the flow of
3 nitrous oxide and the boiling in the tip, the
4 nitrous gas is drawn from the catheter by the
5 vacuum recovery pump. Thus, the system
6 provides for the controlled boiling of the
7 nitrous oxide, which results in stable
8 temperatures through the controlled flow in
9 tube catheter tip and consistent evacuation of
10 the spent gas.

11 This graph shows a typical catheter
12 tip temperature profile as a function of time
13 during an ablation. From the graph, you can
14 see how quickly the maximum cold temperature
15 is achieved. Nitrous oxide flow begins after
16 the catheter is first evacuated shown here at
17 four seconds. Cooling then begins with
18 seconds when the catheter tip reaches minus 30
19 degrees C shown at nine seconds, and the
20 ablation timer begins.

21 The ablation will continue until
22 the timer counts down to zero or the user

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1 stops it. Ablations as long as 10 minutes can
2 be performed, but traditionally operators
3 choose one- to two-minute durations. Once the
4 timer stops, the catheter tip and frozen
5 tissue rapidly warms and a catheter can be
6 moved.

7 For comparison purposes, this slide
8 illustrates what is commonly commercially
9 available and how the CryoCor catheter
10 compares. As you can see, the surface area of
11 the electrode is roughly equivalent to an 8
12 French, 8 millimeter tip catheter similar to
13 the ones that are used currently to treat
14 atrial flutter.

15 Also for comparison purposes, this
16 slide illustrates the difference between our
17 catheter and the cryoablation catheter that is
18 commercially available in the U.S. As you can
19 see, our catheter, because of its larger tip
20 size and diameter, has the ability to deliver
21 significantly more power.

22 DR. FELD: Good morning, ladies and

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1 gentlemen. My name is Gregory Feld. I'm a
2 Professor of Medicine and Director of the
3 Cardiac Electrophysiology Program at
4 University of California-San Diego. I was the
5 principal investigator for this study. I'm a
6 member of the Scientific Advisory Board of
7 CryoCor and a stock option shareholder.

8 I'm going to present some
9 preclinical data today. Cryoablation was used
10 extensively in the '70s for surgery, and as a
11 result we have a large volume of published
12 literature characterizing cryoablation. We
13 also have a fair amount of literature in
14 recent years on catheter cryoablation as well,
15 proving that this technique is safe, it
16 preserves the tissue architecture which is
17 important to maintaining good tensile strength
18 of the myocardium, reducing risk of
19 perforation.

20 There is a limited risk of
21 thrombosis. We do not see steam pops with
22 cryoablation. The lesion is clearly

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1 demarcated and homogeneous. And a number of
2 studies now, both preclinical and clinical,
3 have shown that there is no pulmonary vein
4 stenosis associated with cryoablation or
5 atrio-esophageal fistulas, which have been
6 seen with radio frequency. And there appears
7 to be less pain associated with the use of
8 cryoablation.

9 The primary mechanisms of cell
10 injury with cryoablation begin with an ice
11 ball forming at the tip of the catheter or
12 along any defined ablation surface. And the
13 cells within this ice ball are irreversibly
14 damaged and eventually replaced with fibrotic
15 tissue. There is actual cell death and yet
16 the extracellular matrix remains largely
17 intact.

18 A number of factors may affect the
19 lesion size, which include contact with the
20 tissue, electrode size, the power that is
21 delivered, the regional blood flow actually
22 around the tip of the catheter, and the freeze

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1 time with lesions forming at a minimum of
2 30 seconds of energy application.

3 As an example, we have significant
4 experience with the canine model of atrial
5 flutter, and this is a slide showing the right
6 atrium in a dog where there is a tricuspid
7 valve opening here, and you see the lesions
8 placed along the cavo-tricuspid isthmus which
9 span the entire isthmus and are transmural,
10 which would produce bidirectional conduction
11 block.

12 A number of preclinical studies
13 have been done, but this one we'll show to
14 demonstrate the comparability of lesion size
15 with CryoCor versus radio frequency. This was
16 a study done in swine, 10 swine -- the
17 standard thigh muscle preparation where a
18 constant force of 10 grams of pressure was
19 placed on all catheters against the thigh
20 muscle in a circulating blood pool.

21 We compared the CryoCor catheter
22 with a 6.5 millimeter tip with five-minute

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1 freezes, the standard RF catheter, 7 French
2 with a 4 millimeter tip, the 60-second energy
3 applications at 50 watts and a temperature of
4 50 degrees Centigrade, versus an irrigated
5 catheter with a 3.5 millimeter tip at 60
6 seconds and 50 watts with a salient infusion
7 irrigation at 15 mls per minute. This was an
8 externally irrigated catheter.

9 Now, we've tested both vertical and
10 horizontal tip orientations to the tissue.
11 And as you can see from this slide showing two
12 lesions in thigh muscle, the CryoCor catheter
13 at five-minute freeze with a horizontal tip
14 application to the tissues, you can see this
15 lesion is a bit elongated.

16 And an irrigated tip at one minute
17 with a vertical orientation of the catheter,
18 relatively comparable volumes, as you see here
19 the sharply demarcated lesions with
20 cryoablation.

21 Now, I'll direct you to the two
22 parts of this slide which I think are the most

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1 important -- the horizontal application of the
2 catheter. With both cryoablation, the CryoCor
3 catheter and the irrigated catheter produced
4 similar depths of the lesion larger than the
5 standard RF, and the diameter of the lesions
6 are comparable, again, larger than standard
7 RF.

8 Now, the tip down -- the irrigated
9 catheter appears to be -- do somewhat better.

10 We would normally maintain a horizontal
11 orientation, however, during ablation
12 preferably.

13 And, in conclusion, from this data
14 and others, cryoablation is able to produce
15 lesions that are larger than standard RF and
16 as large as irrigated RF catheters. And the
17 CryoCor system appears to be able to make
18 lesions that are large enough to treat atrial
19 flutter.

20 Thank you.

21 DR. WELLENS: Good morning, ladies
22 and gentlemen. My name is Hein Wellens, and I

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1 am the former head of cardiology at the
2 Academic Medical Center of the University of
3 Maastricht in The Netherlands.

4 What I would like to do is discuss
5 with you data in comparing the creation of
6 bidirectional isthmus conduction block in
7 dogs.

8 CHAIRMAN MAISEL: Excuse me, Dr.
9 Wellens. Can you state for the record your
10 affiliations with the company?

11 DR. WELLENS: Yes. Yes. I'm a
12 member of the Advisory Board of CryoCor.
13 Thank you very much.

14 So what we are going to do is look
15 at the comparison as to cryo versus RF in
16 creating permanent bidirectional block in the
17 dog. We looked at seven adult mongrel dogs,
18 and five were treated with cryo, and two with
19 RF. And all the animals had electro-
20 anatomical mapping at the time of the
21 procedure and six weeks later.

22 The isthmus ablation was either

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1 done by RF -- and here you see the data on the
2 type of catheter which was used and the
3 duration of the lesion -- and here we have the
4 five dogs that underwent ablation using the
5 CryoCor system. And you have data on that
6 system here below.

7 So five dogs cryo, two dogs RF.
8 Here we have information about a number of
9 applications, temperature, procedure time,
10 application time, fluoro time, and in all dogs
11 bidirectional block was created.

12 Here we see an example -- you see
13 this wide line. That is the line created by
14 cryo, and it extended in this dog from the
15 septal leaflet of the tricuspid's health all
16 the way to the inferior caval vein. And like
17 I said, at six weeks all animals had permanent
18 bidirectional isthmus block.

19 One of the two animals who
20 underwent RF had endocardial traumas formation
21 at the transition of the RA to the inferior
22 caval vein.

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1 Here is another illustration. On
2 the left, the cryo lesion, you see a nice
3 transmural lesion. This is the endo side, the
4 epi side. And here we have the RF lesion.
5 That was after six weeks when we looked again
6 at the presence of complete block in the caval
7 tricuspid isthmus.

8 So we can conclude that cryo is
9 able to produce chronic bidirectional block
10 with histologic evidence of full sickness
11 lesions.

12 Now, another important point is
13 that cryo adheres well to the endocardial
14 surface, and the frozen tip glues to the
15 endocardial surface, and especially when you
16 have a trabeculated isthmus area that may be
17 beneficial in comparison to RF.

18 Thank you very much.

19 DR. CALKINS: Good morning. I'm
20 Hugh Calkins from Johns Hopkins. I'm a
21 Professor of Medicine and Director of
22 Electrophysiology. I'm also a member of the

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1 Advisory Board of CryoCor.

2 I'd like to speak today on the
3 objective performance criteria and the
4 published literature on catheter ablation of
5 atrial flutter.

6 When you reviewed the document
7 published in 2000, which established the
8 objective performance criteria which are the
9 benchmark to determine the safety and
10 effectiveness of RF ablation catheters using
11 conventional radio frequency energy, these
12 shown on this slide are the data that was used
13 to develop these criteria.

14 Now, in terms of atrial flutter,
15 there were four studies cited in this document
16 and three surveys that examined complication
17 rates. The four studies that were used to
18 determine the benchmark efficacy for catheter
19 ablation of atrial flutter are shown here, and
20 you can appreciate these studies. They
21 enrolled between 13 and 200 patients. The
22 chronic efficacy in these four trials varied

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1 from 78 percent to 100 percent.

2 But of important note is the fact
3 that the followup used to determine chronic
4 effectiveness in these studies was clinical
5 followup only -- that routine event monitoring
6 to look for asymptomatic recurrences of atrial
7 flutter were not employed in any of these four
8 studies that determined the benchmark criteria
9 for catheter ablation of atrial flutter.

10 As preparation for this panel
11 meeting, we reviewed 75 peer reviewed studies
12 of catheter ablation of atrial flutter
13 published over the past 12 years. Seventy of
14 these studies were with radio frequency
15 energy, and five were with cryo energy. And,
16 again, it is notable that in 72 of these 75
17 studies chronic effectiveness was based only
18 on clinical followup without routine use of
19 event monitoring to look for asymptomatic
20 recurrences of atrial flutter.

21 This is one of the more recently
22 published studies from Gilligan and Ellinbogan

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1 published in PACE in 2003 showing the
2 recurrence rate of atrial flutter in patients
3 in whom acute success was achieved. And I
4 think we can -- you can appreciate that the
5 six-month and one-year followup rate is
6 approximately 20 percent with a success rate
7 of approximately 80 percent in this prior
8 clinical study of catheter ablation of atrial
9 flutter with radio frequency energy.

10 Now, as part of the discussion of
11 this section of this manuscript, they included
12 a review of the published literature of
13 catheter ablation of atrial flutter. And when
14 you look at the recurrence rates that were
15 cited in this paper, which are available in
16 the published literature, you can appreciate
17 the recurrence rates for atrial flutter after
18 an acutely successful procedure range from 1
19 percent to 58 percent with most of the studies
20 reporting a very substantial recurrence rate
21 of atrial flutter over time certainly higher
22 than we have seen with catheter ablation of AV

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1 node reentry or accessory pathways.

2 The study I'm most familiar with is
3 shown here. This was published in 2004, and
4 this was a prospective multi-center clinical
5 trial that enrolled 150 patients with typical
6 atrial flutter at 17 different centers
7 throughout the United States.

8 The ablation system in this trial
9 was an 8 millimeter, 7 French standard RF
10 ablation catheter coupled with a 100-watt RF
11 power generator. The acute success with
12 establishment of bidirectional isthmus block
13 was 88 percent.

14 Of those in whom an acute
15 successful procedure was accomplished, the
16 six-month chronic success rate was 87 percent,
17 and the 12-month success rate with freedom
18 from occurrence of atrial flutter was 79.7
19 percent. The incidence of major device or
20 procedure-related complications in this study
21 was 2.7 percent.

22 This slide shows Kaplan-Meier

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1 survival curves in this study, and it's a
2 little bit complicated, but shown are the
3 recurrence rates from top to bottom for
4 symptomatic atrial flutter, asymptomatic
5 atrial flutter, all atrial flutter, atrial
6 fibrillation, and all atrial fibrillation or
7 atrial flutter.

8 And, again, you can appreciate a
9 significant recurrence rate of atrial flutter,
10 also an important rate of development of
11 atrial fibrillation over time. But I think of
12 most important note was of the 12 occurrences
13 of typical atrial flutter in this study, four
14 were symptomatic and eight were asymptomatic
15 and picked up only with event monitoring or
16 ECG monitoring during followup.

17 So let me just conclude by stating
18 that 96 percent of prior studies of catheter
19 ablation of atrial flutter used clinical
20 endpoints to determine success, and that event
21 recording was not routinely employed in these
22 studies. And because of this, it is my belief

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1 that the published literature underestimates
2 the true recurrence rate of atrial flutter
3 following radio frequency catheter ablation.

4 Thank you for your attention.

5 DR. FELD: Ladies and gentlemen,
6 Dr. Feld again. Again, I'd note that I'm a
7 member of the Scientific Advisory Board for
8 CryoCor, and I was the principal investigator
9 for this study. And I'm going to present the
10 study design and endpoints for the CryoCor
11 pivotal study for atrial flutter ablation.

12 This study was designed as a non-
13 randomized study at 24 U.S. sites. The
14 patients were required to have documented
15 typical atrial flutter by electrocardiography,
16 as well as a number of other screening
17 criteria which I'll mention in a moment. If
18 there was a failure, they were not enrolled in
19 the study.

20 If they didn't meet all of these
21 criteria, they were enrolled and underwent
22 cryoablation using standard electrophysiologic

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1 techniques. At the end of the procedure,
2 bidirectional conduction block in the cavo-
3 tricuspoid isthmus was demonstrated for at
4 least 30 minutes.

5 If this could not be achieved, the
6 patients could switch and cross over to radio
7 frequency ablation. But if it was achieved,
8 the patients then were treated in a standard
9 manner and, when stable, discharged from the
10 hospital to follow up in the clinic at one and
11 three months, and have six-month telephone
12 call contact to assess their condition. All
13 the while during the course of the followup
14 patients underwent symptomatic and weekly
15 event recording transmissions by the LifeWatch
16 Company.

17 The major inclusion criteria for
18 the study were ages between 18 and 75. The
19 patients must have had a symptomatic atrial
20 flutter event with at least one episode within
21 the last six months documented on ECG. During
22 the electrophysiologic study, documentation of

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1 isthmus-dependent right atrial flutter with
2 confirmation by pacing or mapping -- and this
3 could be electrode, standard electrode, or
4 electron atomic mapping, which was performed
5 in the EP lab just prior to ablation.

6 Patients of course had to be
7 willing and able and make a commitment to
8 participate in all the followup evaluations as
9 well to continue in the study.

10 There are a number of exclusion
11 criteria which you have in your packet. I'm
12 not going to go into the details of all of
13 these. There's quite a number listed here on
14 these two slides. I might point out that two
15 of the major ones that had any prior flutter
16 ablation and concomitant use of any anti-
17 arrhythmic drugs other than Class IC or III
18 would result in exclusion from the protocol.

19 Now, this is an example of atypical
20 atrial flutter on a 12-lead ECG you'll see the
21 sawtooth pattern in the inferior leads what we
22 normally expect to be isthmus-dependent

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1 flutter. This is the so-called typical form,
2 counter-clockwise reentry around the valve.
3 The opposite form which is less common, the
4 clockwise form, might also be seen in these
5 patients, but would have to be documented in
6 the EV lab.

7 Now, this is an example of the
8 endocardial recordings electrophysiology
9 study, time from left to right. These are
10 surface leads, one EVF NV1. There is an
11 electrogram recording from the His bundle,
12 from the coronary sinus, and what we call the
13 Halo catheter, which is a 20-pole electrode
14 catheter draped around the tricuspid valve and
15 the right atrium.

16 You'll see that the activation
17 sequence goes from the coronary sinus up the
18 septum to the His bundle, over the top of the
19 atrium, down over the right atrial freewall,
20 and back to the cavo-tricuspid isthmus. So a
21 counter-clockwise macro reentry around the
22 tricuspid valve.

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1 Having confirmed that, patients
2 would undergo ablation. Subjects with a
3 history of A-Fib who had converted to atrial
4 flutter -- oh, I'm sorry, this is a slide
5 showing prior concomitant therapies that were
6 allowed in these patients. Those included
7 patients who had a history of atrial fib who
8 converted to atrial flutter when paced on
9 anaerobic drugs. And those drugs could be
10 Class I or III agents that were allowed for
11 treatment as A-Fib. And the medication
12 changes were made at the discretion of the
13 investigator following the ablation.

14 Now, the acute endpoints of the
15 study were acute safety, serious ad events
16 within seven days of the indexed procedure,
17 and the goal there was that cryoablation
18 should meet the OPC for safety with the upper
19 confidence bound less than or equal to 7
20 percent.

21 Another endpoint was acute
22 effectiveness, which was the bidirectional

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1 cavo-tricuspid isthmus block after a waiting
2 period of 30 or 60 minutes. And I'll explain
3 these two numbers in a moment. The goal was
4 cryoablation should meet the OPC for acute
5 effectiveness with a lower confidence bound of
6 greater than or equal to 80 percent.

7 And we had a chronic endpoint of
8 the study, endpoints which were chronic safety
9 at six months, and chronic efficacy or
10 effectiveness which meant no recurrence of
11 atrial flutter at six months based on the OPCs
12 and strict event recordings.

13 The acute success target was
14 greater than 95 percent with a confidence
15 bound of greater than or equal to 80 percent,
16 chronic efficacy greater than 90 percent, with
17 a 95 percent confidence bound of greater than
18 or equal to 80 percent, and seven-day serious
19 adverse events of less than 2.5 percent, with
20 a 95 percent confidence bound of less than or
21 equal to 7 percent.

22 The sample size was calculated

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1 using a standard statistical approach based on
2 primary safety endpoint, and it was actually
3 determined to be 160 patients for the study.

4 We had an issue of patient
5 censoring. Patients were required to be
6 compliant with event recordings, and that was
7 defined as completing at least three event
8 recordings per month for at least five of the
9 six months of followup observation. If they
10 were not able to be compliant, they were
11 censored at the point where they became non-
12 compliant with their event recordings.

13 Now, during the course of the
14 protocol, there were two major changes. One
15 was the 60- to 30-minute waiting period which
16 I mentioned for bidirectional conduction
17 block. As of January 29, 2004, involving
18 subsequently 109 patients, based on current
19 clinical practice and a review of the
20 literature they wait time to recheck for
21 bidirectional block was decreased from 60 to
22 30 minutes. And, in addition, there was a

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1 catheter model change from the 1100 Series to
2 the 1200 as of May 4, 2004, which subsequently
3 involved 71 patients.

4 The change was made for ease of
5 manufacturing purposes, and there was
6 extensive testing that was performed to
7 demonstrate that the lesion sizes were
8 equivalent with these two devices.

9 The cryoablation procedure itself
10 was performed in a standard manner. The
11 atrial flutter isthmus was ablated. The
12 freezes were up to five minutes with the
13 majority at least two minutes. And following
14 ablation, there was confirmation of
15 bidirectional conduction block, as I
16 mentioned, for either 30 or 60 minutes.

17 And here is an example of how we do
18 that with standard electrode recordings. This
19 is in sinus rhythm. This would be after
20 ablation. We pace on the medial side of the
21 line of block in the coronary sinus against
22 surface leads, the His coronary sinus, and

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1 then the Halo catheter, and focus mainly on
2 this.

3 When you pace the coronary sinus,
4 the wavefront goes up the septum, blocks in
5 the isthmus where there is conduction blockers
6 all the way around, and you see this
7 descending straight limb in the lateral wall.

8 That demonstrates conduction block from
9 medial to lateral.

10 And pacing in the low right atrium,
11 the wavefront proceeds up the right atrium via
12 the Halo catheter, blocks in the isthmus, and
13 comes up over the top to the septal area, the
14 His bundle, and down to the coronary sinus.
15 So it blocks and it goes all the way around
16 the other direction, so demonstrating lateral
17 to medial block. And that's how we confirmed
18 bidirectional conduction block in these
19 patients.

20 Thank you very much.

21 DR. WALDO: I'm Al Waldo. I'm a
22 Professor of Cardiology and Professor of

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1 Medicine and Professor of Biomedical
2 Engineering at Case Western Reserve University
3 School of Medicine. And I'm a member of the
4 Scientific Advisory Board of CryoCor.

5 Well, my topic with you is the
6 initial submission issues. Well, when the
7 data were evaluated, we all know about the
8 importance of the event monitors, and it
9 became clear when we looked at the -- when the
10 CryoCor folks looked at the event monitor
11 data, that it was only looked at by a
12 technician. So the initial analysis, the
13 event recordings, were not interpreted by an
14 experienced electrophysiologist but by a
15 technician from LifeWatch.

16 And when they looked at some of the
17 data it was clear that some of the
18 interpretations were questionable, so they
19 went to the Scientific Advisory Board and
20 that's how I got involved and it became clear
21 to us that this was something that had to be
22 done very well. But we noted that 41 percent

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1 of the patients in the study had atrial
2 fibrillation at some point after the ablation,
3 and we know that misinterpretation of these
4 ECGs was possible, mixing coarse atrial
5 flutter with fibrillation and even atrial
6 tachycardias.

7 And so we suggested that they get a
8 superb electrophysiologist with integrity and
9 expertise, and it was easy for us to recommend
10 to Dr. Melvin Scheinman in the group at his --
11 at University of California-San Francisco as
12 an unbiased and blinded expert, and he was
13 then asked to serve as the core lab to
14 accurately interpret the event recordings.

15 Now, to give you an example of what
16 we're talking about, you can look at this
17 example, and you can see over here that there
18 are clear, positive complexes. But if you
19 look carefully, you'll see they're negative
20 over here. This is a good example of coarse
21 atrial fibrillation, and this is the kind of
22 thing that's misinterpreted as atrial flutter

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1 when it's clearly atrial fibrillation.

2 And we should expect atrial
3 fibrillation to recur after atrial flutter.
4 It has been well documented in many studies.
5 And if you understood the pathophysiology of
6 how atrial flutter evolves, atrial
7 fibrillation is a critical part of it. So
8 there's no surprise.

9 But these interpretations can go
10 both ways when just a technician is looking at
11 it. This is an example in which the tech
12 thought there was sinus rhythm, and if you
13 look carefully you can see this is atrial
14 flutter.

15 So there was really clearly a need
16 to do this properly and well. And so a
17 careful and rigorous approach to have an
18 unbiased blinded expert core lab evaluate the
19 event recordings is what followed.

20 DR. SCHEINMAN: Good morning. Dr.
21 Maisel, friends, my name is Mel Scheinman.
22 I'm from -- I'm a Clinical Electrophysiologist

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1 from California. I have no formal
2 affiliations with CryoCor. I did receive fees
3 for working as a core lab on this project.

4 All events recording -- all the
5 event recordings were read independently by
6 myself and one of my colleagues whose chief
7 research interest is in atrial flutter. We
8 did this because of the known high incidence
9 of atrial fibrillation and the confounding
10 factors that Dr. Waldo outlined. So all
11 strips were read independently by both myself
12 and her, whom we had discrepancies, we
13 adjudicated them, but the final decision was
14 made by me.

15 We read all events for a given
16 patient, but we didn't know when the patient
17 had the ablation or what kind of specific --
18 or any of the specifics of the ablative
19 procedure. In addition, we had absolutely no
20 clinical information regarding the patient.

21 I want to emphasize that this is a
22 somewhat artificial means of trying to make a

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1 diagnosis. Clinicians here would be well
2 aware of it, and I think I'll emphasize this
3 by showing you the strips that we had.

4 Both Dr. Yang and myself are
5 completely blinded to the study protocol, and
6 we did not have access to the original
7 LifeWatch recordings. The form used that was
8 shown here, we were asked to determine whether
9 atrial fibrillation was present, absent, or
10 cannot be determined, and the same was
11 requested for the diagnosis of atrial flutter.

12 Now, the difficulties that we ran
13 into in interpreting the strips were, first
14 and foremost, artifacts. In addition, we had
15 a problem sorting out patients with coarse
16 atrial fibrillation -- that's not working?
17 Yes, coarse atrial fibrillation mimicking
18 atrial flutter, and also at times the problem
19 of so-called slow atrial flutter versus atrial
20 tachycardia.

21 Let me give you some illustrative
22 examples. This, of course, was absolutely

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1 unreasonable. This is an artifact. This was
2 just noted as being indeterminant.

3 Next.

4 This is another example of how
5 someone with just a technical background in
6 this, not a medical background, may have a
7 problem interpreting it. If you look -- if
8 you look over here, you can see the negative
9 deflections which can mimic atrial flutter.
10 There's kind of a picket fence appearance
11 here.

12 Here you'll notice that there's a
13 positive P-wave before each QRS. The RR
14 intervals are constant throughout, so this is
15 clearly sinus rhythm with artifacts. But it
16 could be misinterpreted as a burst of atrial
17 flutter.

18 In the next example, I show a
19 similar kind of a problem. You can see these
20 irregular recordings, and these could be
21 interpreted as atrial fibrillation. But,
22 again, the RR interval is absolutely regular,

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1 and previous recordings did show sinus rhythm
2 at the same rate. So this is not atrial
3 fibrillation. This is sinus rhythm with
4 artifacts.

5 So these were ways in which I think
6 a technician might have problems with making
7 the correct diagnosis. Again, this is another
8 example of something alluded to by Dr. Waldo.

9 Here is a patient who has runs of fairly
10 regular electrical activity, which can be
11 misdiagnosed as atrial flutter, but if you
12 carefully measure the intervals you'll notice
13 that there are gross irregularities in the P-
14 wave intervals as well as the P-wave duration
15 as you look here. So this is clearly coarse
16 atrial fibrillation and not atrial flutter.

17 Perhaps some of the most vexatious
18 problems were found the next few examples.
19 So, for example, we would have a whole stack
20 of recordings from a patient, all of which
21 showed sinus rhythm, and then you would have a
22 recording like this which clearly looks like

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1 atrial flutter and we were interpret -- and we
2 interpreted it as atrial flutter but was
3 trangent. It was only seen on one event
4 recorder from a whole stack.

5 And it's very hard to make very
6 much of this without having additional
7 clinical information.

8 The next slide -- there's another
9 problem that we ran into, and that is that we
10 found patients who had these atrial recordings
11 which have a cycle length of approximately 280
12 milliseconds, which is quite slow for the
13 typical kinds of flutter that we're used to
14 looking at. So we didn't know whether this
15 was atrial tachycardia or could this be atrial
16 flutter that was modified.

17 Now, our mandate in reading these
18 was to -- was very strict, and we even had to
19 note all examples of possible or probable
20 flutter, and this was, of course, put in as a
21 failure.

22 So, in conclusion, let me emphasize

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1 several points. Number one, the event
2 recordings alone can be very difficult to
3 interpret, because of the problems that we
4 alluded to. At times, more information is
5 required to make the appropriate clinical
6 evaluation.

7 For example, if we look at the
8 recordings and we see atrial flutter, we have
9 absolutely no way of knowing whether this was
10 cavo-tricuspid isthmus-dependent or some other
11 flutter which was completely unrelated to the
12 endpoint of the study.

13 In addition, if we found only one
14 episode of atrial flutter, we didn't know
15 whether the patient was symptomatic or
16 asymptomatic, and we didn't know whether this
17 -- how this correlated with clinical events.
18 But for us this was considered -- this was
19 noted and considered a failure.

20 And then, finally, the problem of
21 atrial tachycardias came up. The clinician
22 has a 12-lead EKG. He could look at the pre-

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1 ablation data to see if this was typical
2 flutter. And they were -- they could
3 differentiate ATac from A-Flutter. We were at
4 a disadvantage and could not do so.

5 So, in summary, I wanted to make it
6 clear that we had a very strict mandate to
7 call everything that we thought was -- could
8 possibly be flutter as flutter. These were
9 counted as failures. This was -- this is a
10 departure somewhat from usual clinical
11 evaluation of these patients.

12 Thank you very much.

13 DR. DAUBERT: Good morning, ladies
14 and gentlemen. My name is James Daubert. I'm
15 Associate Professor of Medicine at the
16 University of Rochester Medical Center, and
17 Director of the Electrophysiology Service.

18 I was investigator in this clinical
19 trial, and our center enrolled the largest
20 number of patients. In addition, I'd like to
21 note that I'm a consultant to CryoCor.

22 So I'd like to present the study

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1 results here. First, let's review patient
2 accountability. One hundred eighty-nine
3 patients had electrocardiographic evidence of
4 atrial flutter and were enrolled. However,
5 one patient withdrew consent prior to
6 undergoing catheter ablation.

7 In addition, 26 patients were found
8 not to have isthmus-dependent atrial flutter.

9 Recall that confirmation of isthmus-dependent
10 atrial flutter was required before ablation.

11 These 26 patients and the one who
12 withdrew consent did not undergo cryoablation.

13 Furthermore, one patient developed anti-
14 arrhythmic resistant atrial fibrillation
15 during the electrophysiologic study and did
16 not complete the ablation, and one did not --
17 one had -- patient's procedure was complicated
18 by device failure.

19 The remaining 160 patients, then,
20 were valuable for the acute efficacy and acute
21 safety endpoints.

22 The patient enrollment by site is

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1 shown here. Remember, 160 patients were
2 enrolled at 24 sites with an average
3 enrollment of 6.7 patients per site. Of the
4 24 sites, 17 centers enrolled eight or fewer
5 patients. Please note that this was the first
6 experience with the CryoCor cryoablation
7 system for virtually all of these
8 investigators.

9 The subject demographics are shown
10 on this slide for the 160 patients. Seventy-
11 seven percent were male with a mean age of 63
12 years. As you've heard, atrial fibrillation
13 is an extremely common co-morbid condition in
14 atrial flutter patients, and was present in 59
15 percent of the patients.

16 Remainder of the demographics are
17 shown and are in your panel packet.

18 Please note that two patients had
19 undergone catheter ablation previously for
20 atrial fibrillation and for Wolff-Parkinson
21 White.

22 Anti-arrhythmic drug use was

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1 allowed as treatment for atrial fibrillation
2 in this study. At the time of ablation, 57
3 patients or 36 percent were on anti-arrhythmic
4 drugs, Class IC or Class III, for atrial
5 fibrillation. the majority of these patients
6 were on amiodarone, with flecainide occupying
7 the second most numerous position. The other
8 medications are shown here.

9 Let me tell you about the results
10 that the investigators found during the
11 diagnostic EP study. Using mapping and
12 entrainment criteria, cavo-tricuspid isthmus
13 was confirmed, and it was found that counter-
14 clockwise atrial flutter was noted in 126
15 patients or 79 percent. Clockwise flutter, as
16 seen in other studies, occupied a much smaller
17 minority of the patients, 22 patients or 13.8
18 percent.

19 Both types of atrial flutters were
20 seen in nine patients or five percent. And in
21 three patients the mechanism was not
22 specified.

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1 The cryoablation results are shown
2 here. The mean number of freezes performed
3 during the ablation procedure was
4 approximately 20. 18.6 of these ablations
5 were so-called effective freezes. One or two
6 freezes per procedure were terminated after a
7 few seconds at the operator's discretion if he
8 felt -- he or she felt that the catheter had
9 moved slightly, for instance.

10 The average ablation time was two
11 minutes, 20 seconds. The temperatures
12 achieved are shown, with an average
13 temperature of minus 81 degrees Celsius, and
14 an average minimum temperature for each
15 ablation lesion of minus 85.6 degrees.

16 The procedures required on average
17 35 minutes of fluoroscopy time, and the total
18 procedure, including either a 30- or 60-minute
19 waiting phase was three hours, 20 minutes.

20 Acute safety data are shown. These
21 are the seven-day serious adverse event rates.

22 Please note that in your packets you may have

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1 seen 10 seven-day serious adverse events. On
2 advice from the agency, one of these events
3 was moved to the chronic tally, since it
4 occurred after seven days.

5 The seven-day serious adverse event
6 rate was 5.63 percent with an upper confidence
7 limit of 9.61 percent or 10.35 percent,
8 depending upon methodology. If we restrict
9 this analysis to device and procedure-related
10 serious adverse events, four events are
11 recorded for an event rate of 2.50 percent and
12 upper confidence limits shown here.

13 The four device and procedure-
14 related serious adverse events included post-
15 procedural hematoma, AV block requiring a
16 permanent pacemaker, cardiac tamponade
17 occurring somewhat subacutely six days after
18 the procedure, and acute respiratory failure.

19 All of these serious adverse events have been
20 adjudicated by the Data Safety Monitoring
21 Board.

22 I think overall this speaks to the

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1 safety of the device and its usability without
2 an extensive prior investigator experience.

3 The chronic safety data are shown
4 here. Again, this number changed from 27 to
5 28 within the last few weeks. None of these
6 events were, according to DSMB adjudication,
7 felt to be device or procedure-related events.

8 Three deaths occurred during the course of
9 followup after the ablation procedure. Two
10 were suicides, one was a pulmonary embolus,
11 again deemed unrelated to the procedure. The
12 confidence intervals are shown here.

13 Let's turn to the acute procedural
14 success. Remember that this endpoint was
15 achievement of bidirectional cavo-tricuspid
16 isthmus block and maintenance of that block
17 throughout the waiting phase of 30 or 60
18 minutes. One hundred sixty patients were
19 evaluable, 140 met this acute efficacy
20 endpoint, or 87.5 percent. The lower
21 confidence interval is shown here, exceeding
22 the 80 percent value.

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1 Of the 20 patients who did not meet
2 this acute efficacy endpoint, 19 crossed over
3 to radio frequency ablation, and one patient
4 is the patient we spoke of who had heart block
5 and received a permanent pacemaker. These 140
6 patients, thus, became evaluable for the
7 chronic effectiveness endpoint.

8 Chronic effectiveness was defined
9 as freedom from atrial flutter recurrence at
10 six months after the ablation procedure. The
11 primary analysis method was the expert core
12 lab that you've heard about, which was read by
13 Dr. Scheinman and his group in a blinded
14 fashion.

15 Patients could become a recurrence
16 or become ineffective if they had a single
17 event monitor recording interpreted by Dr.
18 Scheinman as showing atrial flutter or
19 possible atrial flutter. These were weekly
20 event monitor tracings looking for
21 asymptomatic atrial flutter. Note that
22 patients could also be deemed to have a

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1 recurrence, according to 12-lead
2 electrocardiograms performed at one, three,
3 and six months.

4 The freedom from atrial flutter
5 recurrence is shown here using Kaplan-Meier
6 survival analysis methodology. Plotted on the
7 Y-axis is the proportion of patients free from
8 recurrence, on the X-axis days to recurrence
9 or censor.

10 Please note there is a small
11 recurrence rate, especially within the first
12 two to three months after which the curve
13 becomes relatively more flat. The 95 percent
14 confidence intervals are shown in red. The
15 survival estimate at six months was 81.6
16 percent, with a lower confidence interval of
17 74.7 according to the Peto method.

18 Let's look at the 26 patients who
19 were deemed to have a recurrence of atrial
20 flutter and not to have met the chronic
21 effectiveness endpoint according to the expert
22 core lab analysis. Ten of these 26 patients

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1 did indeed undergo retreatment for atrial
2 flutter, five with cryoablation and five with
3 RF. One additional patient underwent
4 cardioversion of the atrial flutter. Two
5 further patients were started on amiodarone
6 for atrial flutter.

7 However, 13 of these 26 patients
8 were deemed to be a clinical success by the
9 local investigator and did not undergo further
10 cardioversion anti-arrhythmic drug addition or
11 ablation. Moreover, none had atrial flutter
12 documented on 12-lead ECG at one, three, or
13 six months.

14 These 13 patients' clinical
15 outcomes are summarized on this slide. I, of
16 course, won't go through the details of this,
17 but this is available to you in your handouts.

18 To summarize, three of these patients were
19 felt by Dr. Scheinman to have possible atrial
20 tachycardia versus slow atrial flutter. Ten
21 of the 13 had a single event monitor recording
22 showing atrial flutter or possible atrial

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1 flutter.

2 In the absence of symptoms or other
3 electrocardiographic documentation, the
4 investigators deemed these patients to be
5 clinical successes, did not add anti-
6 arrhythmic medications. Indeed, two patients
7 had anti-arrhythmic drugs stopped.

8 Another way to look at the chronic
9 effectiveness of this catheter system for
10 atrial flutter is to look at freedom from
11 atrial flutter recurrence using this post hoc
12 analysis. All of the event monitor recordings
13 and other data were reviewed by Dr. Barold and
14 other investigators, and took the clinical
15 interpretation of the patient's entire file
16 into account, especially the treating
17 physician's opinion.

18 Let's review a few examples of
19 these patients. One of these 13 patients was
20 felt to have sinus rhythm on the upper strip
21 and many of the other strips in the event
22 monitor portfolio. One strip was read as

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1 atrial flutter and considered a failure with
2 Dr. Scheinman's comments being -- could be a
3 fortuitous relationship of a biphasic T-wave
4 and P-wave.

5 The patient was asymptomatic during
6 all these event recordings, and only one
7 tracing was called potentially atrial flutter.

8 In another patient deemed to have
9 an atrial flutter recurrence by the event
10 monitor strip below, the expert core lab
11 interpretation by Dr. Scheinman was atrial
12 flutter with variable AV block with coarse
13 atrial fibrillation possible. This was seen
14 in only one tracing. Other tracings all
15 showed atrial fibrillation or sinus rhythm.

16 The treating clinician reviewed all
17 the tracings, interpreted this as atrial
18 fibrillation and not atrial flutter,
19 discontinued propafenone, did not start any
20 other anti-arrhythmics, and, clinically, the
21 patient was felt to be a success.

22 Note that while there are very

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1 suggestive atrial flutter waves here, the
2 cycle length is unusually short -- 160
3 milliseconds -- and quite variable with a much
4 longer interval here, which would be atypical
5 for cavo-tricuspid isthmus flutter.

6 One other patient felt to have
7 atrial tachycardia versus atrial flutter by
8 event monitor recording and deemed a
9 recurrence, the investigator wrote this, "The
10 patient has symptomatic atrial tachycardia,
11 non-sustained, not atrial flutter. We will
12 begin treatment with Rhythmos SR 225 BID."

13 So using these data and additional
14 information over and above the event monitor
15 recordings, one can perform another evaluation
16 of chronic effectiveness. We call this the
17 clinical determination method. Using this
18 methodology, the survival estimate is 90.5
19 percent freedom from recurrent atrial flutter
20 at six months, with lower confidence interval
21 of 85.7.

22 I'd like to summarize the results

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1 at this point. The acute safety endpoint was
2 noted in 5.63 percent of patients, upper
3 confidence limit of 10.35. The acute safety
4 endpoint attributable to device and procedure-
5 related events was 2.5, zero percent, with an
6 upper confidence interval of 6.28.

7 Acute effectiveness was seen in
8 87.5 percent of patients. Lower confidence
9 interval of 81.36. Chronic effectiveness,
10 according to the primary analysis, the core
11 event monitor lab was 81.6 percent with
12 confidence intervals shown here, and objective
13 performance criteria goals shown here.

14 Using the secondary post hoc
15 analysis that we've just gone over, chronic
16 effectiveness could also be measured as 90.5
17 percent with confidence intervals here.

18 In summary, I would conclude that
19 based on these data, and based on my
20 experience as an investigator in this trial,
21 that the CryoCor system is safe, as evidenced
22 by a low seven-day serious adverse event rate.

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1 Furthermore, that is acutely effective at
2 achieving bidirectional cavo-tricuspid isthmus
3 block. And, furthermore, that it's
4 chronically effective.

5 Chronic effectiveness analysis is,
6 as we've heard, challenging and -- in terms of
7 the difficulty of adjudicating the event
8 monitor tracings, and there may be merit to
9 including the whole patient clinical outcome
10 in evaluating this. And, thus, I think the
11 chronic effectiveness rate may be even higher
12 than the 81.6 percent shown here in the
13 primary analysis.

14 Thank you.

15 DR. WELLENS: Hein Wellens again,
16 member of the Advisory Board of CryoCor. What
17 I would like to do is show you data from
18 Maastricht in terms of treatment of atrial
19 flutter using the CryoCor system.

20 All patients who underwent
21 cryoablation with the CryoCor system at the
22 Academic Hospital of Maastricht were

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1 prospectively placed into a database from June
2 2001 to January 2006. And those patients with
3 isthmus-dependent atrial flutter who would
4 have met the inclusion criteria from the U.S.
5 study were evaluated.

6 Here is some information about
7 exclusions, people that underwent a second EP
8 study or ablation of a pulmonary vein, or
9 followup duration of less than three months.

10 Now, this is an important point.
11 All the procedures were performed by two
12 experienced electrophysiologists. Of course,
13 this is a single center study, and all
14 procedures were performed by two experienced
15 electrophysiologists.

16 Patients did not receive sedation
17 for the ablation, and following the ablation
18 there was a 30-minute waiting period after the
19 last ablation with the addition of
20 isoproterenol.

21 Then, what about the followup? In
22 anticipation of questions or comments of the

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1 FDA, I think it's important to stress that
2 these patients came back to the outpatient
3 clinic at one, three, six months, and yearly,
4 or as symptoms developed. And at that time,
5 and they were all seen by the
6 electrophysiologist who had done the ablation.

7 The electrophysiologist had at his
8 or her disposal 24-hour Holter recording, and
9 I'd like to stress that because, as was
10 pointed out by Dr. Scheinman, if you look
11 blinded at event recordings, and you don't
12 have any information about the index
13 arrhythmia, then it becomes very, very
14 difficult to say whether the arrhythmia that
15 is present on the event recording is the same
16 arrhythmia as the index arrhythmia.

17 And that approach, which was used
18 here, allows you in case of an arrhythmia to
19 find out, because you have all the data --
20 preablation data to see whether that is the
21 same arrhythmia as the index arrhythmia before
22 the ablation.

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1 Another important point is the
2 protocol. Nowadays you have a very
3 standardized protocol when you're talking
4 about isthmus ablation -- standardized in
5 terms of localizing the isthmus, standardized
6 in terms after the ablation of evaluating
7 whether you have created complete
8 bidirectional block.

9 Now, if you want to know what
10 actually was done in Maastricht, you should
11 read the message section of this publication
12 and circulation in 2004.

13 So we're talking about 111
14 consecutive patients. The gender buildup is
15 similar to the U.S. study. The average age is
16 somewhat younger, and the incidence of a
17 history of atrial fibrillation is somewhat
18 higher.

19 Now, what about results? So here
20 if you look at acute effectiveness and chronic
21 effectiveness at six months, and as you can
22 see the acute effectiveness was 93.69 percent.

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1 And here you have the confidence limit.

2 Now, seven patients did not have
3 six-month followup, so they have to be
4 deducted from the 104, so we come to 97
5 patients where we have chronic effectiveness
6 studied at six months. And as you can see
7 here, the percentage was 93.81 percent. And
8 here is the Kaplan-Meier curve looking at the
9 followup of these patients.

10 So I think we may come to the
11 conclusion that in Maastricht, the CryoCor
12 system had excellent clinical effectiveness.
13 And the action in the Maastricht situation was
14 more on the clinical evaluation. And as you
15 can see, and as you compare that to the
16 clinical outcome which was reported just
17 before me, there is a similar clinical outcome
18 as the U.S. clinical analysis.

19 And then, an important point is
20 that sedation was not necessary during the
21 ablation. And I'd like to say a bit more
22 about pain. And this was a study which was

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1 published in circulation where we looked at
2 pain during ablation, comparing radio
3 frequency and cryo.

4 So we have 14 consecutive patients
5 with isthmus-dependent atrial flutter. And
6 they were randomized to RF or cryo. And these
7 patients were blinded as to whether RF or cryo
8 was going to be used.

9 A psychologist sat next to the
10 patient and asked questions during the
11 ablation as to the pain. And the pain was
12 evaluated using a visual analog scale that
13 runs from zero to 100. And you have
14 clinically significant pain when you reach 20.

15 Now, what about the reserves? When
16 you compare pain in the RF-treated patients
17 versus the cryo-treated patients, here you see
18 information about the number of applications
19 -- 94 in the RF, 125 in the cryo -- data about
20 the temperature, six out of seven RF patients
21 had complete isthmus block, and seven out of
22 seven cryo.

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1 And this, of course, is important.

2 All patients having RF experience pain during
3 the procedure, and only one patient out of the
4 cryo group. And that is shown here.

5 Let's concentrate on this part of
6 the slide first. That is the percentage of
7 painful applications. And as you can see, we
8 had 94 applications in the RF group, and 71 of
9 those -- 75 percent -- were painful. In
10 contrast, if you look at the cryo group, you
11 see only two out of 125 applications were
12 painful.

13 So if you do a P-value between the
14 number of painful applications here and there,
15 you come to this 0.0001 value.

16 Here you have data about the main
17 pain score using that VAS system, and there's
18 a clear difference between RF and cryo.

19 So, in conclusion about the pain, I
20 think that we have to say that cryoenergy is
21 significantly less painful than RF, and,
22 therefore, much more patient-friendly.

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1 And you all know that when there is
2 a patient on the table, sedation may lead to
3 complications -- for example, in a patient
4 with morbid obesity or chronic obstructive
5 pulmonary disease or sleep apnea. And it's
6 also important that -- and, again, you all
7 know that if you have a patient on the table
8 during the catheterization and the patient has
9 pain, then the patient more easily moves and
10 that may lead to dislodgement of the catheter
11 or even perforation of the catheter.

12 I'd like to conclude by saying that
13 in Maastricht all ablations of atrial flutter
14 are done using the CryoCor system, and that is
15 because of the excellent results, but also
16 because the method is patient-friendly.

17 Thank you very much.

18 DR. WALDO: Al Waldo again. And I
19 want to present our summary and conclusions.
20 So I think we've -- I hope you agree that
21 we've presented a good case, a strong case in
22 fact, to support approval. We've showed you

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1 preclinical data about the lesion sizes as
2 large as for radio frequency ablation when
3 using cryo.

4 The U.S. pivotal trial provided
5 data demonstrating a reasonable level of
6 safety and efficacy. And as you just heard,
7 the Maastricht trial was confirmatory when
8 comparing the clinical study data of that
9 trial with the clinical evaluation of the U.S.
10 pivotal trial.

11 And then, you've just heard again
12 the pain study, which demonstrated a unique
13 advantage of cryoablation over radio
14 frequency. The fact that you don't have to
15 give sedation is important in many types of
16 patients -- for instance, obese patients,
17 patients with chronic obstructive pulmonary
18 disease, sleep apnea, that sort of things.
19 There are other sorts of patients in whom it
20 is already -- it becomes a problem when you
21 have to sedate them. And so this is a niche
22 advantage of sorts.

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1 Moreover, I want to review some
2 other aspects in considering our presentation.

3 Please remember that the results with the
4 CryoCor system are comparable to published
5 radio frequency ablation data in the
6 literature. I think that's important.

7 The objective performance criteria
8 also that the endpoints were based on were
9 based on four studies using radio frequency
10 ablation where chronic success was determined
11 by routine clinical followup alone with the
12 use of event recordings.

13 And then, as you've heard several
14 times now, and I think the perspective is
15 important, that you -- in using event
16 recordings, you can find -- they can lead to
17 increased detection of atrial flutter, but
18 they may also pick up other atrial arrhythmias
19 that are not endpoints for this study -- for
20 instance, atrial fibrillation masquerading as
21 atrial flutter sometimes.

22 Non-isthmus-dependent atrial

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1 flutter, I don't know if you noticed, but in
2 the -- when Jim presented the initial cohort,
3 study cohort of 160 patients, we started off
4 with a little over 180. There were 26
5 patients who didn't qualify, because they
6 didn't have isthmus-dependent atrial flutter.

7 So this is important to remember. Just
8 because there's flutter doesn't mean it's
9 isthmus-dependent.

10 And then, there are also clinically
11 insignificant arrhythmias, and I think that's
12 very important particularly in the 13 patients
13 who were judged to be a clinical success. The
14 atrial flutter that may have been present or,
15 in fact, was present was not considered
16 important enough to treat. May have been
17 transeptal, for instance.

18 And, finally, there may be
19 important populations where correlation
20 provides the distinct advantage. I've just
21 emphasized that earlier with the pain, but the
22 absence of sedation is important, and I think

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1 that's important.

2 And there are -- I would remind the
3 panel -- I think they already know -- there is
4 no other approved cryoablation device for the
5 treatment of atrial flutter, so if this were
6 to get approval it would be the first.

7 And, in conclusion, we believe this
8 study demonstrated a reasonable level of
9 safety and effectiveness.

10 Thank you.

11 CHAIRMAN MAISEL: I'd like to thank
12 the sponsor for a very thorough and well-
13 stated presentation. At this point, I'd like
14 to open up the discussion to the panel for
15 question and answer of the sponsor. I'll
16 remind the panel that we will have time later
17 in the day to discuss many of these issues and
18 would ask you to limit your comments to
19 important points of clarification or burning
20 issues that you feel you need clarified at
21 this time.

22 Sharon?

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1 DR. NORMAND: I have two questions
2 of clarification. The first question relates
3 to the OPC. I just want to get a sense of
4 those numbers that you're using. Should we
5 think of them as compared to radio frequency
6 ablation, or medication treatment? I just
7 want to get a sense of what we should think of
8 that particular number, as sort of in some
9 sense the control group.

10 DR. CALKINS: Yes. The objective
11 performance criteria were -- these criteria
12 were developed for the approval of radio
13 frequency ablation catheters for --

14 DR. NORMAND: Okay.

15 DR. CALKINS: -- for various
16 arrhythmias.

17 DR. NORMAND: Okay.

18 DR. CALKINS: They did not examine
19 the -- did not review the anti-arrhythmic drug
20 effectiveness, but I think we all know --

21 DR. NORMAND: Okay. No, that's
22 perfect.

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1 DR. CALKINS: Yes.

2 DR. NORMAND: I just want to get --
3 because I know he's going to cut me off soon,
4 so -- so we should be thinking of them
5 relative to radio frequency. That's how I
6 should think about it in my head.

7 So I wanted also to ask whether or
8 not medication refractory patients were -- it
9 was only medication refractory patients that
10 were included in your trial.

11 DR. BAROLD: No. The answer to
12 that is no.

13 DR. NORMAND: Okay. And then, one
14 last clarification. The Kaplan-Meier plot for
15 the chronic effectiveness endpoint -- again,
16 is that time to first recurrence of flutter?

17 DR. BAROLD: Yes.

18 DR. NORMAND: First recurrence.

19 DR. BAROLD: Yes.

20 DR. NORMAND: Thank you.

21 CHAIRMAN MAISEL: Dr. Zuckerman.

22 DR. ZUCKERMAN: Yes. I'd like to

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1 amend Dr. Calkins' statement a bit, and
2 certainly there will be significant discussion
3 regarding the point estimates this afternoon.

4 And the FDA will further expand upon how we
5 drew a point estimate or OPC in this
6 particular case.

7 But this is a point estimate for --
8 that should apply in the FDA mind to all
9 catheter therapies designed to treat atrial
10 flutter. So the perspective would be a little
11 bit wider than Dr. Calkins just indicated.

12 CHAIRMAN MAISEL: Other questions?
13 David?

14 DR. SLOTWINER: I'm not sure if
15 this is the right time, but I'm curious to
16 hear a little bit more about the patient who
17 developed heart block.

18 CHAIRMAN MAISEL: Why don't we save
19 that for a little later.

20 DR. SLOTWINER: Okay.

21 CHAIRMAN MAISEL: Clyde?

22 DR. YANCY: Just one or two

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1 protocol-related questions, please. Regarding
2 the acute safety endpoint, was the analysis of
3 device and procedure-related adverse events
4 protocol specified, or post hoc?

5 DR. BAROLD: The answer to that is
6 that the protocol specified that the Data and
7 Safety Monitoring Board adjudicate the serious
8 adverse events. It was not an endpoint, but
9 it did mandate that the Data and Safety
10 Monitoring Board decide if it was a procedure-
11 related event.

12 DR. YANCY: Because as I read the
13 data provided, the safety endpoint was all
14 serious adverse events, but there is a second
15 analysis of all serious adverse events
16 restricted to device or procedural issues.

17 DR. BAROLD: Correct.

18 DR. YANCY: And so that secondary
19 analysis, if I can call it that, was that
20 protocol prespecified or post hoc?

21 DR. BAROLD: It was not protocol
22 specified, although the protocol did specify

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1 that the Data and Safety Monitoring Board
2 adjudicate them. But the endpoint is a
3 subgroup analysis of the total endpoint, yes.

4 DR. YANCY: One more question about
5 the protocol. It seems as if there actually
6 are three analyses of chronic effectiveness.
7 There is the analysis that I presume was done
8 using the LifeWatch data, an analysis that we
9 highly respect done by Dr. Scheinman's lab,
10 and then a post hoc analysis done by another
11 investigator that incorporated clinical
12 information.

13 I haven't seen the analysis from
14 the LifeWatch data set. Do we have those
15 data?

16 DR. BAROLD: We have that
17 available. I think we can present it. If
18 you'd like it now, or we can present it --

19 CHAIRMAN MAISEL: Why don't we hold
20 off on that. Then, we can hear the FDA's take
21 on which is the appropriate analysis. And if
22 the panel still wants to see that data later,

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1 we can see it later. Other -- yes, Mike.

2 DR. DOMANSKI: I have just one
3 question about the -- how the patients were
4 handled. How did you handle anti-coagulation
5 in the differently adjudicated groups?

6 DR. BAROLD: We collected whether
7 or not patients were on coumadin or not was
8 not part -- the protocol specified that if
9 patients were candidates for anti-coagulation,
10 they should be on it. But it wasn't anything
11 that we followed. We didn't follow serious
12 adverse events specifically associated with it
13 and/or INRRs, anything like that.

14 CHAIRMAN MAISEL: We heard a lot
15 about the chronic effectiveness endpoint based
16 on ECG followup, but didn't see any compliance
17 with the protocol. Can you give us an idea of
18 how many patients complied with the --

19 DR. BAROLD: Yes.

20 CHAIRMAN MAISEL: -- weekly
21 transmissions?

22 DR. BAROLD: We actually had

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1 excellent compliance. As you can see, out of
2 the total number of patients that were
3 followed for chronic effectiveness was 140.
4 Only eight of those patients were censored,
5 and three of those were censored for deaths.
6 So there were five patients that were
7 noncompliant at some point with their event
8 recordings.

9 If you look in the panel pack,
10 we've outlined those patients, and you can see
11 there were several patients that were
12 noncompliant for a month or so. And,
13 therefore, they were still considered
14 noncompliant for the entire study. So our
15 compliance was excellent.

16 CHAIRMAN MAISEL: So maybe we
17 should be more specific about what your
18 definition of "compliance" is. The protocol
19 specified weekly transmissions. Is your
20 implication that every patient but five did
21 every weekly transmission.

22 DR. BAROLD: Yes. We defined

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1 "compliance," as Dr. Feld presented in the
2 presentation, as the following: patients had
3 to have at least three out of the four event
4 recordings per month, and at least five out of
5 the six months. That defined somebody as
6 being compliant.

7 CHAIRMAN MAISEL: Great. Thank
8 you.

9 Other panel questions?

10 DR. KARASIK: Bill?

11 CHAIRMAN MAISEL: Yes. Pam?

12 DR. KARASIK: I have just one
13 question. You mentioned that 35 percent of
14 the patients were on anti-arrhythmic drug
15 therapy prior to ablation, but we didn't hear
16 how many patients ended up on drug afterwards.
17 Do you know?

18 DR. BAROLD: Yes. We ended up
19 taking that slide out. There were -- that's
20 something we can talk -- we have a slide that
21 addresses that issue that goes into how many
22 patients were actually -- a fair amount of

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1 patients were taken off of anti-arrhythmic
2 drug therapy. And we do have data that we can
3 provide for you after the FDA presentation.

4 CHAIRMAN MAISEL: Are you able to
5 provide it now?

6 DR. BAROLD: We can. Do you want
7 to put the backup slide up? I think it was
8 somewhere between 11 and 15 patients. We
9 looked at the patients that were -- not this
10 slide. We looked at the patients that were
11 chronic successes, and it's -- not this slide,
12 don't put that up.

13 All right. It may take me a little
14 -- a few minutes to find that slide.

15 CHAIRMAN MAISEL: If you --

16 DR. BAROLD: But I can tell you
17 that it was approximately 10 to 15 patients
18 that had what we called significant anti-
19 arrhythmic changes during the protocol, of
20 which only three of the patients had anti-
21 arrhythmics that were started. All right?

22 Two patients had medication started

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1 for atrial fibrillation, and one patient had
2 it started for atrial tachycardia. And they
3 were started fairly late in the protocol.

4 The rest of them were all
5 physicians that chose to stop the medications.

6 It was approximately 15 percent of the
7 population, though. Okay?

8 CHAIRMAN MAISEL: Other -- yes,
9 Mike.

10 DR. DOMANSKI: I have just one
11 other question, and, Bill, this may not be
12 precisely the right moment, but I want to put
13 it on the table. It seems to me pivotal in
14 this discussion to try to get you to the
15 appropriate level is the redetermination using
16 clinical effectiveness.

17 And, you know, I'm not -- I want to
18 understand what that -- you know, kind of what
19 that really means, because obviously people
20 that have asymptomatic episodes in the
21 clinical determination becomes, frankly, not a
22 very useful -- or potentially not a very

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1 useful construct.

2 So I think it's going to be
3 important as we go forward for you to convince
4 us that that really is a useful construct. I
5 mean, I don't know, for instance, whether I'd
6 feel comfortable stopping anti-coagulation
7 based on that. I know the anti-coag is not
8 critical, but what is critical for sure is
9 meeting those criteria based on the clinical
10 thinking.

11 So I'd like to understand why we
12 should take the -- I don't want to say this in
13 a provocative way, but why the clinical
14 effectiveness is really an effective addition,
15 because that's the key to getting you over
16 their bar.

17 DR. BAROLD: Correct. I think this
18 post hoc analysis is derived from trying to
19 understand how to compare our numbers to the
20 published literature. It's difficult -- if
21 we've done a study that is more rigorous than
22 what is published in the literature, then it

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1 is hard to compare our results to the entire
2 body of published literature.

3 So in order to do that, we
4 evaluated how all of the other studies
5 evaluated their patients, and that would be
6 with a clinical determination. And that would
7 be reviewing the entire patient's file. If
8 the treating physician said, "I don't think
9 this patient had flutter," but there was one
10 event recording that read "possible flutter,"
11 we as a company took this as a strict failure,
12 counted it as a failure, but I think if
13 someone were to publish those results they
14 would have published that as a success.

15 So that's, you know, what we
16 decided to do. We went through every single
17 patient, every single event recording, every
18 single medical change, and every single ECG,
19 and every comment that was made by the
20 treating physician.

21 And at the end, it became obvious
22 whether or not these patients were considered

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1 a treatment failure or a treatment success.
2 Obviously, patients that went on to have a
3 second ablation, those are obviously failures.

4 Any time there was an anti-arrhythmic added
5 for atrial flutter, it's obviously a failure.

6 As you can see, there were 13
7 patients where the treating physician did
8 absolutely nothing. There were no changes in
9 their medication at all, and then handwritten
10 notes saying that, you know, they did not
11 believe that this was not -- that this was
12 atrial flutter.

13 On review of things, they felt, you
14 know -- and that -- and so that's how the
15 analysis was performed. And the reason for
16 performing it was to allow the data to be --
17 to compare sort of apples versus apples versus
18 our study, which we believe to be a more
19 rigorous study.

20 There's nothing that's comparable
21 in the literature to it, so that you can say,
22 "Look, we think this is a -- you know, a

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1 correct value." So that was the purpose of
2 presenting that.

3 And I think he wants to make an
4 additional comment.

5 CHAIRMAN MAISEL: Yes. If I could
6 just make one comment. Mike, I just was going
7 to comment two things. Number one is this
8 panel, I think, should discuss what we think
9 clinical effectiveness means and what is
10 important. And number two is it's not -- the
11 OPC is for us to use, but I'd be interested in
12 hearing from the FDA during their presentation
13 about our latitude in interpreting the OPC.

14 Certainly, my understanding is that
15 it's not a line in the sand. And if think
16 that a product is important and doesn't meet
17 the OPC, but it's important to be approved,
18 then we can recommend approval. If it was as
19 simple as a line in the sand, then we probably
20 wouldn't be having a panel meeting.

21 DR. DOMANSKI: Yes. And, in fact,
22 I would add that one of the panel discussion

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1 things should be the appropriateness of the
2 OPC and how that was arrived at.

3 DR. CALKINS: Mike, the only point
4 I wanted to make is that most atrial flutter
5 is an incessant arrhythmia. It's not
6 paroxysmal. And so these -- you know, this
7 protocol that had weekly event monitoring,
8 picking up these brief, you know, strips like
9 you saw Mel present, you know, that last for
10 10 seconds, are gone the next day, are gone --
11 they aren't present at the clinical followup
12 -- to my mind, that's probably a focal finding
13 from a vein or paroxysmal atrial fibrillation
14 and not really flutter, because once you get
15 into that circuit most flutter is incessant.
16 You stay in it until you get cardioverted,
17 ablated, or whatever.

18 So I think that's an important
19 consideration -- interpreting this very
20 aggressive event monitoring strategy.

21 CHAIRMAN MAISEL: Other panel
22 comments? Yes, Adam.

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1 DR. LOTTICK: Can you explain why
2 you changed the acute success time
3 determination from 30 to 60 -- I'm sorry, from
4 60 to 30 minutes?

5 DR. BAROLD: That was based on the
6 investigator's request. The investigators
7 came to us and said, "Sixty minutes was too
8 long, we'd like to change it to 30 minutes."
9 So after an extensive literature review, we
10 felt that 30 minutes was adequate.

11 And we discussed this with the FDA
12 and a protocol change was accepted, but that
13 is why. It was -- the investigators had asked
14 us to look into this, because 60 minutes was
15 felt to be too -- just too long.

16 DR. LOTTICK: Thank you.

17 DR. BAROLD: Is that --

18 CHAIRMAN MAISEL: Other panel
19 comments? Do you have another question, Adam?

20 DR. LOTTICK: It --

21 DR. BAROLD: Yes. They're
22 reminding me this was an incredible impediment

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1 to recruitment, apparently, as the
2 investigators will tell you.

3 DR. LOTTICK: Because when I look
4 at the time -- I mean, when I look at the data
5 collected over the -- at 60 minutes compared
6 to 30 minutes, it looks like it's a much less
7 successful procedure at the 30-minute -- or,
8 sorry, at the 60-minute time point.

9 DR. BAROLD: Correct. If you run
10 the formal statistics on it, you'll see
11 there's no statistically significant
12 difference between the two. I think it's due
13 to small sample size that you see the changes,
14 but there's no statistical difference between
15 the two.

16 CHAIRMAN MAISEL: Other panel
17 questions or comments at this point? Yes,
18 Pam.

19 DR. KARASIK: Could you comment on
20 the catheter design change that occurred
21 midway through this study?

22 DR. BAROLD: Yes. In fact, why

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1 don't we go ahead and put that slide up, and
2 we can show you the catheter changes. We can
3 have our engineer go through the specific
4 catheter changes, but just to introduce that,
5 the catheter changes were made basically for
6 ease of manufacturing. Extensive studying was
7 done to demonstrate that the catheters are
8 equivalent.

9 And Eric will explain the exact
10 differences between the two catheters used.
11 Yes, put this slide up.

12 MR. RYBA: So the significant
13 changes between the 1100, which was the
14 earlier catheter, and the 1200, one of them
15 was the -- what we call the land length, which
16 is the length of the rigid shaft underneath
17 this electrode band was shortened from 240 to
18 140. This allows greater articulation at the
19 tip of the catheter.

20 There was also the addition of
21 these two radio opaque marker bands here to
22 allow for greater visualization of the

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1 catheter under fluoroscopy. And then, there
2 was also an additional welded steel metal
3 spine segment here that is not in here, and it
4 provides, again, greater articulation.

5 So the manufacturing changes really
6 eased the manufacture of the catheter. But in
7 terms of the function of the catheter, the
8 delivery of liquid nitrous oxide to the tip,
9 the transfer of the cooling power from the tip
10 to the tissue, those were unchanged, and there
11 was extensive studies to prove that.

12 CHAIRMAN MAISEL: This might be a
13 good time to ask about that one device
14 malfunction that was observed. Which catheter
15 was it and/or was it a catheter or the
16 console, what happened?

17 DR. BAROLD: That was one of the
18 1100 catheters. And there was a software
19 change associated around the time between the
20 1100 and the 1200 catheters, such that we had
21 -- we now have extensive experience with the
22 1200 catheter, because we are using it in the

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1 second clinical study that we're doing on
2 atrial fibrillation, and we haven't seen any
3 of the problems that we did see.

4 There were some device failures
5 secondary to the 1100 catheter along the way
6 also. We haven't seen any of those issues
7 with the 1200 catheter.

8 CHAIRMAN MAISEL: Can you be a
9 little more specific about what was observed?

10 DR. BAROLD: About exactly what
11 happened? I would have to look it up right
12 now.

13 CHAIRMAN MAISEL: Okay. Maybe
14 after lunch or later --

15 DR. BAROLD: Sure.

16 CHAIRMAN MAISEL: -- you could give
17 us that information.

18 DR. BAROLD: Sure.

19 CHAIRMAN MAISEL: Other panel
20 comments or questions at this point?

21 (No response.)

22 So why don't we take a 15-minute

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1 break. We'll reconvene at a little before
2 10:00.

3 (Whereupon, the proceedings in the foregoing
4 matter went off the record at 9:43
5 a.m. and went back on the record at
6 10:01 a.m.)

7 CHAIRMAN MAISEL: Welcome back. At
8 this point, I would like to invite the FDA to
9 the podium to give their presentation.

10 DR. FARIS: Good morning. My name
11 is Owen Faris and I'm FDA's lead reviewer for
12 this PMA. I'd like to acknowledge the many
13 members of FDA that took part in this review.

14 Here is a diagram of the sponsor's device. I
15 won't go into detail describing it since the
16 sponsor has already done so.

17 The sponsor's proposed indications
18 for use reads as follows. "The CryoCor
19 Cryoablation System is intended to be used for
20 the treatment of isthmus-dependent atrial
21 flutter in patients 18 years or older". FDA
22 conducted an extensive engineering review of

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