

UNITED STATES OF AMERICA

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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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MEDICAL DEVICES ADVISORY COMMITTEE
CIRCULATORY SYSTEM DEVICES PANEL

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OPEN SESSION

+ + + + +

Thursday
March 6, 2003

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The meeting came to order in Salons A, B, and C of the Gaithersburg Marriott, 9751 Washingtonian Boulevard., Gaithersburg, Maryland, at 10:30 a.m. Warren K. Laskey, M.D., Temporary Chair, presiding.

PRESENT:

WARREN K. LASKEY, M..D.	Temporary Chair
SALIM AZIZ, M.D.	Voting Member
CYNTHIA TRACY, M.D.	Voting Member
MARK C. HAIGNEY, M.D.	Voting Member
CHRISTOPHER J. WHITE, M.D.	Voting Member

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GEORGE W. VETROVEC, M.D.	Voting Member
RICHARD LEIGHTON PAGE, M.D.	Voting Member
ALBERT WALDO, M.D.	Voting Member
FRANCIS R. GILLIAM, III, M.D.	Voting Member
MITCHELL W. KRUCOFF	Voting Member
MERCEDES DULLUM, M.D.	Voting Member
KENT R. BAILEY, Ph.D.	Voting Member
GERETTA WOOD	Executive Secretary
MICHAEL MORTON	Industry Representative
ALLEN A. HUGHES, Ph.D.	Consumer Representative
BRIAN ZUCKERMAN	Director, Division of Cardiovascular Devices

FDA PARTICIPANTS:

JAMES CHENG	Lead Reviewer
LESLIE EWING, M.D.	Clinical and Animal Review
LILLY YUE, Ph.D.	Statistical Review
CINDY DEMIAN	Biocompatibility Review
ELAINE MAYHALL	Sterilization Review
KEVIN HOPSON	Bioresearch Monitoring Review

SPONSORS:

JEAN-PIERRE DESMARAIS, M.D.	Vice President, Scientific Affairs, CryoCath Technologies, Inc.
JEREMY RUSKIN, M.D.	Massachusetts General Hospital
MARC DUBUC, M.D.	Montreal Heart Institute
PETER FRIEDMAN, M.D., Ph.D.	Harvard Medical School
MARWAN ABOUD	Director of Engineering, CCT

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PATRICK CHAUVET

Pre-clinical
Scientist, CCT

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ANDREW SKRYLOV	Consultant,	Cato
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RICHARD HOLCOMB, Ph.D.	Consulting	
	Statistician	
JOHN LEHMANN, M.D.	Consultant,	CCT
	Medical Director	
JOSE NAZARI, M.D.	Illinois Masonic	
	Hospital, Chicago	
MARK NIEBAUER, M.D.	University	of
	Nebraska, Omaha	
DAVID KEANE, M.D.	MGH, Boston	

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P R O C E E D I N G S

10:41 a.m.

CHAIRMAN LASKEY: Good morning. I would like to call us to order.

The topic before us is a PMA for the CryoCath Technologies' French Freezor Cardiac Cryoablation Catheter, P020045.

I would like to ask Ms. Wood to read the paragraph regarding the Chair, Committee, and conflict-of-interest statement. Ms. Wood, please.

MS. WOOD: Just a couple of reminders: If you haven't signed in at the table outside, please do so. Also, please turn your cell phones to silent or off during the meeting. Thank you for your cooperation.

Dr. Cynthia Tracy has been excluded from chairing recent meetings as a result of the regulation governing covered appearance relationships. Since it is expected that for most future Panel meetings Dr. Tracy's covered relationship will continue to preclude her from functioning fully as the Panel Chair, she has

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1 graciously stepped down as Chairperson, but will
2 continue as a voting member of the Panel until the
3 expiration of her term. Dr. Warren Laskey will be
4 the Temporary Voting Chair for this meeting.

5 The following announcement addresses
6 conflict-of-interest issues associated with this
7 meeting and is made part of the record to preclude
8 even the appearance of an impropriety. To
9 determine if any conflict existed, the agency
10 reviewed the submitted agenda for this meeting and
11 all financial interests reported by the Committee
12 participants.

13 The conflict-of-interest statutes
14 prohibit special government employees from
15 participating in matters that could affect their or
16 their employer's financial interest. The agency
17 has determined, however, that the participation of
18 certain members and consultants, the need for whose
19 services outweighs the potential conflict-of-
20 interest involved, is in the best interest of the
21 government. Therefore, waivers have been granted
22 for Drs. George Vetovec, Kent Bailey, Mercedes

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1 Dullum, and Albert Waldo for their interest in
2 firms that could be affected by the Panel's
3 recommendations.

4 Dr. Vetovec's waiver involves stock in
5 the parent of a competitor. The stock is valued
6 from \$50,001 to \$100,000.

7 Dr. Bailey's waiver involves a grant to
8 his institution for the sponsor's product study in
9 which he had no involvement and for which funding
10 was between \$100,001 and \$300,000 per year.

11 Dr. Dullum's waiver involves stock in a
12 competitor. The stock is valued from \$25,001 to
13 \$50,000.

14 Dr. Waldo's waiver involves consulting
15 for a competitor's unrelated product, for which he
16 receives an annual fee of less than \$10,001.

17 Copies of these waivers may be obtained
18 from the agency's Freedom of Information Office,
19 Room 12A-15 of the Parklawn Building.

20 We would like to note for the record that
21 the agency took into consideration other matters
22 involving Drs. Vetovec, Dullum, Mark Haigney,

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1 Mitchell Krucoff, and F. Roosevelt Gilliam. Each
2 of these panelists reported interests in firms at
3 issue, but in matters that are not related to
4 today's agenda.

5 The agency has determined, therefore,
6 that they may participate fully in all discussions.

7 In the event that the discussions involve any
8 other products or firms not already on the agenda
9 for which an FDA participant has a financial
10 interest, the participant should excuse him or
11 herself from such involvement, and the exclusion
12 will be noted for the record.

13 With respect to all other participants,
14 we ask in the interest of fairness that all persons
15 making statements or presentations disclose any
16 current or previous financial involvement with any
17 firm whose products they may wish to comment upon.

18 CHAIRMAN LASKEY: Thanks, Geretta.

19 At this point I would like to have the
20 Panel members introduce themselves, starting to my
21 left, please.

22 DR. ZUCKERMAN: Brian Zuckerman, FDA,

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1 Division Director, Cardiovascular Devices.

2 DR. GILLIAM: Roosevelt Gilliam with the
3 Virginia Cardiovascular Specialists in private
4 practice of electrophysiology, Richmond, Virginia.

5 DR. PAGE: Rick Page, Cardiac
6 Electrophysiologist, now at the University of
7 Washington in Seattle.

8 DR. WALDO: I'm Al Waldo, Cardiac
9 Electrophysiologist, Case Western Reserve
10 University in Cleveland.

11 DR. BAILEY: Kent Bailey, Biostatistician
12 at Mayo Clinic.

13 MS. WOOD: Geretta Wood, Exec. Sec. of
14 the Circulatory System Devices Panel.

15 CHAIRMAN LASKEY: Warren Laskey. I'm an
16 Interventional Cardiologist at the National Naval
17 Medical Center.

18 DR. WHITE: Chris White. I'm an
19 Interventional Cardiologist in the Ochsner Clinic
20 Foundation in New Orleans, Louisiana.

21 DR. VETROVEC: George Vetrovec, Chairman,
22 Division of Cardiology, Virginia Commonwealth

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1 University.

2 DR. DULLUM: Mercedes Dullum, Cardiac
3 Surgeon, cryo practice, Washington Hospital Center.

4 DR. TRACY: I'm Cindy Tracy. I'm at
5 Georgetown University Hospital, and I not so
6 graciously did try to get my brother fired, but it
7 didn't work.

8 (Laughter.)

9 DR. HAIGNEY: I'm Mark Haigney. I'm a
10 Cardiac Electrophysiologist at the National Naval
11 Medical Center and Director of Cardiology at
12 Uniformed Services University.

13 DR. HUGHES: Alan Hughes, Assistant
14 Professor of Decision Sciences and MIS at George
15 Mason University, and I'm the consumer
16 representative.

17 MR. MORTON: I'm Michael Morton. I'm an
18 employee of Sorin-COBE Cardiovascular, and I'm the
19 industry representative to the Panel.

20 CHAIRMAN LASKEY: Thank you, colleagues.

21 Geretta, if you could read the voting
22 status statement, please?

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1 MS. WOOD: "Pursuant to the authority
2 granted under the Medical Devices Advisory
3 Committee charter, dated October the 27th, 1990,
4 and as amended August the 19th, 1999, I appoint the
5 following individuals as voting members of the
6 Circulatory System Devices Panel for this meeting
7 on March the 6th, 2003:

8 "Mark C. Haigney, M.D.; Christopher J.
9 White, M.D.; George W. Vetovec, M.D.; Kent R.
10 Bailey, Ph.D.; Mitchell W. Krucoff, M.D.; Richard
11 L. Page, M.D.; Albert L. Waldo, M.D.; Francis R.
12 Gilliam, M.D., and Mercedes K. Dullum, M.D.

13 "For the record, these individuals are
14 special government employees and are consultants to
15 this Panel under the Medical Devices Advisory
16 Committee. They have undergone the customary
17 conflict-of-interest review and have reviewed the
18 material to be considered at this meeting.

19 "In addition, I appoint Warren K. Laskey,
20 M.D., to act as Temporary Chairperson for the
21 duration of this meeting."

22 And it is signed by David W. Feigal, Jr.,

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1 M.D., MPH, Director, Center for Devices and
2 Radiological Health, on February 26th, 2003.

3 CHAIRMAN LASKEY: I would like to open
4 the public hearing portion of this morning's
5 program. Is there anyone in the audience who
6 wishes to address the Panel on today's topic or any
7 reasonably-germane topic?

8 (No response.)

9 If not, then I will close the open public
10 hearing session.

11 I would like to begin with the sponsor's
12 presentation.

13 MS. WOOD: I would also like to remind
14 the speakers to introduce themselves and to state
15 your conflict of interest before speaking.

16 DR. DESMARAIS: Good morning, ladies and
17 gentleman, Mr. Chairman, and Panel members.

18 My name is Jean-Pierre Desmarais. I am
19 CryoCath Vice President of Scientific Affairs. It
20 is my pleasure to present our technology to this
21 Panel. As well, we will present the results of our
22 pivotal study. Here is the agenda of the meeting:

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1 I'm introducing the group. Then we will
2 present the evolution of technology, the details of
3 the freezor device, a brief synopsis of the pre-
4 clinical testing, the pivotal clinical study, and a
5 few concluding remarks.

6 The presenters will be myself, Dr. Jeremy
7 Ruskin, Director, Cardiac Arrhythmia Service,
8 Massachusetts General Hospital.

9 Dr. Marc Dubuc, Co-Principal
10 Investigator, Chief of Electrophysiology Service,
11 Montreal Heart Institute.

12 Dr. Peter Friedman, Co-Principal
13 Investigator, also Professor of Medicine, Harvard
14 Medical School, Brigham and Women's Hospital.

15 Also available for questions will be from
16 CryoCath: Marwan Abboud, Director of Engineering;
17 Patrick Chauvet, Pre-Clinical Scientist.
18 Consultants: Susan Bondy, VCRA, Cato Research;
19 Andrew Skrylov, Study Statistician, Cato; Richard
20 Holcomb, Consulting Statistician; John Lehmann,
21 Consultant, CryoCath Medical Director.

22 Investigators present with us as well

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1 are: Dr. Jose Nazari from Illinois Masonic
2 Hospital in Chicago; Dr. Mark Neibauer, University
3 of Nebraska, Omaha, and Dr. David Keane from
4 Massachusetts General Hospital in Boston.

5 CryoCath is a public-traded company that
6 was founded in 1995 and which counts over 150
7 employees now. CryoCath designs, develops,
8 manufactures, and distributes products from its
9 location in Montreal, Canada, as well as the
10 freezor catheter which is the subject of this PMA.

11 CryoCath offers products to
12 interventionalists and cardiac surgeons for the
13 treatment of arrhythmia.

14 Our catheter and probe-based products
15 include Freezor and Freezor Xtra for the treatment
16 of cardiac arrhythmia, Arctic Circler for the
17 treatment of AF originating from pulmonary veins,
18 and SurgiFrost, a cryosurgical probe for the
19 surgical treatment of cardiac arrhythmia.

20 Our products have been on the market
21 since 2001 in Europe, Canada, Australia, and other
22 countries. Several clinical trials are being

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1 conducted in Europe and elsewhere with the Freezor
2 Catheter, and CryoCath has put in place an
3 international patient registry to collect data from
4 the use of its various products, including Freezor.

5 In the USA, a feasibility trial is
6 underway with the Freezor Catheter to assess the
7 feasibility of treating posterseptal pathways
8 through the coronary sinus.

9 Today we will present the results of the
10 FROSTY trial, as well as other pre-clinical and
11 clinical information related to this PMA.

12 CryoCath has proposed the following
13 indications for use: The CryoCath Freezor is
14 indicated for the cryoablation of the conducting
15 tissues of the heart in the treatment of patients
16 with atrioventricular node reentrant tachycardia,
17 AVNRT, and for identification of aberrant tissue
18 responsible for supraventricular tachycardia, using
19 reversible electrophysiological cryomapping near
20 the AV node to minimize AV block.

21 We will now show you the evidence that we
22 believe supports the following conclusion:

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1 Cryoablation with Freezor has an excellent safety
2 profile. No permanent AV block is clinically
3 effective in AVNRT patients, has excellent long-
4 term success, and has reversible cryomapping.

5 I would like to introduce Jeremy Ruskin,
6 who will present the evolution of cryoablation.

7 DR. RUSKIN: Thank you, and good morning.

8 Mr. Chairman, Panel members, ladies and gentlemen,
9 I am Jeremy Ruskin. I am a paid consultant to and
10 own a small equity position in CryoCath, and my
11 travel expenses are paid by CryoCath.

12 The purpose of my talk is to address very
13 briefly with you some of the history and specific
14 technologic aspects of cryoablation therapy. This
15 form of ablation is not new. In fact, it dates
16 back over a century and currently is widely used in
17 a number of areas of clinical therapeutics,
18 including gynecology, urology, tumor surgery, and
19 dermatology.

20 There's also extensive experience with
21 cardiac surgery using cryoablation for the
22 treatment of cardiac arrhythmias, and this goes

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1 back more than 30 years.

2 While they are working on the slides, in
3 the interest of time, I will try to do the best I
4 can from memory. There are several areas of
5 cardiac surgery in which cryoablation therapy has
6 been applied. The first was intentional creation
7 of AV block in patients with disabling or life-
8 threatening drug-resistant supraventricular
9 tachycardias. It became obvious, when the
10 technique was applied in this setting, that it was
11 both safe and highly effective in producing cold
12 injury that would result in the induction of AV
13 block.

14 It subsequently was applied to treatment
15 of both AV nodal reentrant tachycardias and Wolf
16 Parkinson-like syndrome and, in fact, was the
17 mainstay, the only nonpharmacological option
18 available for the curative treatment of AV node
19 reentry and accessory AV connections until catheter
20 ablation emerged, particularly that using
21 radiofrequency current in the late 1980s.

22 Cryoablation has also been used in the

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1 treatment of ventricular tachycardia, primarily as
2 an adjunct to endocardial resection, but also as a
3 primary therapy in some situations.

4 That's it. Thank you. And I will note
5 in this particular indication, it became evident
6 that, because of the ability of cryoablation to
7 preserve the underlying tissue architecture while
8 destroying myocytes, one was left with intact
9 tissue with good tensile strength, and surgeons
10 became comfortable applying this therapy to the
11 papillary muscles in the intraventricular septum,
12 sites at which incisional therapy and heat-based
13 therapies could not be used because of concerns
14 about perforation.

15 More recently, cryotherapy has been
16 applied for the treatment of atrial fibrillation by
17 surgeons using both open and minimally-invasive
18 techniques.

19 Next, please. What I would like to do in
20 the next few minutes is speak briefly about the
21 mechanisms of tissue destruction, make a few
22 comments about the histologic characteristics of

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1 cryolesions, and then comment briefly on two unique
2 properties of cryoablation, that of adhesion and
3 reversibility.

4 Next, please. When applied to the
5 myocardium, cold energy produces a very well-
6 demarcated area of freezing that results in a zone
7 of irreversible cell injury. This, then,
8 progresses to replacement fibrosis. Interestingly,
9 as mentioned previously, despite the destruction of
10 myocytes, the integrity of fibrous stroma is
11 preserved, so that the underlying tissue
12 architecture and the tensile strength of the tissue
13 is maintained, even during the acute application of
14 cryoablation.

15 Next, please. This is an artist's
16 rendition of application of a cryocatheter to the
17 endocardium of the heart, resulting in a zone of
18 freezing that produces irreversible cell injury and
19 results in the long-term formation of a dense,
20 fibrous scar. There is an outer halo which is
21 cooled to lower temperatures and at which the
22 effects of the cryoapplication are reversible.

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1 Next slide, please. This is a typical
2 histologic section. This is taken from a canine
3 heart one week after application of cryo energy.
4 The key features are illustrated here.

5 First, there is an extremely homogeneous
6 dense fibrous scar with very well-demarcated
7 margins, and there is preservation of the
8 endocardial surface. These features are relatively
9 unique to cryotherapy.

10 Next slide, please. This is just a
11 photograph from our institution in the late 1970s
12 illustrating the use of a surgical cryoprobe in a
13 patient with ventricular tachycardia, and you can
14 see the frost forming on the probe at this point.
15 As mentioned, the surgeons were particularly
16 comfortable using this form of energy because of
17 their ability to treat tachycardias over the
18 papillary muscles and also the septum without major
19 concerns about the risk of perforation.

20 Next slide, please. Cryo has a number of
21 unique properties, two of the most important of
22 which are illustrated in the next two slides.

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1 The first is that, when a cryoablation
2 device is applied to the myocardium, it adheres
3 firmly to that tissue during the freeze period.
4 Loss of adhesion occurs immediately upon rewarming.

5 This is a unique attribute of cryoablation, and it
6 allows application of cold energy in close
7 proximity to critical structures like the AV node
8 without concern about catheter migration or
9 slippage. This property is distinctly different
10 from what is seen with heat-based energy sources.

11 Next, please. This slide is a movie of a
12 cryocatheter, outlined in blue, introduced through
13 the neck and into an anterioseptal position on the
14 tricuspid annulus.

15 I hope that this continues to play. If
16 we can run that one more time, what you will see
17 during this is remarkable stability of this
18 catheter on the tricuspid annulus in an
19 anterioseptal position. You see termination of the
20 tachycardia, restoration of sinus rhythm with
21 literally no movement of the catheter except in
22 conjunction with the cardiac cycle. In that

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1 position, which is a very delicate position, that
2 kind of stability is almost impossible to achieve
3 with radiofrequency devices. That is a result of
4 adherence during the freeze.

5 Next, please. The other unique property
6 is that reversibility, which is defined as using
7 warmer temperatures or shorter durations of
8 application to cause reversible alterations in
9 cardiac conduction. This is currently referred to
10 as cryomapping and historically was known as ice
11 mapping, something that was used extensively by the
12 surgeons, and in some cases still is.

13 It is used most commonly when working in
14 close proximity to the AV conduction system, and is
15 a unique attribute which allows reversible
16 interruption of cardiac conduction without creating
17 permanent electrophysiologic effects.

18 Next, please. This is another artist's
19 rendition, just to emphasize the fact that
20 cryomapping and cryoablation are part of a spectrum
21 and that cryomapping, which is defined as a
22 reversible change in the electrophysiology of the

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1 tissue, occurs at warmer temperatures and with
2 shorter durations of exposure, whereas true
3 ablation occurs at colder temperatures and with
4 longer durations of exposure.

5 Next, please. In conclusion, then,
6 cryoablation is a unique technology that has been
7 used safely and effectively in the surgical
8 treatment of cardiac arrhythmias for more than 30
9 years. So this is not a new form of ablation.
10 What is unique about today's presentation is the
11 availability of this energy source in a catheter-
12 based platform.

13 Cryoablation has different properties
14 from heat-based energy and results in the following
15 unique attributes: One, it produces well-
16 demarcated, homogeneous, dense fibrous lesions with
17 minimal to no disruption of the endocardium and a
18 low propensity to thrombus formation.

19 Cryoablation devices adhere to cardiac
20 tissue, providing an inherent stability to
21 catheters during the ablation itself, and
22 cryoablation provides the ability to cause

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1 reversible alterations in cardiac conduction, which
2 provide operators with the potential for targeting
3 desirable sites for ablation while avoiding
4 undesirable sites, such as the AV conduction
5 system.

6 Thank you for your attention, and I would
7 like to turn the podium back to Jean-Pierre
8 Desmarais.

9 DR. DESMARAIS: Thank you, Dr. Ruskin.

10 I would like to present a technical
11 aspect of this device. First, I will begin with
12 some definitions of cryoablation terms.
13 Cryocatheter, an ablation catheter which causes
14 necrosis by application of low temperature.
15 Cryoapplication, cooling a specific portion of the
16 heart with either diagnostic mapping or therapeutic
17 ablative intent. Cryoablation, cryoapplication at
18 the coldest attainable temperature for a period
19 sufficient to cause tissue necrosis. In the FROSTY
20 study, cryoablation consisted of one four-minute
21 cryoapplication at a set temperature of minus 68
22 degrees Centigrade or colder.

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1 Cryoadhesion, the adherence of the tip of
2 a cryocatheter to tissue during a cryoapplication.

3 Cryolesions, lesions created by cryoablation.
4 And, finally, cryomapping, a limited
5 cryoapplication intended to cause reversible
6 alteration in cardiac conduction, achieved by using
7 shorter times or warmer temperatures.

8 This table shows the differences between
9 cryoablation and RF ablation catheters, and I would
10 like to point to the main difference. The energy
11 source is nitrous oxide for cryocatheters, which is
12 widely used as anesthesiology gas. The mode of
13 action and ablation mechanism cryofreezes tissue,
14 leading to ice formation and disruption of cellular
15 membranes while RF heats tissues and denatures
16 protein. Finally, cryo energy has the ability to
17 provide reversible mapping, a unique feature,
18 unlike RF current energy.

19 The system is comprised of a console
20 which contains a refrigerate, the user interface,
21 and the safety-monitoring system, a 7 French
22 catheter with a 4-millimeter deflectable tip,

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1 electrical and mechanical umbilical to transport
2 the refrigerant and electrical signals between the
3 console and the catheter.

4 The major safety features include a
5 vacuum system that maintains the catheter shaft
6 under negative pressure to prevent any potential
7 release of refrigerant gas into the bloodstream,
8 flow detection monitoring and vacuum sensors to
9 monitor key operating parameters to prevent
10 catheter pressurization.

11 A leak detection system which disables
12 refrigerant injection, in the unlikely event of a
13 catheter breach; a blood detector in the handle to
14 prevent the aspiration of blood through the
15 catheter. We believe these were well-designed and
16 tested features and will offer unparalleled safety
17 for this device.

18 This slide presents the extensive design
19 verification testing done on the safety system and
20 the device attribute. All the testing conformed to
21 FDA guidance and industry standards.

22 I would like now to introduce Dr. Marc

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1 Dubuc from the Montreal Heart Institute, who will
2 summarize the pre-clinical experimentation.

3 DR. DUBUC: Thank you. Ladies and
4 gentlemen, Mr. Chairman, and Panel members, my name
5 is Marc Dubuc. I am Co-Principal Investigator of
6 the FROSTY trial and I am also a paid consultant to
7 CryoCath. I do not have an equity position in
8 CryoCath. My travel expenses for this meeting have
9 been paid by the company.

10 I would like to present a pre-clinical
11 testing. Extensive animal testing in over 250
12 animals confirmed cryocatheters' handling
13 characteristics, safety features, and ability to
14 make cryolesions.

15 In addition, we demonstrated the ability
16 to cryomap, and we compared cryolesions to RF
17 lesions, demonstrating reduced thrombogenicity
18 compared to RF lesions.

19 We also have demonstrated the ability to
20 ablate safely adjacent to coronary vessels. These
21 studies provided sufficient evidence of feasibility
22 and safety to proceed to IDE clinical study.

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1 On the left is a typical cryolesion,
2 homogeneous, sharply-demarcated, and dense. This
3 lesion was made with the four-minute
4 cryoapplications at minus 70 degrees Centigrade.
5 Note the intact endocardium.

6 On the right is representative RF lesions
7 for comparison made with temperature-controlled RF
8 at 70 degrees Centigrade for 60 seconds. Note the
9 adherent thrombus.

10 Next slide. A study randomizing RF and
11 cryolesions in the canine heart demonstrated that
12 the median depth for cryoablation of 5 millimeters
13 and RF lesions 5.3 millimeters, shown in the first
14 column, were the same. However, lesion volumes for
15 RF ablation, 95 cubic millimeters, were roughly
16 twice as large as cryoablation lesions at 49 cubic
17 millimeters. This resulted directly from the
18 larger surface area of RF lesions in comparison to
19 cryolesions.

20 Note that the interquartile range for
21 cryolesions are much smaller than those for RF
22 ablation. Cryolesions are more focused at equal

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1 lesion depths with less tissue destruction and have
2 much less dimensional variability than RF ablation
3 lesions.

4 Next. In this same study, lesion-
5 associated thrombus was compared using computerized
6 morphometry. Only 13 percent of cryolesions had
7 lesion-associated thrombus compared with 76 percent
8 of the RF lesions. This difference was highly
9 significant.

10 In addition, the median thrombus volume
11 was zero for cryolesions and 2.8 cubic millimeters
12 for RF ablation lesions. This difference was also
13 highly significant.

14 This slide shows the lesion-associated
15 thrombus in this study. On the left you see
16 cryoablation lesions of 23 lesions with no detected
17 thrombus and three lesions with thrombus volumes of
18 0.4, 0.6, and 5.5 cubic millimeters.

19 On the right you see that the RF lesions
20 at over 75 percent of the lesions with associated
21 thrombus ranging in size to several thrombi lighter
22 than 20 cubic millimeters. The association of RF

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1 lesions with increased frequency and size of
2 thrombus remain even after all other variables were
3 controlled for.

4 Next. The use of the freezor catheter to
5 ablate accessory pathways via the coronary sinus
6 system was also studied in a canine model.
7 Ablation was performed within 2 millimeters of the
8 adjacent coronary artery, using RF at 30 to 50
9 watts for 60 seconds. Cryoablation was
10 administered at minus 75 degrees Centigrade for
11 either one or two four-minute cycles. Sacrifice
12 was performed at one week for RF and one week and
13 three months for cryo. Assessments were made for
14 transmuralty of the coronary sinus lesions and for
15 stenosis by IVUS and geography and histology.

16 These slides depict the placement of the
17 ablation catheters in the coronary venous system .

18 On the top, three angiograms of RF animals, we see
19 the development of a significant stenosis in the
20 left coronary artery one week after RF ablation in
21 the CS adjacent to the artery. Compare this to the
22 lower panel in which no stenosis developed in

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1 cryolesion animals one week and three months after
2 cryoablation.

3 This study showed that both RF and
4 cryoablation led to transmural coronary sinus
5 lesions. At all subsequent time points, measures
6 of stenosis were much worse in the RF-ablated
7 hearts as compared to cryoablated hearts with no
8 cryoablated lesions showing atrial stenosis.
9 Histology at three months showed healed and
10 endothelialized with no stenosis, only minor
11 intimal proliferation, two to three cell layers.

12 In summary, our animal experimentation
13 with the CryoCath cryoablation catheter
14 demonstrated that cryolesions are dense,
15 homogeneous, and well-demarcated. Cryolesions are
16 focused as deep as RF lesions with a smaller volume
17 of tissue destruction. Cryolesions are associated
18 with significantly less frequent and significantly
19 smaller thrombi, even when lesion dimensions are
20 controlled for.

21 Cryoablation in proximity to coronaries
22 is significantly less likely to produce coronary

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1 artery stenosis. These studies provided sufficient
2 evidence of feasibility and safety to proceed to
3 IDE clinical study.

4 Now I would like to introduce Dr. Peter
5 Friedman.

6 DR. FRIEDMAN: Thank you, Marc. Ladies
7 and gentlemen, Mr. Chairman, and Panel members, my
8 name is Peter Friedman. I am Co-Principal
9 Investigator for the FROSTY trial. I'm also a paid
10 consultant to CryoCath. I do not have an equity
11 position in CryoCath. My travel expenses for this
12 meeting have been paid by the company.

13 I would like to present the FROSTY study.
14 Next, please. The FROSTY study was a non-
15 randomized, single-arm, multicenter study. It
16 utilized FDA's previously-determined objective
17 performance criteria, or OPCs, that were developed
18 during RF catheter testing.

19 The primary safety endpoint was acute
20 major complications, or AMCs, and the primary
21 effectiveness endpoint, acute procedural success,
22 or APS. The safety secondary endpoint was the

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1 occurrence of long-term major complications and the
2 effectiveness secondary endpoint, freedom from
3 recurrence of the targeted arrhythmia.
4 Furthermore, this study was designed to investigate
5 the cryomapping effect and the reversibility of
6 cryomapping.

7 Next, please. The inclusion criteria for
8 FROSTY were a documented history of
9 supraventricular tachycardia, either AV nodal
10 reentrant SVT, AV reentrant tachycardia utilizing a
11 bypass track, or atrial fibrillation requiring AV
12 node ablation for rate control.

13 Patients had been referred for
14 radiofrequency ablation. The ejection fraction had
15 to be greater than or equal to 35 percent, age
16 greater than or equal to 18 years.

17 Finally, the diagnostic
18 electrophysiologic study had to document inducible
19 sustained AVNRT or AVRT in the baseline state or
20 the presence of a rapid ventricular response in the
21 setting of AF, requiring AV nodal ablation.

22 Next slide, please. These are the

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1 exclusion criteria in the trial, typical for what
2 one would expect. Note that atrial tachycardia was
3 an exclusion criterion, and the others are ones
4 that you would predict.

5 Next, please. These are the FROSTY study
6 hypotheses for safety: the 95 percent, double-
7 sided upper confidence bound of the proportion of
8 safety subjects with AMCs was greater than 7
9 percent for the null hypothesis and less than or
10 equal to 7 percent for the alternative hypothesis.

11 For effectiveness, acutely, the 95
12 percent double-sided lower confidence bound of
13 acute procedural success, or APS, for intent-to-
14 treat subjects was less than 85 percent for the
15 null hypothesis and greater than or equal to 85
16 percent for the alternative hypothesis. Long-term
17 clinical success, freedom from recurrence at six
18 months would be greater than or equal to 85
19 percent.

20 We estimated that a sample size of 165
21 evaluable safety subjects was required to establish
22 a 95 percent upper confidence bound of less than or

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1 equal to 7 percent, when the acute major
2 complication did not exceed a target value of 3
3 percent.

4 We also estimated that a sample size of
5 150 subjects intent to treat was required to
6 establish a 95 percent lower confidence bound of
7 greater than or equal to 85 percent, when the acute
8 procedural success exceeded a target value of 91
9 percent.

10 Next, please. One hundred and sixty-six
11 subjects were enrolled at 14 sites. Eleven of
12 these were in the United States; three were
13 Canadian.

14 The first subject enrolled on March 23rd
15 of 2001. The last six-month followup was on
16 October 23rd of 2002. Protocol compliance
17 supported the scientific validity of the study
18 conclusions.

19 Next, please. Overall, 166 patients were
20 enrolled with a mean age of 48 years. Patients
21 with AVNRT and patients with AVRT tended to be
22 older than the atrial fibrillation patients.

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1 As one can see, the mean of body surface
2 indices were typical for what one would expect in
3 North America, and there was a female preponderance
4 in each of the three groups in a ratio of
5 approximately two to one.

6 Next, please. One hundred and sixty-six
7 subjects were enrolled. All of these are
8 considered safety subjects, and they were comprised
9 of 103 patients with AVNRT, 51 patients with AVRT,
10 and 12 with atrial fibrillation. This distribution
11 of diagnoses closely matches that seen in routine
12 clinical practice.

13 Two patients with AVRT were not treated
14 because of equipment failures, which left a total
15 of 164 intention-to-treat patients. One of the
16 subjects initially diagnosed as AVNRT turned out to
17 have atrial tachycardia, which was an excluded
18 arrhythmia in this trial, and, therefore, cryo
19 treatment was abandoned in that individual. Six
20 other subjects did not have a protocol-specified,
21 qualifying cryoablation; namely, one lasting for
22 four minutes at less than or equal to minus 68

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1 degrees. Excluding these seven patients yields 157
2 per-protocol patients who were correctly diagnosed
3 and had at least one qualifying cryoablation.

4 Next slide, please. Basic study
5 procedures were nearly identical to standard
6 diagnostic and therapeutic RF ablation procedures
7 with the addition of protocol-mandated assessments.

8 All of the preparation of these patients and the
9 diagnostic portion of the EP study were identical.

10 When the cryocatheter had been introduced
11 into the body and correctly positioned, the console
12 was activated, either for cooling to achieve
13 ablation or for mapping at the ablation catheter
14 tip. A physician monitored the response at the
15 tip, noting particularly temperature and time of
16 application. When the cryoapplication was
17 complete, the console stopped the flow of
18 refrigerant gas, the catheter was allowed to thaw,
19 and the catheter was then moved, if desired.

20 Next, please. This slide shows a typical
21 panel from the cryo console during the
22 cryoablation. On the righthand side are the

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1 controls to set the pre-determined tip temperature
2 and the time of application. In the mid-panel note
3 the orange tracing which depicts the pre-determined
4 tip temperature that was set. The white tracing
5 represents the actual tip temperature in the
6 catheter, recorded by a thermocouple. We can see
7 how closely it mirrors the pre-determined desired
8 temperature during the cryoapplication.

9 At the end of 240 seconds, the injection
10 is halted and very quickly one sees a return of the
11 tip temperature to body temperature; namely, 37
12 degrees. The total application here was 240
13 seconds.

14 Next, please. This slide illustrates the
15 procedural details for all the patients. One
16 hundred and sixty-four patients underwent
17 cryoablation. There were 1,230 cryoapplications
18 for ablation with a mean of 7.5, ranging between 1
19 and 36. One hundred and thirty-five subjects had
20 cryomapping with a total of 820 cryomapping
21 attempts, a mean of 6.1 per patient, ranging from 1
22 to 37. Mean fluoroscopy time was 25 minutes, mean

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1 procedural duration 265 minutes. The mean
2 cryoablation temperature, minus 71.2 degrees
3 Centigrade, and mean cryomapping temperature, minus
4 26.6 degrees Centigrade.

5 Next, please. I would like to now
6 present the safety results. I will discuss major
7 safety outcomes; namely, acute major complications,
8 or AMCs, deaths and serious adverse events, SAEs,
9 and other device-related adverse events. I would
10 then like to present the safety results for the AV
11 nodal reentry tachycardia subjects specifically.

12 I would like to add that all adverse
13 events were reviewed by the investigators, study
14 monitors, and the medical monitor, and were then
15 reviewed and adjudicated for final characterization
16 by an independent adverse event adjudication
17 committee which convened on three separate
18 occasions.

19 Next, please. Seven subjects experienced
20 a total of eight acute major complications, for an
21 AMC rate of 4.2 percent with a 95 percent
22 confidence interval ranging from 1.7 to 8.5

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1 percent.

2 No AMC was device-related, as adjudicated
3 by the independent committee. All subjects
4 recovered completely. However, the primary safety
5 hypotheses based on OPC with a 95 percent upper
6 confidence bound of less than or equal to 7 percent
7 was, therefore, not met.

8 Next, please. This slide illustrates the
9 AMC in each subject. One subject had a minor
10 pulmonary embolism requiring brief hospitalization.

11 One subject developed prostatitis after traumatic
12 placement of a Foley catheter.

13 One subject, after a lengthy procedure
14 utilizing cryoablation which failed and then RF
15 ablation, was found the day after the procedure by
16 echocardiography to have adherent thrombus in the
17 inferior vena cava. This patient's procedure began
18 at 9:00 in the morning, and heparin was not
19 administered until three or four o'clock in the
20 afternoon. The patient was treated with
21 anticoagulation, and a follow-up echocardiogram
22 revealed resolution of the thrombus.

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1 One subject with a left lateral accessory
2 pathway failed cryoablation and then was treated
3 with radiofrequency catheter ablation. Several
4 hours after the procedure he developed evidence of
5 acute myocardial infarction. Emergency angiography
6 revealed occlusion of the right coronary artery, a
7 site distant from the site of ablation. This was
8 treated by angioplasty and stenting, with complete
9 resolution of the symptoms and of the evidence of
10 infarction. He was discharged some days later with
11 a normal ejection fraction.

12 One subject was noted to have a
13 partially-sheared introducer sheath during removal
14 of a diagnostic catheter. One subject had
15 perforation of the right ventricle during
16 manipulation of the RV apex diagnostic catheter.
17 This patient required pericardial centesis. The
18 same subject was also noted to have deep venous
19 thrombophlebitis on day two after the procedure

20 Finally, one subject with failed
21 cryoablation -- this was the subject with the
22 atrial tachycardia -- had the cryoablation catheter

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1 removed from the body, and preparations were then
2 initiated for a transseptal catheterization because
3 the focus was located in the left atrium. An
4 intracardiac echo was performed that revealed
5 thrombus that was adherent to a diagnostic catheter
6 extending down the IVC. That catheter and the
7 thrombus were removed. A small, residual thrombus
8 remained on the right atrial wall. The patient was
9 anticoagulated and had no permanent sequelae.

10 Next, please. This slide shows deaths
11 and serious adverse events. One unrelated death
12 occurred in an 89-year-old subject who was
13 hospitalized for cholecystectomy and who had a
14 stroke. This was four months after successful
15 cryoablation.

16 Twenty subjects, or 12 percent of the
17 total, had a total of 26 serious adverse events.
18 None of these was device-related, as adjudicated by
19 the independent committee. Seventeen of 20
20 subjects recovered completely and three did not:
21 the subject who died, another with unrelated
22 compression fractures, and a third unrelated

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1 depression.

2 Next, please. All device-related adverse
3 events were various kinds of AV conduction
4 disturbances. The duration of these was a median
5 of 45 seconds, ranging between 10 seconds and 24
6 hours. All of the longer-duration AV conduction
7 disturbances were examples of incomplete or
8 complete right bundle branch block. No patient
9 developed permanent AV block.

10 The etiology of these conduction
11 disturbances was felt to be related to cryoablation
12 in seven, related to cryomapping in one, due to
13 mechanical trauma in one patient during pacing and
14 was noted post procedure in one patient.

15 Next, please. This table shows you all
16 14 instances of AV conduction disturbance in the 11
17 patients. You see that the longest duration
18 abnormalities were those of incomplete or complete
19 right bundle branch block. AV block, ranging from
20 first degree to complete AV block, generally was
21 very, very short-lasting, often resolving within a
22 matter of seconds. I would like to emphasize how

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1 dramatically different this is compared to
2 radiofrequency catheter ablation.

3 During RF ablation, an accelerated
4 junctional rhythm is induced which impairs the
5 operator's ability to assess anterograde AV
6 conduction. When transient AV block occurs during
7 RF ablation, 30 to 50 percent of those patients go
8 on to have permanent conduction abnormalities that
9 require a permanent pacemaker. The chance of that
10 developing ranges from 1 to 4 percent, depending on
11 the site of ablation.

12 Cryoablation is very, very different.
13 There is no junctional rhythm. One can assess
14 anterograde conduction during the ablation, and if
15 AV block develops, it resolves very quickly.
16 Indeed, the investigators in this trial quickly
17 obtained a high degree of confidence with this
18 technology in using it very close to the AV node.

19 Next, please. This slide shows the
20 procedure-related acute major complications in the
21 AV nodal reentry track of cardio subjects.
22 Specifically, three of the 103 patients, or 2.9

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1 percent, had procedure-related acute major
2 complications. One was the subject with the
3 pulmonary embolism; another with prostatitis due to
4 a traumatic Foley placement, and the third, the
5 patient we have mentioned already, with atrial
6 tachycardia who developed thrombus on a diagnostic
7 catheter.

8 There were, of course, again no permanent
9 AV blocks in this group. This is a clinically-
10 excellent safety profile in this patient group.
11 You can see that the 95 percent confidence interval
12 for the AMC rate was .6 to 8.3 percent, and with
13 the Bonferroni correction for multiple comparisons,
14 it ranged from .4 to 9.6 percent.

15 Next, please. To summarize the safety
16 results in FROSTY, it is true that the overall
17 statistical endpoint was not met. However, as an
18 experienced electrophysiologist, I can assure the
19 Panel that this outcome represents an excellent
20 safety profile overall, particularly for the AVNRT
21 patients.

22 I should emphasize again there were no

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1 device-related AMCs. There were no device-related
2 SAEs, and there were no instances of permanent AV
3 block in 151 patients at risk.

4 Next, please. Now I would like to
5 present the effectiveness data. I'll present the
6 acute procedural success for all intent-to-treat
7 subjects and for the AVNRT subjects specifically.
8 Then I will discuss those subjects who were acute
9 cryoablation failures who were treated with
10 radiofrequency ablation. Finally, I will discuss
11 long-term clinical success.

12 With regard to acute procedural success
13 in the intent-to-treat subjects, there were 164
14 such subjects with AVNRT, including the one
15 misdiagnosed who had atrial tachycardia, AVRT, or
16 AF. One hundred and thirty-six subjects had acute
17 procedural success, yielding a point estimate of 83
18 percent with 95 percent confidence intervals
19 ranging from 76 to 88 percent. The primary
20 effectiveness endpoint, a 95 percent lower
21 confidence greater than or equal to 85 percent,
22 was, therefore, not met.

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1 Acute procedural success, however, was
2 significantly different among the three diagnostic
3 groups. This slide shows overall procedural
4 success of 83 percent in the 164 patients overall.

5 Note that the acute procedural success in the
6 patients with AVNRT was 91 percent compared with 69
7 percent in the AVRT patients and 67 percent in the
8 AF subjects.

9 Next, please. A number of subjects were
10 also treated with RF ablation when cryoablation had
11 not been successful. Twenty-five of 28 subjects
12 with acute procedural failure during cryoablation
13 went on to have RF ablation; two subjects did not.

14 Sorry, three subjects did not. Twenty-three of
15 these 25 of the RF-treated subjects had acute
16 clinical success.

17 Considering both cryoablation and RF
18 ablation, acute clinical success was achieved in
19 161 of 166 patients. This was a point estimate of
20 97 percent with confidence intervals ranging from
21 93 to 99 percent. Adverse event measures in the
22 cryoablation plus RF ablation patients did not

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1 differ from those in the cryoablation-alone
2 subjects.

3 Next, please. I would like now to
4 discuss long-term clinical success. There are two
5 ways of assessing long-term outcome. One is by
6 life table analysis, another by Kaplan-Meier
7 survival analysis.

8 This slide shows the life table analysis
9 for all 136 patients who had acute procedural
10 success. We see that the long-term clinical
11 success rate in this group was 91 percent with 95
12 percent confidence intervals ranging from 86 to 96
13 percent.

14 This outcome is clinically excellent,
15 exceeds the protocol-specified rate of 85 percent
16 and exceeds the subsequently-published FDA RF
17 ablation guidance of a conditional long-term
18 clinical success rate of 90 percent with a 95
19 percent lower confidence bound of 80 percent.

20 This slide shows the Kaplan-Meier
21 analysis with the same 136 patients, all of whom
22 had acute procedural success. Using this method of

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1 analysis, we get essentially the same long-term,
2 chronic success rate of 91 percent with 95 percent
3 confidence intervals ranging from 86 to 96 percent.

4 Note that there was no recurrence of the
5 targeted arrhythmia after the third month of
6 followup. This durable response is exactly what we
7 are accustomed to seeing with radiofrequency
8 ablation.

9 This is the life table analysis for the
10 AVNRT subjects and demonstrates that the long-term
11 clinical success rate was 94 percent with a
12 corrected 98.3 percent confidence interval ranging
13 between 87 to 100 percent. Again, this outcome
14 exceeds the FDA generic RF ablation guidance of a
15 conditional long-term success rate of 90 percent
16 with 95 percent lower confidence bound of 80
17 percent.

18 Here is the Kaplan-Meier survival
19 analysis for the AVNRT patients. This results in a
20 very similar outcome as the life table analysis
21 with a long-term clinical success rate of 94
22 percent, corrected 98.3 percent, with a confidence

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1 interval ranging from 87 to 100 percent.

2 Next slide. Thank you. To summarize the
3 FROSTY effectiveness outcomes, for all 164 intent-
4 to-treat subjects, the primary endpoint was not met
5 with an overall acute procedural success rate of 83
6 percent. The secondary effectiveness endpoint,
7 however, was met with a long-term clinical success
8 rate of 91 percent at six months of followup. For
9 the 103 AVNRT subjects, acute procedural success
10 was 91 percent with a long-term clinical success
11 rate of 94 percent at six months of followup.

12 Post-hoc analyses need to be carefully
13 assessed. The analysis of the AVNRT group has
14 substantial clinical and statistical validity for a
15 number of reasons.

16 To begin with, this is a clinically-
17 relevant group. Furthermore, the group was defined
18 a priori in the protocol. There was a highly
19 significant correlation between diagnosis and acute
20 procedural success.

21 The univariate relationship between
22 diagnosis and acute procedural success was for

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1 AVNRT 91 percent; AVRT, 69 percent, and AF, 67
2 percent. By chi square, this was highly
3 significant with a p-value of .002.

4 The multivariate relationship
5 demonstrated that diagnosis was a highly-
6 significant factor in predicting acute procedural
7 success. With a stepwise logistic regression, the
8 p was .022.

9 Finally, there is a significant amount of
10 additional clinical information, much of it filed
11 with the PMA, that supports the FROSTY AVNRT safety
12 and effectiveness results, as we have reported
13 here. For these reasons, we believe that this
14 analysis of the AVNRT subjects is valid and is
15 clinically useful.

16 Next, please. I would like now to
17 discuss cryomapping, which I believe is one of the
18 most unique and potentially most important features
19 of this new technology. Cryomapping is defined as
20 a limited cryoapplication intended to cause a
21 reversible alteration in cardiac conduction.

22 In the FROSTY study, cryomapping was done

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1 at minus 30 degrees Centigrade for up to 80
2 seconds. This allowed for a reversible assessment
3 of the potential effects of cryoablation at a
4 chosen target site.

5 Next, please. I would like to show you
6 just one example, and for the non-
7 electrophysiologists on the Panel whose eyes may
8 glaze over, please bear with me. We see two panels
9 here during cryomapping. In the top panel and in
10 each panel you see surface electrocardiographic
11 leads one, two, three, V1 and V6, and then high-
12 right atrial electrograms here from the high-right
13 atrium, from the ablation catheter, and from the
14 his bundle electrogram.

15 In the baseline state, this patient had
16 sustained AV nodal reentrant supraventricular
17 tachycardia of the typical variety. These atrial
18 electrograms represent retrograde conduction to the
19 atrium over the fast AV nodal pathway. The impulse
20 then turns anterograde and conducts through the AV
21 node over the slow AV nodal pathway to complete the
22 reentrant circuit. The cycle length here is 390

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1 millisecons.

2 During cryomapping one sees progressive
3 slowing of the tachycardia cycle length here and
4 here, and then, finally, termination of the
5 tachycardia. Note that the termination occurs in
6 the anterograde limb, the slow pathway, which is
7 exactly where the catheter had been placed. When
8 the catheter was then rewarmed, this patient again
9 had inducible, sustained AVNRT.

10 Next, please. One hundred and thirty-
11 five intent-to-treat subjects had a total of 820
12 cryomap attempts. The remaining 29 intent-to-treat
13 subjects had no attempted cryomaps.

14 On a per-subject basis, 87 of the 135
15 subjects, or 64 percent, with an attempted cryomap,
16 had one or more effective cryomaps. On a per-
17 cryomap basis, 164 of 820 attempts, or 20 percent
18 of the attempts, resulted in effective cryomaps.
19 So a majority of study subjects and about two-
20 thirds of those in whom it was attempted had one or
21 more effective cryomaps. Any given cryomap attempt
22 had a 20 percent chance of being positive.

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1 With regard to cryomapping reversibility,
2 of the 164 effective cryomaps, 102 were converted
3 immediately into cryoablation without warming to
4 assess reversibility; 62 of the effective cryomaps
5 were warmed after mapping. Forty-nine of these
6 reversed immediately and completely; nine reversed
7 in one to six minutes after rewarming, and four
8 went on to cryoablation from four to twenty-one
9 minutes after cryomapping but before complete
10 reversal had been observed. Ninety-four percent,
11 58 out of 62, of the effective cryomaps definitely
12 and rapidly reversed.

13 A subject with one or more effective
14 cryomaps was significantly more likely to have
15 acute procedural success than patients with only
16 ineffective cryomaps or patients in whom
17 cryomapping was not attempted at all. Looking at
18 the total group, for patients with effective
19 cryomaps, the acute procedural success rate was 94
20 percent as compared to only 67 percent in patients
21 with ineffective maps or 76 percent in patients
22 with no cryomapping attempted.

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1 Thus, considered as a diagnostic tool for
2 catheter location, having one or more effective
3 cryomaps predicts a group significantly more likely
4 to have acute procedural success. This significant
5 difference is present in the AVR patients, but the
6 trend in the AVNRT patients and the AF patients was
7 not significant.

8 I suspect that the effect in the AVRT
9 patients represents the much greater localization
10 challenge inherent in treating accessory pathways
11 and the corresponding benefit that cryomapping
12 offers in that group.

13 To summarize cryomapping, the FROSTY
14 study demonstrates that cryomapping can reversibly
15 alter cardiac conduction in the majority of
16 subjects in whom it is attempted. Effective
17 cryomaps are associated with a higher procedural
18 success rate, but this trend did not reach
19 statistical significance in the AVNRT diagnostic
20 group.

21 Cryomapping utility has many interesting
22 possibilities. Clinical applications at the moment

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1 include the ability to map in order to confirm a
2 desirable site for ablation, but also to identify
3 sites that are undesirable where ablation would
4 likely result in an unintended outcome.

5 To summarize the FROSTY study with regard
6 to safety and effectiveness, cryoablation with the
7 Freezor catheter is a safe modality in patients
8 with supraventricular tachycardia. There were no
9 instances of permanent AV block in 151 ablated
10 AVNRT and AVRT subjects, despite frequent ablations
11 near the AV node. AV block can be monitored and is
12 quickly reversible. There were no device-related
13 AMCs or serious adverse events.

14 Cryoablation with Freezor is a
15 clinically-effective treatment for AVNRT subjects,
16 resulting in an acute procedural success rate of 91
17 percent and a long-term clinical success rate of 94
18 percent.

19 Cryomapping with Freezor was observed in
20 64 percent of subjects attempted. Cryomapping was
21 quickly reversible in almost every case, and
22 subjects with effective cryomaps had a

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1 significantly higher acute procedural success rate
2 compared to subjects without an effective cryomap,
3 94 percent versus 67 percent.

4 From FROSTY, I think we can conclude that
5 Freezor is safe for the treatment of patients with
6 supraventricular tachycardia. Freezor is a
7 clinically-effective treatment for patients with
8 AVNRT, and cryomapping with Freezor may offer
9 advantages for safely confirming desirable ablation
10 sites and also avoiding undesirable ablation sites.

11 Thank you for your attention. I will now
12 turn the podium over to Mr. Desmarais.

13 DR. DESMARAIS: Thank you, Dr. Friedman.

14 Here are my concluding remarks:
15 Cryoablation for arrhythmia has a long history of
16 safety. Cryoablation has been shown to be safe and
17 effective for the treatment of cardiac arrhythmias
18 in surgery over 30 years.

19 Freezor has many proven safety systems
20 included in the catheter and console to ensure
21 patient safety. In over two years of worldwide
22 commercial distribution and over a thousand

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1 procedures, there is no reported instance of
2 permanent AV block. In studies of almost 600
3 cryoablated SVTs there have been no instances of
4 permanent AV block as well.

5 Freezor cryoablation, as demonstrated, an
6 excellent safety profile with no permanent AV
7 block. It is clinically effective in AVNRT
8 patients, has excellent long-term success and
9 reversible cryomapping.

10 Ladies and gentlemen, Mr. Chairman, Panel
11 members, thank you for your attention.

12 CHAIRMAN LASKEY: Thank you very much,
13 and congratulations on adhering to schedule. It
14 was much appreciated up here.

15 Barring any burning questions from the
16 Panel, which I would like to hold until after
17 lunch, I would like to proceed with the FDA's
18 presentation. Does anybody have a question for the
19 sponsor? If not, we will just hold until after
20 lunch.

21 MR. CHENG: Good morning. I'm James
22 Cheng, and I am the Lead FDA Reviewer for the

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1 CryoCath Cryoablation System submitted under PMA
2 P020045.

3 The FDA review team was comprised of
4 myself, our Medical Officer, Dr. Leslie Ewing, who
5 will present the FDA clinical review summary; our
6 Statistician, Dr. Lilly Yue, who will present the
7 FDA's statistical review summary; Cindy Demian, who
8 performed the biocapability review; Elaine Mayhall,
9 who performed the sterilization review, and Kevin
10 Hopson, who performed the bioresearch monitoring
11 review.

12 The sponsor-proposed indications for use
13 as seen earlier, the basic components of
14 cryoablation system, the Freezor catheter, the
15 cryoconsole, and the umbilicals and accessories:

16 The Freezor catheter is a 7 French
17 single-use catheter with a 4-millimeter gold-plated
18 metal tip, 3 EGE ring electrodes, a thermocouple
19 sensor, and a flexible, maneuverable shaft. The
20 catheter lumen contains a refrigerant injection
21 tube, ECG wires, a leak detection wire, and a
22 thermocouple wire. The catheter handle contains a

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1 deflection mechanism.

2 The cryoconsole provides refrigerant
3 delivery and recovery. It maintains a vacuum
4 condition inside the catheter lumen. It controls
5 the refrigerant pressure and flow rate to achieve
6 the target temperature range. It contains a device
7 safety system. It monitors the integrity of
8 umbilical connections, and injection control is
9 implemented in dedicated hardware and has a manual
10 override function for shutting down injection.

11 The umbilicals and accessories consist of
12 the coaxial umbilical which delivers liquid nitrous
13 oxide under pressure to the catheter and evacuates
14 the nitrous oxide gas; the electrical umbilical,
15 which carries the catheter electrical signals to
16 the auto connection box; the auto connection box,
17 which connects the electrical umbilical and ECG
18 cable to the console, and the ECG, which carries
19 the catheter ECG signals to an external monitor.

20 The basic principles of operation of the
21 system, cryogenic temperatures are generated only
22 at the catheter tip. Pre-cooled liquid nitrous

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1 oxide is injected under pressure to the tip, where
2 the liquid nitrous oxide expands to a gas. The
3 face change that the nitrous oxide undergoes is an
4 endothermic reaction which generates the cryogenic
5 temperatures at the catheter tip.

6 Cryoablation involves achieving a
7 catheter tip target temperature of between minus 68
8 to minus 75 degrees Centigrade and maintaining that
9 temperature for up to 240 seconds.

10 Cryomapping involves achieving a catheter
11 tip target temperature of between minus 25 to minus
12 30 degrees Centigrade and maintaining the
13 temperature for 60 seconds.

14 The FDA pre-clinical review goals were to
15 ensure the safety and reliability of the device.
16 For safety, we want to ensure that the device has
17 been appropriately designed and tested, that
18 potential device hazards have been analyzed and
19 mitigated, and that the device safety features have
20 been qualified for use. For reliability, we want
21 to ensure that the design and manufacture of the
22 device provide us with assurance of consistency

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1 with performance specifications.

2 Testing of the catheter included
3 biocompatibility testing of the catheter materials,
4 reliability testing of the catheter design,
5 mechanical and electrical testing of catheter
6 performance, and qualification of a sterilization
7 process.

8 Qualification of the console included
9 software and hardware qualification. For software,
10 we assess the sponsor's design and development
11 methodology, the device software hazards analysis,
12 and the software verification and validation
13 process. For hardware, we assess the design of the
14 nitrous oxide injection and recovery systems, the
15 temperature controller performance, the device risk
16 analysis, and the design and performance of all
17 device safety features.

18 The major hazard posed in the device
19 design is the potential for causing a gas embolism.

20 The manufacturer addressed this hazard with
21 several mitigation features. One mitigation
22 features involves the design and qualification of

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1 the catheter, which included burst and leak
2 testing. Another mitigation is that the catheter
3 lumen is kept under continuous vacuum during the
4 procedure, which prevents the release of the
5 refrigerant gas into the patient's bloodstream if
6 there is a catheter breach. There is also a
7 catheter safety interlock which prevents device
8 operation until all the catheter connections have
9 been properly configured.

10 Additional mitigation features include
11 redundant blood and fluid detector systems that
12 would detect the presence of blood or fluid in
13 various parts of the catheter as a result of a
14 catheter breach.

15 The flow profile of recovered injectant
16 gas is also monitored to detect any unusual
17 catheter performance. The pressure relief valve
18 helps ensure that the catheter doesn't become
19 pressurized, and any loss of vacuum will
20 immediately disable the injection. To minimize the
21 risk of exsanguination, again, you have the blood
22 and fluid leak detectors and the catheter design

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1 and qualification.

2 Another hazard that was addressed by the
3 sponsor was the risk of experiencing freezing
4 temperatures along the catheter shaft, instead of
5 only at the tip. Catheter qualification testing
6 demonstrated that a break in the injection tube
7 inside the catheter did not allow external shaft
8 temperatures to approach freezing, and the
9 injection flow profile monitoring also helps
10 monitor for catheter failure conditions.

11 One last device hazard is the risk of
12 software controller failure. This hazard was
13 addressed by the use of a dedicated, hardware-based
14 injection controller with a manual override for
15 stopping injection delivery and by the use of
16 hardware-based watchdog circuitry to monitor the
17 software for failure.

18 In conclusion, based on the documentation
19 provided to the FDA by the sponsor, the pre-
20 clinical testing performed by the sponsor is
21 appropriate and acceptable. Specific hazards posed
22 by the device have been appropriately analyzed and

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1 addressed by the sponsor's device design and
2 qualification testing. Overall testing shows that
3 the device is reliable for human use.

4 Now to present the FDA clinical review
5 summary, it is Dr. Leslie Ewing.

6 DR. EWING: Good morning. I am Leslie
7 Ewing, and I have no conflicts to report. I will
8 be presenting the results of the study, and
9 following me will be Dr. Lilly Yue, who will talk
10 about the statistical analysis of those results.

11 The initial purpose of the study, as you
12 have heard, was to study the safety and
13 effectiveness of this cryoablation system to treat
14 the two types of SVT AV node reentry SVT and SVT
15 due to an accessory pathway, and to treat patients
16 with atrial fibrillation who have rapid ventricular
17 response.

18 The study was a single-arm, randomized,
19 multicenter study using OPCs, as previously
20 described. These OPCs were based on the medical
21 literature on RF ablation and designed to be used
22 for the entire pooled study population. These OPCs

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1 have been used in previous ablation clinical trials
2 reviewed by the FDA.

3 As also was mentioned, since the
4 beginning of this clinical trial, the FDA has put
5 out a guidance document which was issued on July
6 1st, 2002 entitled, "Cardia Ablation Catheters
7 Generic Arrhythmia Indications for Use, Guidance
8 for Industry." It can be found at the web address
9 as listed. These recommendations were put out and
10 intended for radiofrequency ablation catheters and
11 were based on medical literature for RF catheters.

12 This is a table from that guidance
13 document, and I will point out, as has been
14 previously mentioned, the chronic success or
15 freedom from recurrence was 80 percent, as is
16 listed here.

17 In this study there were three patient
18 populations included: AV node reentry, AVRT,
19 patients with accessory pathway, SVT, and patients
20 with atrial fibrillation.

21 The inclusion criteria is as stated here
22 and has been previously discussed, and the

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1 exclusion criteria have been previously discussed.

2 The primary effectiveness endpoint for
3 the study was acute procedural success. For the
4 patients with the AV node reentry and accessory
5 pathway SVT it was absence of spontaneous or
6 inducible sustained SVT at the end of the
7 procedure, and for the patients with atrial
8 fibrillation it was absence of AV node conduction.

9 The lower-bound OPC for the acute
10 procedural success, as you can see here, is 85
11 percent. For a secondary effectiveness endpoint or
12 long-term success for the patients with SVT, there
13 was to be no recurrence of sustained SVT by the
14 time of their three-month followup, and for the
15 patients with atrial fibrillation, there was to be
16 no evidence of AV node conduction at the three-
17 month followup.

18 For the study, the chronic success lower
19 bound was to be 85 percent with the asterisk
20 pointed out to the recently-published FDA guidance,
21 which would be 80 percent.

22 The safety endpoint for the study is that

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1 the number of major complications following the use
2 of the device should have 95 percent upper bound of
3 less than 7 percent.

4 The definition of major complications
5 used for the study is the standard for FDA, the
6 definition of major complications, and it is any
7 adverse event which occurs within the first week
8 following the use of the investigational device and
9 is life-threatening or results in permanent
10 impairment of a body function or permanent damage
11 to a body structure, or necessitates significant
12 intervention such as major surgery to prevent
13 permanent impairment of a body function or
14 permanent damage to the body structure or requires
15 hospitalization or an extended hospital stay,
16 results in moderate transient impairment of a body
17 function or transient damage to a body structure,
18 or requires intervention such as medication or
19 cardioversion to prevent permanent impairment of a
20 body function or damage to the body structure. In
21 previous ablation studies the definition has been
22 consistently applied by the FDA in a fairly strict

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1 fashion.

2 As has been described, the patients all
3 had screening and enrollment into the study and all
4 had diagnostic electrophysiology studies. Some
5 patients had cryomapping, and the determination of
6 which patients were to have cryomapping was at the
7 investigators' discretion.

8 Cryoablation occurred in all patients
9 that passed the diagnostic electrophysiology study,
10 and the followup occurred at seven days, one,
11 three, and six months. The followup at seven days
12 was by telephone and also at six months was by
13 telephone.

14 A hundred and sixty-six patients were
15 enrolled and 164 patients received cryoablation
16 lesions. This was at 14 study sites, 11 in the
17 U.S. and three in Canada. The diagnosis after the
18 EP study showed that 61 percent of the patients had
19 AV nodal reentry; 31, accessory pathway; 7 percent,
20 atrial fibrillation, and as was discussed, one
21 patient was diagnosed after a short cryoablation
22 lesion to have -- or cryoablation application to

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1 have atrial tachycardia.

2 Of the 166 patients enrolled, as I said,
3 164 had cryoablation. There were 157 that had per-
4 protocol lesions, per-protocol cryoablation
5 application, and that is a full duration, 240-
6 second ablation application. Six had less than
7 full duration lesions and were, therefore,
8 qualified as acute failure of the device. All
9 those patients went on to have radiofrequency
10 ablation.

11 There were, of the total of the patients
12 who received cryoablation, 28 failures, procedural
13 failures, and there were 136 acute successes.
14 There were 122 of that patient group that had
15 chronic success, and one of those patients, as has
16 been described, is the one patient who had at four
17 months post ablation.

18 So, to reiterate what has been described
19 by the sponsor, there were 91 percent of the AV
20 node reentry patients that had acute success, 69
21 percent of the accessory pathway tachycardia
22 patients, 67 percent of the atrial fibrillation,

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1 and as the total there were 83 percent. As has
2 been described, this did not achieve -- so they did
3 not achieve their acute procedural success or their
4 primary effectiveness endpoint.

5 The chronic results are the patients who
6 had no recurrence of tachycardia or AV node
7 function at three months. Also previously
8 discussed, of the total groups, 90 percent and 91
9 percent for AV node, for the accessory pathway
10 patients 88 percent, and 75 percent of the atrial
11 fibrillation -- so of the patients who had acute
12 procedural success, the ones that remained long-
13 term success.

14 There were seven patients with acute
15 major complications within seven days of the
16 procedure, which also has been stated by the
17 company exceeds the safety endpoint of the study.
18 Three of these patients had the AV node reentry
19 ablation procedure and four with an accessory
20 pathway procedure. The company has very clearly
21 identified and discussed these patients, so I will
22 not go into detail with these patients.

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1 Cryomapping was performed on a subset of
2 the entire patient population. As you have heard,
3 this mapping was performed by using a reversible
4 cryo effect on the conduction system. The use of
5 cryomapping was decided on a per-case basis by the
6 investigator, and the decisionmaking process was
7 not collected as part of the study.

8 The criteria for effective cryomaps were
9 pre-determined per tachycardia. Cryomapping was
10 not part of the pre-determined endpoints of the
11 trial in terms of effectiveness and safety.

12 A hundred and thirty-five patients out of 164
13 had cryomapping attempts. Of those patients, 65
14 percent had effective cryomaps and 35 percent had
15 only ineffective cryomaps. The total number of
16 cryomaps attempts was 812 with 20 percent of those
17 being effective cryomaps, but also negative
18 cryomaps may have helped the investigator determine
19 unsuccessful cryoablation with patients.

20 In the data-collection form process for
21 this study, the investigator could mark
22 "reversible," "not reversible," and that they had

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1 gone immediately to cryoablation attempt without
2 attempting rewarming. There were seven AV node
3 patients who had "not reversible" marked on their
4 data-collection form. All of these seven patients
5 had successful cryoablation procedures with no
6 adverse events reported and, as has been previously
7 stated, no patients had unintentional AV block.

8 Dr. Yue will present the statistical
9 analysis.

10 DR. YUE: Good morning. My name is Lilly
11 Yue, Statistician at FDA. Following Dr. Ewing, I
12 will speak on the study results and give clinical
13 and statistical conclusions.

14 As specified in the protocol, the primary
15 effectiveness endpoint: acute procedure success.
16 The primary safety endpoint: major complication
17 occurrence. The secondary effectiveness endpoint:
18 long-term clinical success at the three-month
19 followup conditional on acute procedural success,
20 evaluated for the entire SVT patient population.

21 Protocol indicated that the study's, like
22 I said, criterion for the acute procedure success

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1 was that the lower 95 percent two-sided confidence
2 bound of the acute success rate for all intent-to-
3 treat patients should be larger than 85 percent.

4 Please note that the two-sided confidence
5 interval here is necessary when the acute success
6 rate could be larger or smaller than 85 percent, as
7 it was agreed upon by the sponsor and the agency at
8 the design stage. We will see this, indeed,
9 necessary in a few minutes.

10 The intent-to-treat patients are those
11 who have a prior ablation catheter activated. For
12 the major complication occurrence, the study
13 success criterion was the upper 95 percent two-
14 sided confidence bound of the major complication
15 incidence rate for all safety patients should be
16 less than 7 percent.

17 Here the 15 patients are those who have a
18 cryoablation catheter inserted.

19 For the conditional long-term success
20 there were statistical hypotheses specified in the
21 protocol. The alternative hypothesis said the
22 conditional long-term success rate should be larger

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1 than or equal to 85 percent. It is the basic
2 statistical concept that the success rate indicated
3 in the statistical hypotheses are in the population
4 parameter, not an observed point estimate. So
5 the study success criterion for this endpoint is
6 the lower 95 percent two-sided confidence bound
7 should be larger than 85 percent for all intent-to-
8 treat patients.

9 Let's look at the study results. As we
10 can see, the point estimate of the acute success
11 rate is 83 percent, less than the OPC 85 percent.
12 So the two-sided confidence interval is, indeed,
13 necessary, and there is no way for the lower
14 confidence bound to be larger than 85 percent.

15 The lower confidence bound is 76 percent.
16 Therefore, the study has failed to meet the OPC 85
17 percent for the acute success for planned patient
18 population.

19 Also, the upper confidence bound of major
20 complication incidence rate, 8.5 percent, exceeded
21 the OPC 7 percent. Therefore, the study has failed
22 to meet the primary safety OPC for planned patient

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1 population.

2 For the conditional long-term success,
3 using the protocol specified exact confidence
4 interval approach, if we consider the crude
5 probability of success, that is, classified the two
6 lost-to-followup patients as failures, the lower
7 confidence bound is 83 percent, less than the OPC
8 85 percent.

9 If we use a more liberal method and
10 exclude the two lost-to-followup patients from the
11 dataset, the lower confidence bound is 85 percent,
12 just on the border line.

13 The agency also suggested survival
14 analysis, either Kaplan-Meier or life table cohort
15 analysis, which should give a lower confidence
16 bound between 83 percent and 85 percent, and closer
17 to 85 percent in this case.

18 Then after looking at the data, the
19 sponsor performed two types of post-hoc subgroup
20 analysis for endpoint statistical hypotheses. The
21 first one is a retrospective subgroup analysis on
22 the ablation safety and effectiveness endpoints for

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1 the three individual subpopulations, using the OPCs
2 originally developed for the entire patient
3 population.

4 The second one is the retrospective
5 subgroup analysis on the impact of effective
6 cryomapping on ablation acute success. However, in
7 the protocol, there were no statistical hypotheses
8 and no study success criteria and claims generated
9 for all cryomapping at all.

10 According to the post-hoc subgroup
11 analysis results, the sponsor made two new claims
12 to support the new indications for use. No. 1,
13 the AVNRT subgroup met the FDA OPCs for the safety,
14 acute procedure success, and the long-term success.

15 No. 2, there was a significant association between
16 effective cryomapping and ablation acute success to
17 support these two new indications for use.

18 Question: Can the post-hoc subgroup
19 analysis results be used as valid evidence for the
20 new claims? First of all, when should we perform
21 subgroup analysis?

22 Generally speaking, subgroup analysis is

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1 to determine if there is a reportable subset for
2 which the treatment effect is either significantly
3 more effective or harmful. So, when the study has
4 succeeded in pre-specified overall analysis,
5 subgroup analysis may be useful in suggesting
6 hypotheses to be tested in future studies or help
7 refine labeling. If the data shows a significant
8 overall treatment effect, but non-significant
9 treatment effect in subgroups, then the device
10 still could be approved for general use.

11 However, subgroup analysis is not
12 intended to be used to rescue a study with non-
13 significant overall treatment effect. So, when the
14 study has failed in pre-specified overall analysis,
15 generally, we do not perform subgroup analysis
16 because the risk of false positive results from
17 subgroup analysis increases.

18 Particularly, here are some criteria to
19 check if a subgroup analysis is appropriate:

20 No. 1, is the hypothesis for subgroup
21 analysis pre-specified? Pre-specified is more
22 believable than post-hoc-specified.

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1 No. 2, is the subgroup classification
2 clinically relevant?

3 No. 3, is there significant treatment
4 effect in overall analysis? If yes, may do
5 subgroup analysis; otherwise, generally, we do not
6 do.

7 No. 4, is there significant interaction
8 of treatment with subgroup variable? This question
9 generally refers to a two-arm trial, but here we
10 just have one arm.

11 Let's check if the subgroup analysis of
12 ablation safety and effectiveness for the three
13 individual patient subpopulations is appropriate:

14 No. 1, in the protocol, no statistical
15 hypothesis was generated for the three individual
16 subpopulations; no study success criteria and
17 claims were developed for the subpopulations. And
18 the sample size estimation was not based on the
19 three individual subpopulations.

20 No. 2, yes, the three subpopulations are
21 generally referred to SVT patients.

22 No. 3, no, there is no significant

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1 treatment effect in pre-planned overall analysis.

2 No. 4, not applicable, but, indeed, there
3 is a big difference in the performance of the
4 device between the three patient subpopulations.
5 That is why the OPCs developed for the entire
6 patient population cannot be directly used for
7 subpopulations. It is just our second concern on
8 the next slide.

9 OPCS developed for the entire patient
10 population may be wrong for all subpopulations. So
11 it cannot be directly used in a subpopulation. In
12 fact, from medical literature, the acute success
13 rate for AVNRT patients is significantly higher
14 than those for AVRT and AF patients. Therefore,
15 the acute success OPC for AVNRT should be higher
16 than 85 percent.

17 Our other concern is, if the subgroup
18 analysis and the data analysis had been planned in
19 the protocol, a multiplicity adjustment for a
20 significance level, such as Bonferroni adjustment,
21 should have been performed. Otherwise, the overall
22 Type I error rate of the study, that is, the

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1 probability of incorrectly approving the device,
2 would be inflated and could be close to 15 percent.

3 Let's back up one step and let's suppose
4 the original OPCs were appropriate for the
5 subgroups. The point estimate of acute success
6 rate is 91, 69 and 67 percent for the three
7 subpopulations, respectively; 91 percent for AVNRT
8 is significantly better than 69 percent and 67
9 percent. You can see a huge difference here.

10 Here the 95 percent confidence interval
11 is the analysis result without multiplicity
12 adjustment. We also suggested Bonferroni-adjusted
13 confidence intervals. The highlighted numbers here
14 are the lower confidence bounds, but none of them
15 match the OPC 85 percent in a group.

16 Similarly, for the major complication
17 incidence rate, none of these upper confidence
18 bounds reached the OPC 7 percent, no matter the
19 confidence intervals are multiplicity-adjusted or
20 not adjusted.

21 For the conditional long-term success,
22 the second column in the table gives the results of

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1 crude probability of success for AVNRT subgroup.
2 None of these lower confidence bounds reached the
3 OPC 85 percent. The last column gives the result
4 of excluding the two lost-to-followup patients from
5 the data analysis. The lower bounds, 86 percent
6 and 85 percent, they are omitted for the AVNRT
7 subgroup.

8 So suppose the OPCs were appropriate for
9 the subgroups. For any patient subgroup, with or
10 without multiplicity adjustment, the study has
11 failed to meet the primary safety and effectiveness
12 OPCs.

13 In conclusion, none of the three
14 subgroups met the OPCs for either primary safety or
15 primary effectiveness.

16 Let's look at a second subgroup analysis
17 on the association of effective cryomapping and
18 ablation acute success. Of 164 patients with
19 cryoablations, 135 had cryomap attempts and 29
20 didn't. Of the 135 patients with cryomapping
21 attempts, 87 had effective cryomaps and 48 had
22 ineffective cryomaps. So the point estimate of the

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1 effective cryomapping rate is 64 percent. Of 87
2 patients with effective cryomapping, 80 had
3 reversibility so the rate is 92 percent.

4 Now we have three patient subgroups
5 according to cryomapping: effective, ineffective,
6 and no attempts. The ablation acute success rate
7 is 94 percent for effective, 65 percent for
8 ineffective, and 79 percent for no attempts.

9 The sponsor groups "ineffective" with "no
10 attempts" and called it "without effective," then
11 compared "effective" with "without effective" in
12 terms of ablation acute success, and claimed that
13 "effective" was significantly better than "without
14 effective" in ablation acute success.

15 These claim was supported by a p-value
16 less than .05 from exact test for the overall
17 intent-to-treat patient population. However, the
18 significant result was driven by 49 AVRT patients.

19 You can see the p-values in the last column.
20 However, the AVRT subgroup is not the one the
21 sponsor is currently claiming for.

22 Instead, the AVNRT is the only group

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1 indicated in the new indication for use. However,
2 there is no significant difference detected in the
3 ablation acute success between "effective" and
4 "without effective" patients for this subgroup,
5 with a p-value of 0.45 from exact test.

6 For this post-hoc comparison, we have the
7 following concerns:

8 No. 1, what is the meaning of this
9 comparison?

10 No. 2, why grouping "ineffective" with
11 "no attempts"?

12 No. 3, is the subgroup classification
13 "effective" versus "without effective" clinically-
14 relevant?

15 It seems that if we try to attach the
16 impact of the effective cryomapping on ablation
17 acute success, we could compare the "effective"
18 group with the "ineffective" group and use "no
19 attempts" as a control.

20 The ablation acute success rate, 94
21 percent for the "effective" group, is significantly
22 better than 65 percent for the "ineffective" group,

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1 but a patient had only 64 percent of a chance to
2 have a successful cryomapping when he had cryo
3 attempts.

4 On the other hand, if we try to test the
5 impact of attempted cryomapping on ablation acute
6 success, we could compare "attempt" with "no
7 attempts." Here "attempt" includes "effective" and
8 "ineffective."

9 We performed the comparison and found
10 that there was no significant difference detected
11 in the ablation acute success between "attempt" and
12 "no attempt" groups, with a p-value of .59 from the
13 exact test. The point is made that the ablation
14 acute success rate is 84 percent and 79 percent for
15 the two subgroups, respectively.

16 From these post-hoc subgroup analyses, we
17 can see that there are many ways to generate a
18 subgroup hypothesis after fact. Different post-hoc
19 hypotheses and data analyses could lead to
20 different results, either significant or non-
21 significant.

22 This is the situation we always try to

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1 avoid, in which subgroups are defined by the data
2 and the unplanned statistical hypotheses are
3 generated by study results. Often, a treatment
4 effect is so suggested and then confirmed with
5 statistical significance on that same dataset.

6 Clearly, the subgroup hypotheses and the
7 data analysis on the association of effective
8 cryomapping and ablation acute success were not
9 pre-defined. We are not sure if the subgroup
10 classification "effective" versus "without
11 effective" is clinically-relevant. Also, we do not
12 have information on why those 29 patients did not
13 have cryomapping attempts, purely by chance or due
14 to some patient characteristics.

15 No. 3, there is no significant treatment
16 effect in overall analysis of ablation acute
17 success. So, the sponsor's significant subgroup
18 analysis result used as evidence of device
19 performance is questionable.

20 Clinical and statistical conclusions:
21 The device did not meet the primary effectiveness
22 of 50 OPCs for either the overall study population

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1 or any patient subgroup. No patient had
2 unintentional, permanent AV node block at the end
3 of the procedure or during followup. There were a
4 low number of recurrences after successful
5 cryoablation. Cryoablation adherence appears to
6 have a durable effect.

7 The post-hoc assessment of cryomapping
8 effectiveness is questionable. There was no
9 significant association detected between effective
10 cryomapping and ablation acute success for the
11 AVNRT subgroup. There was no adverse event
12 reported due to cryomapping.

13 Thank you.

14 CHAIRMAN LASKEY: Thank you, Lilly.

15 At this point, for the record, we will
16 read the questions. We are still, fortunately, a
17 tad early here for the one o'clock break. So are
18 the questions from the Panel to the sponsor or to
19 the FDA, for that matter, the FDA presenters?

20 I had one question for the sponsor. I
21 was very interested in some of the acute and
22 subacute and chronic changes in the subjacent

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1 coronary artery in your pre-clinical studies. Do
2 you have any further information on the pathology
3 or histopathology of these lesions? What is it
4 that is acutely constrictive there? Is it dynamic?
5 Is it fixed? Is it something that we need to
6 worry about, if the latter?

7 DR. DESMARAIS: Mr. Chairman, I will ask
8 Patrick Chauvet, our pre-clinical scientist, to
9 answer your question.

10 MR. CHAUVET: Thank you. My name is
11 Patrick Chauvet. I am a pre-clinical scientist for
12 CryoCath, a full-time employee, and I own equity.
13 My trip was also paid for by CryoCath.

14 The question was dealing with the
15 cryoablation lesions in the coronary sinus and the
16 effect on the adjacent left circumflex coronary
17 artery: What were the histological changes
18 acutely, subacutely, and chronically?

19 In the early trials that we performed we
20 had noticed histological changes both with RF and
21 cryo that were significantly different. In the RF
22 lesions, the coronary artery acute constructs, and

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1 the hypothesis there is because of heating of the
2 collagen fibers in the medial area of the coronary
3 artery, this effect is quite dramatic, and acute
4 constriction is evident; whereas, with cryoablation
5 there is no heating of the collagen fibers, and our
6 hypothesis is that prevents acute constriction.

7 In the subacute and chronic cases, we
8 have noticed in both cases medial necrosis of the
9 coronary artery in similar amounts. However, due
10 to the differences in human processes, the
11 cryoablated coronary sinus and adjacent coronary
12 artery healed very well, and there was no
13 subsequent stenosis up to three months in the
14 cryoablation regions.

15 CHAIRMAN LASKEY: So is the acute
16 stenosis reversible with nitroglycerin, for
17 example? You alluded to spasm. It is spasm? Did
18 you give nitro and make it go away or some other
19 anti-spasm?

20 MR. CHAUVET: Nitroglycerin was given
21 during the study. As you saw in the presentation,
22 stenosis was still present one week after the

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1 procedures. So it is not just an acute phenomena.

2 CHAIRMAN LASKEY: One question from Dr.
3 Waldo and then Dr. Dullum.

4 DR. WALDO: Actually, I have a few, but I
5 will just take one then. I have a question about
6 the definition of efficacy of the cryomap. I'm not
7 sure I understand the definition because to me, if
8 you apply adequate cooling, almost anything is
9 effective, the way I look at it. If you don't get
10 an effect, I think that was implicit in some of the
11 things that presented, if you don't get an effect,
12 then are you sure you know you're in an area that
13 is not useful to ablate?

14 Do you also know that it is safe to
15 ablate if you want to ablate with something else?
16 In your instance, your presentation, it wouldn't be
17 like atrial flutter where you might want to ablate
18 and you would want to make sure you're not close to
19 any structure.

20 I don't see why all the cryoablation
21 shouldn't be considered effective if adequate
22 cooling is applied, because it is telling you

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1 something each time. I am not sure why you have to
2 have reversibility as part of it.

3 DR. DESMARAIS: We will ask Dr. Lehmann,
4 our medical monitor, to answer the question with
5 regards to the definition.

6 In terms of the cryomapping clinical
7 applicability, I would like to ask Dr. Friedman to
8 answer that question.

9 DR. LEHMANN: My name is John Lehmann. I
10 am a paid consultant to CryoCath. I do not own
11 equity, and my expenses were paid by the company to
12 come.

13 Dr. Waldo, your question bedeviled us as
14 well. There is a kind of cryomapping where you are
15 looking for an effect, in which case we ultimately
16 simply defined that as, when you cool to a non-
17 destructive level, did you see a physiologic change
18 or not? And there is a kind of cryomapping where
19 you wouldn't like to see an effect, or what is
20 loosely called "negative cryomapping," where you
21 are working with it at the node and you cool and
22 you don't see it. Exactly how to determine those

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1 in study was less clear to us a couple of years
2 ago.

3 But at the moment we use the terminology
4 "cryomapping effect" in a positive sense, in a
5 place we would like to see the change, and we do or
6 don't with a non-destructive cryomapping
7 application, and cryomapping reversibility just for
8 those situations when we do see change in
9 physiology and with warming that change goes away.

10 DR. WALDO: So then, with Dr. Yue
11 presenting the statistical analysis, if I
12 understand it, when you were ineffective, it was
13 because you didn't see anything. There was nothing
14 reversed. But I would suggest to you, why is that
15 ineffective? It doesn't strike me that that is
16 ineffective. It might be very effective. You know
17 you're not in a place you don't want to be, for
18 instance. That is the most obvious example. I
19 don't know why that is ineffective. If you
20 look at just the statistics, that would clearly
21 affect this.

22 DR. FRIEDMAN: Peter Friedman.

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1 I think that is a very good point, Dr.
2 Waldo. As John Lehmann alluded to just a moment
3 ago, we struggled with how to gauge and how to
4 measure mapping, because it is not something that
5 has been available with any other technology and
6 had never been done before.

7 You're right in the sense that, if you do
8 cryomapping in a site and you don't see the
9 intended effect, that's a negative cryomap, but, on
10 the other hand, it tells you that you are in a
11 place where it is actually probably safe to ablate.

12 DR. WALDO: Or not the place you want to
13 ablate.

14 DR. FRIEDMAN: Or not the place that you
15 want to be. So it is another way of analyzing the
16 data. Of course, we could include those all as
17 effective, and then the numbers would be very
18 different.

19 DR. WALDO: It would certainly affect the
20 statistical analysis we just heard, which was
21 suggesting that it was useless, and I think that
22 statistical analysis doesn't make any sense to me

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1 in terms of how we understand it.

2 DR. FRIEDMAN: Yes, I think as the study
3 went on, we learned more about what the true
4 utility of this technology is. It is true that, if
5 during cryomapping one sees block in an accessory
6 pathway or block in the slow pathway, that
7 indicates that it is a good place to do ablation.

8 But we learned about what we called
9 "negative cryomaps" or "safety cryomaps," also,
10 that if you're applying cryo energy to an area and
11 you see an unintended effect, that is an area not
12 to ablate and it is another utility for mapping
13 that was not addressed when the protocol was
14 written.

15 DR. WALDO: Am I wrong in that, do you
16 think? If you apply it to an area where nothing
17 happens, why would you continue? Did you find
18 that, if you don't see any effect, you're sure that
19 that is an area that is not desirable to ablate?
20 For instance, if you don't see any effect on a slow
21 pathway, which would be critical for your
22 presentation, did it prove in your data that this

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1 was an area clearly that you should not ablate,
2 that you were wasting your time to ablate that?

3 DR. FRIEDMAN: No, and it is difficult to
4 analyze those data from the way they were
5 collected. But, for example, there were
6 investigators who did cryomapping specifically to
7 localize the slow pathway and were unable to show a
8 reversible block in the slow pathway.

9 Now one could conclude from that either
10 you're too far away or that the temperature you
11 achieved during the mapping procedure was not
12 adequate to reach the slow pathway which may have
13 been further below the endocardial surface. So
14 there were actually instances in the study where
15 people, after mapping and being unable to find an
16 effective, quote, "cryomap area," actually went
17 back and ablated at those areas, and some of those
18 turned out to be successful.

19 CHAIRMAN LASKEY: We do that in
20 interventional cardiology as well. So it is not an
21 uncommon precedent.

22 Dr. Dullum, you had one question?

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1 DR. DULLUM: I just wanted to ask a
2 followup to your question about the coronary
3 occlusion. I noticed the intravascular ozone
4 catheter was in the heart in one of your pictures
5 with the RF ablation but not on the cryo. Did you
6 have it in during the ablation procedures for both
7 of them or did that just happen to be that one
8 picture that we saw?

9 MR. CHAUVET: Patrick Chauvet.

10 No, the AFIS catheter was positioned in
11 every single animal whether it was for RF or
12 cryoablation.

13 DR. DULLUM: So during the ablation
14 procedure the AFIS was in there, in the animals?

15 MR. CHAUVET: That's correct, yes.

16 CHAIRMAN LASKEY: Dr. Krucoff?

17 DR. KRUCOFF: You mentioned that you have
18 an experience in Europe. Is the catheter in
19 clinical use outside of the United States? Are
20 there any data available that would support any of
21 these discussions from your U.S. activity?

22 DR. DESMARAIS: Jean-Pierre Desmarais,

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1 CryoCath.

2 F7, the presentation, the catheter is in
3 commercial use in Europe, in various countries in
4 Europe, and in Australia and other countries in the
5 world.

6 We found with the PMA there's two
7 separate studies which are not sponsored by us
8 which are an individual initiative from the German
9 Heart in Munich and from the Rotterdam in The
10 Netherlands which compared the NRT to RF, and we do
11 have data on that. We have submitted those data to
12 FDA during the PMA.

13 We are trying just to plug the computer
14 and present the data to you in a minute.

15 DR. ZUCKERMAN: Okay, I think I have to
16 take issue as to whether the agency has seen these
17 data. I don't believe so. And the Panel needs to
18 recognize that any data not contained in the PMA
19 Panel pack have not been thoroughly reviewed by the
20 agency and need to apply the appropriate caveats to
21 such data.

22 DR. DESMARAIS: Thank you, Dr. Zuckerman.

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1 CHAIRMAN LASKEY: I am sorry, are we
2 looking for summary of the European data here?

3 DR. DESMARAIS: In about 30 seconds.

4 CHAIRMAN LASKEY: Sure, and then at that
5 point I would move to adjourn for lunch. So we
6 will end on that response.

7 Oh, I'm sorry. I'm sorry, Dr. Waldo.

8 DR. WALDO: Just a very quick followup to
9 what I was asking before: Have you any instances
10 where you looked for parahisian pathways? I mean,
11 this is one of the areas where --

12 DR. DESMARAIS: I would like to have Dr.
13 Nazari to answer that question. Excuse me, I will
14 let Dr. Chauvet to answer that question.

15 DR. DUBUC: Mark Dubuc.

16 As you know, the product is commercially
17 available in Canada, and we have used that to do
18 about 17 cases with parahisian.

19 DR. WALDO: Seventy or 17?

20 DR. DUBUC: Seventeen, 1-7. Actually, we
21 were successful in 15 of these cases, and we were
22 able to make what we call a negative cryomap or

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1 safety cryomap, and we had clearly a his
2 electrogram on the ablation catheter when we did
3 that.

4 I can say that maybe in two cases we had
5 transient AV block and we had to cancel the
6 procedure. This is why we have the 15 out of 17
7 were successful.

8 DR. WALDO: So you also used the mapping,
9 the cryomapping technique?

10 DR. DUBUC: Yes. Well, mainly, the
11 negative cryomapping. I want to be sure not to
12 ablate at the same time that I'm doing --

13 DR. WALDO: Precisely.

14 DR. DUBUC: So another thing interesting
15 with cryo is that during the application what you
16 cannot do with RF, you can do program stimulation;
17 you can pace the atrium, pace the ventricle, to see
18 if the AV conduction is still there during the
19 application. The catheter is very, very stable.

20 CHAIRMAN LASKEY: Dr. Bailey had a
21 question.

22 DR. BAILEY: Yes, I was wondering if you

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1 have compiled data on all initially-enrolled
2 patients as far as their rhythm status at the end
3 of the -- I know there was combining the ones who
4 were successful after radiofrequency ablation.

5 DR. DESMARAIS: Dr. Lehmann will answer
6 that question.

7 DR. LEHMANN: Could I clarify that you
8 want the overall clinical success at the end of the
9 procedure?

10 DR. BAILEY: With the strategy of
11 cryoablation, followed perhaps by radiofrequency.

12 DR. LEHMANN: Right. That was in the
13 presentation. There was a slide that shows that,
14 of 166 enrolled subjects, 161 had the endpoint
15 success at the end of the procedure.

16 DR. BAILEY: And then what about at three
17 months or six months? Did you follow the
18 radiofrequency cases for their status at three
19 months?

20 DR. LEHMANN: We don't have that data
21 here today.

22 CHAIRMAN LASKEY: Do you have the non-

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1 U.S. --

2 DR. DESMARAIS: This is partly the non-
3 U.S. As explained earlier, that was part of the
4 PMA that FDA maybe did not have the chance to
5 review.

6 There is a study by Dr. Zrenner at the
7 German Heart. At the time of filing of the PMA,
8 that was the data we had available showing
9 comparable success rate fluoroscopy induration in
10 terms of AV study.

11 And there is a second study by the group
12 of Dr. Jordaens in Rotterdam, The Netherlands. In
13 this case, he was doing it at the NRT and right
14 septal pathways. Again, the success rate is
15 comparable at this point in time, and that was what
16 we had at the time of filing. Obviously, these
17 studies are continuing, but we don't have formal
18 updated data at this point.

19 Does that answer your question?

20 DR. KRUCOFF: Yes. I guess you had
21 references to thousands of uses. Obviously, these
22 are smaller trials then.

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1 DR. DESMARAIS: Correct.

2 DR. KRUCOFF: You were talking about your
3 commercial use?

4 DR. DESMARAIS: Correct. We do have
5 registry data.

6 DR. LEHMANN: We have four IDE-like
7 studies to either Canada or the U.S., which
8 comprise roughly 300 subjects with AVNRT and AVRT.

9 Those had no permanent block. There's a total of
10 600 patients in the registry collection, and then
11 there's between 1,000 and 2,000 commercial uses for
12 which there are no event-reporting systems of any
13 permanent AV block.

14 DR. KRUCOFF: Can you just flip back to
15 the first data slide?

16 DR. LEHMANN: Yes.

17 DR. KRUCOFF: So on the cryo side, does
18 that four third-degree heart blocks only transient?

19 So "no block," you mean permanent --

20 DR. LEHMANN: No permanent AV block.

21 DR. KRUCOFF: Correct.

22 CHAIRMAN LASKEY: Okay, thank you. On

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1 that note, we're at the magic hour, and I think
2 we'll have plenty of opportunity for each panel
3 member to ask additional material after lunch.
4 Let's break for lunch and let's meet again at 1:55
5 sharp. Thank you.

6 (Whereupon, the foregoing matter went off
7 the record for lunch at 12:56 p.m. and went back on
8 the record at 2:05 p.m.)

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A F T E R N O O N S E S S I O N

2:05 p.m.

CHAIRMAN LASKEY: I would like to begin this afternoon's portion of the proceedings by having our Lead Reviewer, Dr. Cynthia Tracy, present her review and ask questions.

I also want to make a bold, and perhaps indefensible request, for Panel members to limit their exegesis to no more than 10 to 15 minutes, so we can get through the afternoon, if that is possible.

I'm assuming we actually got through all the panelists' questions before the lunch break. Is that a fair assumption? That is not? Can you hold them until it is on your round? Would that be okay?

Great. So, Dr. Tracy, the floor is yours.

DR. TRACY: I think it is appropriate that this is room is very frosty for this discussion.

(Laughter.)

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1 With that in mind, I would like to
2 congratulate you on your presentation. You covered
3 a lot of data and did it very well. One thing that
4 I thought was remarkably well done was the pre-
5 clinical testing. I think this device has a lot of
6 potential safety issues that have all been
7 addressed very carefully with excellent safety
8 features built into the device.

9 It strikes me that both the strength and
10 the weakness of this device is the small, uniform
11 lesion that is created. I think that is why
12 effective in many instances, but ineffective -- it
13 is effective and safe in many instances, but
14 ineffective in places where you might want to
15 create a larger lesion.

16 Just a brief question relative to that:
17 Is there any way that a lesion or any development
18 that might be done could increase the size of the
19 lesion to make the device more applicable for a
20 greater number of arrhythmia substrates? Is that
21 something that is potentially planned? Would a
22 larger catheter tip be useful or some other

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1 modification?

2 DR. DESMARAIS: At the current time, we
3 believe that the catheter that we have is adequate
4 for the treatment of AVNRT, but in our design
5 strategies, you know, to pursue other indications,
6 we have a lot of design strategies and looking and
7 addressing other arrhythmia. We will surely
8 approach FDA in due course on how best to bring
9 those products to market.

10 DR. TRACY: Okay. I think the cryolesion
11 has the nice feature of not being very
12 thrombogenic, and that might have potential
13 implication for left-sided structures in the
14 future. So it was just a passing thought. But I
15 think at this point you are correct that AVNRT is
16 probably your most approachable lesion with the
17 current device setup.

18 In terms of the device itself, you
19 mentioned that there were equipment failures in two
20 cases. In looking through the packet, I think one
21 was a console failure, and it looked like on the
22 second one multiple catheters were connected to the

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1 console and it was failure to deliver the nitrous
2 oxide, I think.

3 Can you explain, if I am doing math
4 right, about a 1.2 percent device failure? Are you
5 happy with that? What exactly were the problems?

6 DR. DESMARAIS: I believe that the
7 catheter consumption throughout the study was about
8 1.14 catheter on average, I believe. The console
9 failure was a technical failure where a valve did
10 not open and did not let refrigerant into the
11 catheter. So that case never took place with trial
12 as such.

13 In the other failure there was a catheter
14 that kinked on two occasions, and one the injection
15 tube was blocked, so we could not inject.
16 Unfortunately, the site ran out of catheter, so we
17 could not complete the case with trial.

18 DR. TRACY: Okay.

19 DR. DESMARAIS: And just to answer your
20 last question, in general, we are very happy with
21 the catheter as it is, and in terms of its
22 reliability and the way it is used.

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1 DR. TRACY: Okay. I'm only going to
2 touch on this because I assume Dr. Bailey will be
3 asking much more detailed questions regarding the
4 whole statistical analysis issue, but if you had
5 designed this study for AVNRT alone, what endpoints
6 would you have had to achieve in order to prove
7 statistically that the device was safe and
8 effective? Have you put thought into that?

9 DR. DESMARAIS: I will ask Dr. Lehmann to
10 answer that.

11 DR. LEHMANN: The short answer is that we
12 have not at this point attempted to design just a
13 trial for AVNRT. In this trial we used the OPCs,
14 which, as Dr. Yue stated, were for a cooled
15 population, and those were the numbers that we
16 used.

17 DR. TRACY: Okay. I suspect this issue
18 will get much more discussion as we go around the
19 room, but I will leave it at that for the moment.

20 A couple of procedural questions: The
21 procedure time average was 265 minutes. Does that
22 include from the moment the patient is put on the

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1 table until the moment they are pulled off the
2 table?

3 DR. DESMARAIS: Yes, it is skin to skin.

4 DR. TRACY: Skin to skin? Okay. So that
5 is probably a bit long, I think. Is that related
6 to device issues, people having to set things up?
7 Is it hard to set up to deliver refrigerant?

8 DR. FRIEDMAN: I think there are a number
9 of factors that go into that procedure time. I
10 think it is true that any investigational study by
11 its very nature, because of the data collection
12 that occurs, takes longer than a routine clinical
13 case.

14 Some of the time was certainly getting
15 familiar with hook-up procedures, the umbilicals.
16 Mapping I think took some time. There was a new
17 technology, and people were interested in exploring
18 how it could be used. That added to the procedure
19 time. I think all those things together would
20 explain that.

21 I think in routine clinical practice, not
22 in the context of a clinical trial, procedure times

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1 would not be dramatically different than RF. In
2 fact, in the data that you saw just before the
3 lunch break, where patients had been randomized RF
4 versus cryo in Europe, there was really no
5 significant difference in overall procedure
6 duration.

7 Maybe Dr. Dubuc from Montreal would care
8 to comment on that because he probably has the
9 largest experience and has been using it a lot
10 since it is commercially available in Canada.

11 DR. DUBUC: Well, I had a chance to use
12 this product because it is commercially available.

13 I did in my institution more than 150 cases with
14 this technology. Actually, even our group decided
15 to do all AV nodal reentries with this technology
16 since last August.

17 The time is comparable, and I mean the
18 time of the procedure is comparable, and also the
19 fluoroscopy time. Even the fluoroscopy time has a
20 tendency to be a little bit lower because you don't
21 have to watch or monitor the position of the
22 catheter during cryoapplication because of the

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1 adherence of the catheter.

2 DR. TRACY: You are comfortable enough
3 that that thing is really going to stick on there,
4 that you don't wash --

5 DR. DUBUC: Oh, sure, no doubt about it.

6 DR. TRACY: Okay.

7 DR. DUBUC: No doubt.

8 DR. TRACY: Okay. A procedural question
9 that relates to one of the major adverse events:
10 I'm assuming that that right corner infarct either
11 was a catheter inadvertently positioned down the
12 right coronary artery during a retrograde approach
13 or was a completely unrelated event. Do you have a
14 comment on that particular complication?

15 DR. DESMARAIS: Dr. Friedman will answer
16 that.

17 DR. FRIEDMAN: It's difficult to know
18 precisely. That, I think, was a case from Canada.

19 My understanding of that procedure was that
20 cryoablation for the left lateral accessory pathway
21 was done via a retrogradic aortic approach, and
22 there were no technical difficulties encountered

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1 crossing the aortic valve. That was not difficult.

2 So I think it is unlikely, based on what was
3 reported, that that catheter went down a coronary.

4 The RF catheter ablation procedure was
5 actually done by a transeptal approach. That also
6 turned out to be unsuccessful. So this was a very
7 lengthy procedure in a patient with pre-existing
8 coronary disease, and the occluded vessel, as you
9 alluded to, was actually the opposite side of the
10 heart.

11 DR. TRACY: Okay, thanks.

12 I wanted to ask a few questions about the
13 cryomapping. The whole concept of it is a new
14 concept that we have to try to figure out exactly
15 what it means.

16 I think that part of the idea of doing
17 cryomapping is that it is a way of testing where
18 you are without creating permanent damage, and yet
19 I note that there's a little bit of contradictory
20 information that is being given. In one part of
21 the packet it mentions that 100 percent of
22 cryomapping was reversible. Yet, we talked this

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1 morning about seven not reversible cryomaps. Are
2 those cryomaps, were they actually cryoablations,
3 or what's the difference there?

4 DR. DESMARAIS: I think what I would like
5 to do is to answer that question twofold: first,
6 with Dr. Friedman, to really explain cryomapping
7 and make an attempt in re-explaining that, and,
8 secondly, for Dr. Lehmann to discuss exactly the
9 reversibility in terms of the data collection.

10 Dr. Friedman?

11 DR. FRIEDMAN: I can answer that question
12 with some assurance because two of those seven
13 patients were patients that were done at our
14 institution, and I remember the details. Those
15 were patient who actually had cryomapping, not
16 cryoablation, of the slow pathway during AVNRT.

17 In the baseline state, both patients had
18 inducible, sustained SVT, and during cryomapping we
19 showed that the slow pathway was completely blocked
20 and SVT was no longer inducible. With cryomapping
21 turned off, the slow pathway recovered function and
22 there were single, occasionally two, echoes, but

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1 not sustained SVT. We waited a while, and still
2 there was no sustained SVT, although the slow
3 pathway had recovered.

4 We marked that as non-reversible because
5 it did not return to baseline, although I think it
6 was a function of time. Had we waited 20 or 30
7 minutes, in all likelihood it would have.

8 DR. DESMARAIS: Dr. Lehmann?

9 DR. LEHMANN: Part of your question
10 related to data that doesn't seem to match, and
11 that is really the record of our good collaboration
12 with the FDA, to clarify what we felt the true
13 situation was. So the report in the FDA
14 presentation was that 80 out of 87 cryomap subjects
15 with an effective cryomap had "reversible" marked
16 on their form and seven had the "not reversible."

17 We went back and looked at that. Part of
18 the issue was, what was "reversible,"
19 quote/unquote? Is it seconds? Is it minutes? So
20 we did the additional analysis of actually looking
21 at the cryoapplication data to see how long it was
22 before the next application occurred either with

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1 normal conduction restored or not. That is the
2 data that we showed. Either way, you get a better
3 than 90 percent reversibility assessment in short
4 notice and no adverse events related to
5 cryomapping.

6 DR. TRACY: Okay. In terms of the
7 clinical utility of cryomapping, how useful is
8 this? There was, I think it was, 84 percent
9 attempted and successful, 79 percent not attempted,
10 and yet the ablation was successful. So it is 79
11 percent versus 84 percent. Is that hugely
12 different?

13 DR. DESMARAIS: Dr. Friedman will answer.

14 DR. FRIEDMAN: Well, I'm a believer in
15 cryomapping. I think that it is useful. Having
16 used this technology, in my mind, it is very
17 useful.

18 I think there are differences among the
19 different patient groups, and that is partly why we
20 presented the data that we did. For AVRT, if you
21 think about patients with an accessory pathway,
22 these tend to be very discrete structures and they

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1 are not the sorts of things that one can localize
2 simply by looking at catheter position
3 fluoroscopically. It requires very careful mapping
4 technique. It needs to be very precise.

5 In my mind, the clearly-demonstrated
6 effect of this, of cryomapping, in that group
7 relates to the fact that, with cryomapping, you're
8 affecting a relatively small area with the tip of
9 that catheter. You need to be very close to the
10 accessory pathway in order to interrupt conduction
11 in that pathway temporarily. If you see that
12 effect, then that predicts effective cryoablation
13 because you're right on the spot.

14 With AV nodal reentry, it may be
15 different because in many cases patients are
16 undergoing AV node re-entry ablation based on
17 anatomy fluoroscopically. You can position the
18 catheter in what you think is the slow pathway
19 position without regard to mapping -- this is
20 typical of radiofrequency ablation -- and often get
21 a successful ablation.

22 So the area of ablation for the AVNRT may

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1 be larger and mapping precisely may be less
2 critical, but, conversely, the negative cryomap in
3 that group I think is a very important and useful
4 thing clinically, because to map during the slow
5 pathway ablation a spot and find transient AV block
6 identifies a place that you do not want to do
7 ablation. So it is useful in a different kind of
8 way.

9 DR. DESMARAIS: I would like also to ask
10 Dr. Keane from MGH comment on that.

11 DR. KEANE: My name is David Keane. I'm
12 an investigator, and I practice at the Mass General
13 Hospital in Boston. I have no equity, am not a
14 consultant, but my travel trip expenses, my
15 flights, were paid for by CryoCath.

16 The reason I came down here today is
17 because I'm strongly motivated to see it be
18 introduced to the clinical practice that we have in
19 Boston, and it has implications just not imminent
20 to mapping but also ablation alone.

21 I get a call once every two to three
22 weeks from New England physicians with patients who

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1 have -- typically, younger patients than older
2 patients with parahisian pathways -- and I have
3 over 10 patients whom I have sort of held off over
4 the last five years on the basis that I was
5 involved in the animal work with this system and
6 have always told them that it is only a matter of
7 time before you will see this thing come through.

8 They have been holding out for a number
9 of years with recurrent SVT, treated on medication,
10 and a lot of these are teenagers who are treated
11 with beta blocker and anti-arrhythmic drugs. Some
12 of them are young females who wish to become
13 pregnant and they continue to take their anti-
14 arrhythmic drugs. That is the real downside for
15 them. I think it is a shame that they have to
16 wait, in particular, for this system to come along
17 and kind of eradicate their arrhythmia on a
18 permanent basis.

19 For us, it is really key to see an
20 approval for parahisian pathways because they are
21 the folks that suffer the most in that they have
22 had enough SVT to come for ablation; they have

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1 turned down. They have been brought all the way,
2 almost like being a horse to the water, but they
3 haven't been allowed to drink. We have mapped
4 these very accurately and found them to be truly
5 parahisian.

6 There are a lot of patients out there
7 waiting in the wings, not only directly on our own
8 waiting list, but also on the referring docs. So
9 the answer today has been for AVNRT. I think the
10 real value for cryomapping, actually the relevant
11 importance of cryomapping greatly exceeds the AVNRT
12 group for people with parahisian pathways.

13 As Dr. Waldo referred to it, it is a
14 negative predictive value of a cryomap that has
15 been more important than a positive predictive
16 value for these people with parahisian pathways.
17 The issue is that you have total adhesion to the
18 spot. It is the same with the mahine fiber. If
19 you have mahine fiber, if you do a bump map, there
20 is a good possibility that by the time you go on
21 and your tachycardia terminates, again, it is like
22 Dr. Ruskin's video this morning: If the

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1 tachycardia terminates, the catheter moves, you
2 never get it back there again.

3 With the adhesion, the ability to do a
4 map down to 30 degrees, go on at that spot, if you
5 have elimination of your target physiological
6 endpoint, to be able to go straight on from minus
7 30 to minus 69 or minus 70 without having to rewarm
8 is the biggest plus of this system, because you are
9 guaranteed that your spot is exactly where you
10 mapped. If you do it with an RF, either by bump
11 mapping or even a low temperature, 10-watt output,
12 you are still getting smudge lesion. With every
13 other system, you are constantly smudging, the same
14 way with microwave and ultrasound.

15 With this cryo, because it is a pinpoint
16 lesion, as you point out, they are very small
17 lesions, and that's why it is critical for these
18 accessory pathways that they are precisely mapped.

19 Perhaps that was underappreciated in the trial,
20 the critical importance because you get so much
21 collateral damage with an RF. If you're not
22 exactly on the spot but close to it, you have

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1 success. With cryo, you have to be absolutely on
2 the spot. I think that may have been
3 underappreciated when we were performing this
4 trial.

5 But, for me, the biggest issue about
6 mapping is the ability to map a parahisian pathway,
7 particularly for these teenagers and young people
8 who have been waiting now for several years to see
9 this system come through.

10 Thanks.

11 DR. TRACY: I appreciate that comment,
12 but I think that the device isn't being considered
13 for parahisian pathways at this point. I think our
14 discussion is just related to AVNRT.

15 DR. DESMARAIS: I think Dr. Lehmann has a
16 final comment on that.

17 DR. LEHMANN: I have just redisplayed
18 this slide from this morning's presentation that I
19 think relates to your question.

20 First, I would like to point out that
21 this display doesn't relate to our indications for
22 use, but we thought it was a fascinating finding

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1 from the study. In the effective cryomap column,
2 at the bottom you see the 94 percent success rate
3 for those 87 subjects who had an effective cryomap.

4 For the 48 subjects who had cryomapping attempted
5 but didn't think demonstrated, they had a 67
6 percent complete procedural success. For subjects,
7 the 29 who had no cryomapping attempted, it was 76
8 percent. The comparison of the first to the second
9 and third columns is clearly significant.

10 So there is this positive predictive
11 value. That is really all we were saying, that if
12 you do happen to cryomap and get an effective
13 cryomap, your certainty about ultimate success is
14 high, and so that is really the remark.

15 DR. TRACY: Thank you.

16 Moving on to the cryoablation itself, it
17 strikes me that 11 of 103 patients had transient
18 heart block, and that is high for even -- I would
19 not expect that high of a level of transient heart
20 block with RF energy. What explains that, and what
21 explains the development of a right bundle branch
22 block when you're working in a slow pathway zone?

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1 I can't quite figure that piece out.

2 DR. DESMARAIS: I will ask Peter, Dr.
3 Friedman, to answer that.

4 DR. FRIEDMAN: You have touched on a
5 number of important issues, and I think, Dr.
6 Lehmann, if we could have that one slide that I had
7 asked you to show, we will talk about this.

8 With regard to the right bundle branch
9 block, there is a spectrum of catheter stiffness or
10 flexibility among the catheters that are available
11 in the marketplace, with EPT catheters being
12 probably the most flexible and on the other end of
13 the spectrum maybe a Biosense Webster being less
14 flexible. Different catheters are used to
15 different degrees in different institutions, and
16 people are accustomed to certain kinds of handling
17 characteristics.

18 This catheter is probably in the middle
19 part of that spectrum, but tending toward the
20 Biosense Webster. I think if someone is used to an
21 EPT catheter, which is very flexible, then all of a
22 sudden picks this catheter up, it is a little bit

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1 stiffer and it takes a little time to get
2 accustomed to.

3 I think some of the right bundle branch
4 blocks that you are seeing there are not
5 necessarily related to ablation or mapping. It is
6 just the mechanical handling characteristic of the
7 catheter. After all, we see right bundle branch
8 block just with diagnostic his catheters on
9 occasion. So I think those are my comments about
10 the right bundle branch block.

11 With regard to the high incidence of
12 transient AV block, I think this relates to the
13 fact again that this was an investigational
14 procedure with a new technology, and the
15 investigators really were set on giving this
16 technology a good test. So, for example, this is a
17 case actually that we did at our institution. A
18 woman with AVNRT -- I don't have a laser pointer --
19 but a woman with AVNRT who had, I don't remember
20 the exact number, a few cryoablations, and after
21 the last of those, the sustained SVT was no longer
22 inducible. There were still single echo beeps that

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1 were inducible.

2 Now in radiofrequency ablation, that
3 would be an endpoint. Most people would stop at
4 that point and not go on. But this is a new
5 technology, and we didn't know whether that was an
6 adequate endpoint or not. So we persisted, and we
7 did ablations closer and closer to the compact AV
8 node.

9 So here's an ablation actually in the
10 high to mid-portion of the septum, fairly close to
11 the compact AV node. You see the artifact on the
12 ablation catheter because of the ice formation
13 around the catheter, and you see here the surface
14 ECG, and here's an atrial electrogram. That's
15 conducted; that's conducted. Here's a blocked P
16 wave.

17 The first blocked P wave is right there,
18 and you can see within one or two seconds the
19 ablation was turned off and you see disappearance
20 of the ice ball this quickly. Now this is a
21 continuous strip, and you can see that this
22 transient AV block now is gone within four or five

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1 seconds.

2 So this may relate to why we saw
3 transient AV block perhaps more frequently than you
4 would have expected, because people were using this
5 technology aggressively, knowing that if AV block
6 occurred, it would disappear.

7 I would conclude by just drawing your
8 attention to the Calkins data in a previous
9 submission with a different kind of catheter, where
10 if one looks at the -- yes, and here we have the
11 data for you.

12 So this is the previously-submitted
13 Calkins data that was reviewed prior to that
14 catheter's approval. This shows you the incidence
15 of any block during ablation of AVNRT or AVRT. The
16 incidence was 3.4 percent, so maybe a little bit
17 higher than people are accustomed to seeing. Ours
18 was 7.2 percent.

19 But here's where the major difference
20 resides, and I alluded to this in my comments
21 earlier. Of this 3.4 percent, you know, nearly a
22 third or a half went on to have persistent AV block

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1 and needed a pacemaker. Here is where our
2 difference is: that AV block is transient.

3 DR. TRACY: It is interesting, the
4 electrophysiologic definition of the substrate is
5 not the traditional thing that we look at for
6 success. It talks about the success being measured
7 as not inducible to 15 seconds or more of SVT. I
8 would never stop with 15 seconds of AVNRT residual.

9 Why was that chosen, and how often did you see an
10 effect on both slow and fast in the cryo?

11 DR. FRIEDMAN: That endpoint was chosen
12 not for its own value, but we struggled with what
13 were the appropriate inclusion criteria. We didn't
14 want to do ablation in people who had non-sustained
15 arrhythmia at baseline because it would be so
16 difficult to judge the effect of the intervention.

17 So we arbitrarily chose greater than 15
18 seconds' duration as a definition for sustained SVT
19 at baseline. Once we established that, then the
20 endpoint of a successful ablation was anything less
21 than that. But I would argue that the success rate
22 long term attested to the fact that that was a

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1 clinically-useful endpoint.

2 DR. TRACY: And the 94 percent long-term
3 success rate, that's of the cryo patients, not of
4 those cryo-plus-rescue? That is cryo alone?

5 DR. FRIEDMAN: That's correct, that is
6 just the cryoablation alone.

7 DR. TRACY: Okay. In patients with
8 recurrence, at what point was that seen? Is that
9 an early recurrence, within a day or two, or is
10 that -- it's early?

11 DR. FRIEDMAN: It is usually within a day
12 or two, certainly within the first month. No
13 recurrences after three months.

14 DR. TRACY: Okay. How many patients had
15 first re-AV block following ablation?

16 DR. FRIEDMAN: I think we have the slide.
17 None of them was permanent. I think the table
18 that I showed you there -- go back. So there was
19 one, two, three, four, and all of them resolved
20 with 24 hours.

21 DR. TRACY: None were permanent? And
22 none developed first re-AV block in the first month

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1 or at a point later?

2 DR. FRIEDMAN: No, no.

3 DR. TRACY: Okay. There was sort of a --
4 we didn't talk about it in your presentation this
5 morning, but the learning curve seems to be -- it
6 seems to take quite a bit of learning to get to use
7 this catheter correctly. It looked like there was
8 an acute success rate of 85 percent early versus 97
9 percent late.

10 How hard is it to learn how to use this
11 catheter and what does that mean in terms of how
12 you would train physicians to use the system?

13 DR. DESMARAIS: I think I'll have a
14 multiple answer to that question. I'd like to
15 start with Dr. Friedman to discuss how to use the
16 device. Secondly, there is a real number where we
17 have Dr. Lehmann that can answer some of that.

18 Then, in real practice, Dr. Ruskin. In
19 the real practice, then we can talk, Dr. Dubuc can,
20 who has been using the catheter now for over 150
21 cases, as he reported earlier.

22 DR. FRIEDMAN: As a clinician who has

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1 been around longer than I care to recall, I think
2 it is fair to say that there is a learning curve
3 with any new technology, and that was true of
4 radiofrequency ablation. If one goes back and
5 looks at acute procedural success in some of the
6 older trials, you know, 85 percent was acceptable.

7 Now we use an OPC of 92 or 93 percent. So,
8 seemingly, there is an evolution in the field as
9 people do more and more and get more comfortable,
10 but that is true of also the cryoablation catheter.

11 It is difficult to demonstrate that
12 statistically within the confines of a small study.

13 So we actually didn't demonstrate statistically a
14 learning curve. Maybe Dr. Lehmann can comment on
15 that further.

16 DR. LEHMANN: I think it is worth just
17 keeping it very simple. There was a very minor
18 trend. There were a couple of difficulties.

19 One is there were a number of
20 subinvestigators, and when you take 166 or 164
21 cases and divide them amongst 13 sites with
22 multiple subinvestigators, it is just impossible to

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1 do any -- you don't get enough case accrual. That
2 was really a major issue. When we did it on a per-
3 site basis, there was nothing significant.

4 DR. DESMARAIS: And Dr. Dubuc?

5 DR. DUBUC: As I said before, we did more
6 than 150 cases in our institution. I did myself
7 100 cases of these. When we switched to -- we
8 decided to go for cryo for all our AV node reentry
9 cases afterwards, I mean since last August; my
10 colleagues started doing it, but they knew about
11 the technology; they knew about the result of the
12 studies we performed in Canada previously. And
13 they quickly got it. Right after three or four
14 cases, they were able to do these things by
15 themselves.

16 You have to realize that actually the
17 thing you learn from the technology is that you
18 don't expect the same response from the energy
19 source. Like when you do RF ablation, you expect
20 irradiated junctional rhythm during the ablate.
21 You don't have that.

22 The catheter adheres to the under-cardial

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1 surface. So it is different. You don't have to
2 monitor on the fluoroscopy. This is what you have
3 to learn.

4 More than my colleagues, also the
5 personnel working in the lab, they know what to
6 expect and they make the connection quickly, and we
7 know what to expect from the technology. So it
8 comes very, very quickly, if you have somebody --
9 not everybody has to go through the same learning
10 curve, I would say, you know, like I did. My
11 colleagues near me, they did it very quickly.

12 In closing, your question about the
13 complexity of the system itself, you have a
14 catheter; you have, compared to RF, you have two
15 connections instead of one, and you have an on-and-
16 off button. So from a complexity standpoint, it is
17 not very complex.

18 DR. TRACY: Okay, thanks. Just to return
19 to some of the labeling issues, I don't know if you
20 want to look at your labeling section, but I think
21 that, based on what you have presented today, I
22 agree these are the appropriate indications that

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1 you should be seeking approval for.

2 Under the precautions, just a couple of
3 statements: The one, two, three, four, fifth
4 bullet down, "Consider periprocedural coagulation
5 therapy for patients undergoing left-sided and
6 transeptal catheter procedure and for selected
7 patients undergoing right-sided procedure." That
8 doesn't quite fit with the indication, but I
9 understand why that might be there.

10 DR. DESMARAIS: Well, obviously, when we
11 wrote the indication originally, we understood that
12 indications and instructions for use is something
13 that has to be worked on at a later date,
14 obviously.

15 DR. TRACY: Okay. And down further, the
16 third-from-the-bottom precaution: If patients need
17 to be defibrillated during the procedure,
18 disconnect the catheter's electrical connection
19 part to do defibrillation. Why?

20 DR. DESMARAIS: I would have Marwan
21 Abboud to answer that question. He is our Director
22 of Engineering.

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1 DR. TRACY: Okay

2 MR. ABOUD: Ladies and gentlemen, Mr.
3 Chairman and Panel members, I am Director of
4 Engineering.

5 The different relation issue is mainly --

6 DR. TRACY: Excuse me. Could you please
7 tell what your conflict of interest is?

8 DR. DESMARAIS: Marwan Abboud is an
9 employee of CryoCath.

10 DR. TRACY: Okay.

11 MR. ABOUD: Director of Engineering at
12 CryoCath.

13 DR. TRACY: Okay. I'm sorry I didn't
14 understand.

15 MR. ABOUD: The defibrillator issue is
16 mainly to protect the console. As any equipment,
17 when you defibrillate, since we have a thermocouple
18 measurement, in order to prevent destroying the
19 temperature measurement circuit, we recommended to
20 disconnect the catheter.

21 DR. TRACY: Okay. That's fine. All
22 right, that's basically all the questions I have at

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1 this point, but I sort of reserve the issue of the
2 statistical questions, might come back to that. I
3 am hoping others will do that, too.

4 CHAIRMAN LASKEY: Great. Thank you,
5 Cynthia.

6 While Dr. Tracy had the luxury and
7 prerogative of spending 15 minutes, you can
8 appreciate the number of people up here who need
9 their moment in the sun. So I would like to ask
10 the Panel members to share their thoughts and
11 direct their questions to the sponsor and the
12 principal investigators in less than five minutes,
13 five minutes or less, if they can summarize the key
14 issues that they have before us. That way,
15 everyone can have a fair shake.

16 MS. WOOD: Actually, at this time it
17 would be general questions for either the FDA or
18 the sponsor. We would ask the sponsor to vacate
19 the table at this time, please.

20 CHAIRMAN LASKEY: I would like to begin
21 the Panel's questions and comments with Dr.
22 Gilliam.

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1 DR. GILLIAM: I have a few questions
2 related. I think Cindy touched on several, but I
3 am looking at your labeling. You do say, "The foot
4 switch is available only in Europe." Is that the
5 plan? I am just wondering, why was that set up
6 that way, your foot switch for your console?

7 DR. DESMARAIS: Obviously, every device
8 has design evolution. When we designed this trial,
9 we designed it with the current product that we
10 had. At that time there was no foot switch that
11 existed with the design of the console that we
12 have, but the design evolution in Europe is moving
13 faster. So it is available there. But, in due
14 course, when it is time to file amendments to the
15 current product, we will do so within the
16 boundaries of the FDA regulations.

17 DR. GILLIAM: Another thing, looking at
18 the first panel of your labeling, I guess that is
19 on the first page on the righthand side, the third
20 point down: "Do not connect CryoCath to
21 radiofrequency generators as it may result in
22 patient electrocution." It seems pretty drastic.

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1 Is there a real possibility of that? I
2 guess I would direct that to your engineering.

3 DR. DESMARAIS: I will ask now our
4 Director of Engineering to answer that.

5 MR. ABOUD: I think, as any RF, you,
6 even for the eruption rater, they do recommend not
7 to put a diagnostic catheter. Since our catheter
8 printout on the connection are different from
9 regular RF catheter, we recommend not to do it at
10 this time. Thus, we are using different
11 thermocouple. Since we have a cold temperature, we
12 use a different thermocouple.

13 DR. GILLIAM: I'm not opposed to not
14 hooking up to an RF. It was just quite drastic
15 when you saw electrocution. Have you all had some
16 experience with that perhaps? You don't have to
17 answer.

18 (Laughter.)

19 While you are there, I do have one
20 question.

21 MR. ABOUD: Yes.

22 DR. GILLIAM: Your panel that you viewed

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1 the temperature that is right on the console, is
2 that exportable to any type of monitor that an
3 operator could see if they are not directly looking
4 at the console?

5 DR. DESMARAIS: At the current time, it
6 is not exportable. It is not designed to be in
7 such a way. However, again, in Europe we are
8 looking to introducing that concept. Whenever it
9 is ready for us to introduce in the USA, we will do
10 so again, within the boundaries of the FDA
11 regulations.

12 DR. GILLIAM: This may be one of your
13 investigators could answer this. Looking at your
14 AV node reentry population, is it typical that you
15 would be doing the slow pathway ablation while the
16 patient would be in tachycardia insofar as you will
17 not have the junctional rhythm that we typically
18 see with RF? How would you, other than looking at
19 a negative map, cryomap, how would you know you
20 have achieved some degree of success with slow
21 pathway modification during an ablation run?

22 DR. FRIEDMAN: There are a number of ways

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1 that one can do that. The example I showed you
2 this morning was cryomapping, just to illustrate
3 how the tachycardia would terminate, and in the
4 anterograde slope pathway direction.

5 During ablation, most typically, the
6 ablation is actually during a sinus rhythm. The
7 advantage to that is that the patient's in sinus;
8 you can monitor the PR interval. Indeed, you can
9 even do atrial pacing or programmed atrial
10 stimulation during the ablation application.

11 That catheter tip is fixed to the
12 myocardium and will not move, and that allows you
13 to monitor during sinus rhythm or during atrial
14 pacing, while the ablation is going on, when the
15 slow pathway disappears.

16 DR. GILLIAM: As far as the shipping and
17 storage of the catheters, are there any special
18 precautions of this catheter, given it is sort of a
19 multi-lumen catheter? I notice the kinking is a
20 concern, obviously, for reasons, but how does the
21 catheter come in storage?

22 DR. DESMARAIS: The catheter is packaged

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1 into a tray system. It is packaged flat and it is
2 not coiled on itself, and the storage conditions
3 for catheters and console is standard of any
4 ablation catheter out there.

5 DR. GILLIAM: Those are all the questions
6 that I have right now.

7 CHAIRMAN LASKEY: Thank you, sir. Thank
8 you twice. Mitch?

9 DR. KRUCOFF: I also will try to be
10 brief. I guess I am most interested in the use of
11 the OPC-based trial design. Obviously, that is
12 consistent with the precedence in this area of
13 industry.

14 But I think it has been remarkable to me,
15 in listening to your presentation, the difference
16 between the fascinating findings from this study,
17 which is to me the investigator's view of what
18 happens in a patient and how it works, versus what
19 you have welded yourself to with an OPC-based trial
20 design that I think Dr. Yue did a very eloquent job
21 of illuminating. It is really a population kind of
22 statistic.

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1 So the observed behavior of the catheter
2 in individual patients, the PI sort of view, and
3 how it will behave in the population, and whether
4 or not you qualify based on boundaries for your
5 endpoints as successful or not are two very
6 different worlds.

7 I guess what I would like to hear is, why
8 do you think you failed to show the boundary
9 outcomes?

10 DR. FRIEDMAN: I think there are a couple
11 of points to mention in answering that question.
12 When the protocol was being designed, we were faced
13 with a choice of either using an OPC, an
14 historically-derived OPC, or doing a randomized
15 comparison between cryo and RF. The randomized
16 comparison would not have allowed us to look at
17 cryomapping because there is no way to map with
18 radiofrequency. So we were, basically, stuck with
19 the OPC comparator for the purpose of this trial.

20 I would point out that that OPC is
21 derived from results recently, and RF is a very
22 mature technology. It has been around for nearly

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1 20 years now. This is a very young technology. So
2 we are comparing ourselves to a very high bar.

3 Beyond that, I think that the technology
4 was demonstrated to be clinically effective in the
5 group for which an indication is being sought:
6 Ninety-one percent in the AVNRT patients is a
7 clinically-valuable result.

8 The reasons why the OPC weren't met I
9 think relate to the fact that some of the ablations
10 were in AVRT, left-sided accessory pathways. This
11 technology is very different than radiofrequency.
12 I think you saw the acute effectiveness results
13 were less dramatic in the AVRT group than the AV
14 nodal reentry group.

15 I think you have to think about the
16 biophysics of ablation and the differences between
17 these two technologies to understand that. With
18 radiofrequency ablation of the left free-wall
19 pathway, typically done along the mitral valve
20 annulus, this is a high blood-flow area. That high
21 blood-flow actually serves to cool the
22 radiofrequency tip, and in a way it is almost akin

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1 to a saline-irrigated RF ablation.

2 From Dr. Dubuc's animal studies, we know
3 that radiofrequency ablation causes a larger area
4 of damage on the endocardial surface. That relates
5 to the fact that the catheter is moving. It is not
6 stuck to a certain point. It paints back and forth
7 across the endocardial. So that one doesn't need
8 to be exactly on the accessory pathway to achieve a
9 successful ablation.

10 It is very different for cryoablation.
11 Cryoablation adheres to the point and does not move
12 from that point. That high blood-flow along the
13 mitral valve actually acts as a heat source that
14 minimizes the efficiency of the cryoablation. I
15 think that relates to why there may be a difference
16 in effectiveness in that group, which affected the
17 overall results.

18 But, conversely, I would look at it a
19 different way, because in high-flow areas where
20 cryoablation may not have an advantage, in contrast
21 to low-flow areas, it may have a very real
22 advantage, and specifically in post-receptal

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1 accessory pathways within the coronary sinus, for
2 example, where radiofrequency often can't be done
3 because of high impedance and low-energy delivery,
4 and in the slow pathway position, which is not as
5 high a blood-flow area. It results, I think, in
6 the fact that in that circumstance it is highly
7 effective.

8 DR. KRUCOFF: Well, I mean, I hear you,
9 but I'm honestly not sure to which side of my
10 question this -- you know, again, to me, what I
11 hear is an enormous amount of conceptual and
12 intellectual fascination in why and where this
13 technology really might be an advance beyond RF.

14 But how much of that is reflected in this
15 clinical trial or can be deduced, or even in the 91
16 percent in AVNRT, is the actual observation? It is
17 the boundaries around that that become even
18 relevant to talk about with an OPC. As was
19 described, it is not the boundaries around the
20 whole population. It would be the boundaries
21 around the RF population and AVNRT. Again, at
22 least my understanding of the data, unless I missed

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1 something, is that even the boundaries around the
2 91 percent for AVNRT do not compare favorably to
3 the RF historical boundaries that you would pre-
4 define if you had prospectively pre-defined for
5 that population.

6 So, I mean, I get that there are a lot of
7 theoretical both safety and effectiveness possible
8 subpopulations that this instrument might be
9 terrific for. On the other hand, I also get that,
10 like so many things that we do, it is possible that
11 the more damaging milia that RF creates may have
12 areas where it is actually more effective.

13 The fact that I saw two different sets of
14 numbers, but whether it is 23 out of 25 or 25 out
15 of 27 of the cryo failures that were successfully
16 done with RF, I don't need an explanation of that.

17 To me, it just says that one is more
18 histologically pleasing to look at than the other.

19 It ultimately begs the question of when you start
20 applying this to a population of human beings,
21 where is the data that gives you confidence that
22 this is a safe and effective approach?

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1 And with an OPC set of boundaries that,
2 even in the group who you are asking for an
3 indication, if you drill down retrospectively to
4 your point control population, you still don't make
5 the boundaries for the AVNRT.

6 So I am just missing a link as to, if you
7 bought into this trial design from the beginning,
8 which obviously you must have at some level, how do
9 you come to see the data supporting the
10 fascination? The fascination is self-evident? The
11 data that this is safe and effective compared to a
12 well-established, as you say, mature technology is,
13 I think, what the patient or user side question is.

14 I am really interested in why you think,
15 both in the safety and in the effectiveness, you
16 failed to make your boundaries?

17 DR. LEHMANN: I will just briefly comment
18 on the design. As you do know, sponsors don't have
19 a free hand in choosing a clinical study design.
20 It is negotiation with the agency.

21 We either had the choice of a --

22 DR. KRUCOFF: Well, you could have done a

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1 randomized trial.

2 DR. LEHMANN: Yes, we could have done a
3 randomized trial, but there are a number of
4 problems with that, including standardizing RF
5 therapy procedures and equipment, which is actually
6 rather hard to do -- it will cause a large study --
7 and the difficulty with cryomapping.

8 As to the implications of what we have
9 demonstrated, I think Dr. Friedman will just have a
10 few remarks.

11 DR. FRIEDMAN: I will try to answer your
12 question. I understand what you are wrestling
13 with, and it is a difficult issue. I will try to
14 answer it by putting it in clinical perspective.

15 I think it is very helpful to step back
16 and try to look at things from the perspective of
17 the patient. If I'm a 20-year-old patient with AV
18 nodal reentry that is interfering with my lifestyle
19 and a physician gave me two choices: One choice, I
20 can have radiofrequency ablation with a 94 percent
21 chance of acute success; however, there is a 1 to 2
22 percent chance that I am going to wind up with a

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1 permanent pacemaker. Or I could have a
2 cryoablation with a 91 percent acute procedural
3 success rate and no chance -- no chance -- for a
4 pacemaker. It is very clear in my mind what I
5 would choose, and I would venture to say that most
6 individuals faced with that decision would make the
7 same decision that I have just made.

8 CHAIRMAN LASKEY: I must say I need to
9 object to that last statement. It is not zero.
10 The confidence intervals of zero events observed in
11 150 patients go out on my back-of-the-envelope,
12 amateur stat. program here to 2 percent. It's not
13 zero. I think you do need to be rather
14 intellectually honest to some of these questions.

15 I think we are on the threshold of
16 perseverating as well. So I'm not sure we are
17 going to get to what you really need to know.

18 DR. KRUCOFF: I think a question is on
19 the table, and I think, you know, again, I am just
20 going to move on because I only have a couple of
21 other brief questions.

22 In your European experience, are you

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1 aware of any instances where RF ablation has failed
2 and cryoablation has succeeded?

3 DR. DESMARAIS: Well, in fact, every time
4 that there has been ablation in AVNRT and do
5 defibrillation near the aveno where the physician
6 either pulled back, because of fear of I think an
7 AV block and subsequently tried trial, there is a
8 lot of data that concurs that we have successful
9 cryoablation after RF.

10 DR. KRUCOFF: Okay. Thank you. So what
11 I am hearing is, in situations that the operator
12 sort of judged to be too risky to actually fire RF
13 energy --

14 DR. DESMARAIS: Or has fired RF and
15 failed in that, as well I think there's a current
16 trial in the U.S. Again, this was filed initially
17 by the PMA. The data we have, we know that these
18 are patients that failed RF, that the study
19 conducted by Dr. Chapman right now, which is a
20 small subset study, but we don't have any data to
21 present on that.

22 DR. KRUCOFF: Okay, and are you aware of

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1 any experience with cryo patients that were not
2 durable, that came back, that were redone with
3 cryoablation? Can you go back and freeze the same
4 site twice. Do you have any experience with that?

5 DR. DESMARAIS: Yes, and I think Dr.
6 Dubuc can answer that. He has done some of those
7 patients.

8 DR. DUBUC: I think I have two parts of
9 this question, if we have patients who have failed
10 RF and they went to cryo or if they had two
11 sessions of cryo?

12 DR. KRUCOFF: Yes.

13 DR. DUBUC: Okay. Well, yes, with no
14 problem. No problem at all.

15 DR. KRUCOFF: Have you looked at that in
16 animals, if you repeatedly cryoablate the same
17 tissue?

18 DR. DUBUC: Nothing will happen because
19 the process is already in evolution. Actually, I
20 could say that, even if you stand there, and why we
21 picked that time of four minutes is because we know
22 that after three minutes you reach a plateau that

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1 the ice ball inside the tissue will not grow
2 anymore. It will stop there, and that has been
3 proven by cardia ultrasound, because you can see
4 the ice ball with ultrasound, with intracardiac
5 ultrasound. Actually, we can monitor that.
6 Actually, the correlation coefficient between the
7 measurement done by echo and the histology was .95.

8 DR. KRUCOFF: Okay, I have no other
9 questions.

10 CHAIRMAN LASKEY: Thank you, Mitch. Dr.
11 Page?

12 DR. PAGE: Thank you. I will try to keep
13 this as short as possible.

14 The first question is -- actually, the
15 first two questions have to do with the footprint
16 of this device. Peter, maybe you could answer
17 this, Dr. Friedman.

18 In terms of looking for biological
19 plausibility for why you found what was, I guess,
20 an unexpected result, that AVNRT was successful and
21 AVRT was not, as I wrestled with the biological
22 plausibility of that finding, as opposed to just

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1 chance, which is what we always have to be
2 concerned about with a post-hoc analysis. Would
3 you say it has to do with the footprint of this
4 device being smaller and being adherent at the time
5 of ablation lesion?

6 DR. FRIEDMAN: I think those are the
7 answers, as I alluded to earlier, yes.

8 DR. PAGE: Okay, fair enough. Do you
9 have an idea, how long is it before you get
10 adherence of this catheter at the ablation site?

11 DR. FRIEDMAN: It occurs within a matter
12 of 10 or 15 seconds. It depends a little bit on
13 how stable the catheter is to begin with and what
14 kind of contact one has with the tissue.

15 But by the time the artifact on the
16 catheter that I showed you there indicating
17 freezing appears, that catheter is stuck.

18 DR. PAGE: And, likewise, would you say
19 that it detaches at about the same interval that we
20 saw on that electrogram? So a few seconds, but
21 pretty promptly?

22 DR. FRIEDMAN: Within three or four

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1 seconds.

2 DR. PAGE: Within three or four seconds,
3 good.

4 And as someone who performs ablation, I
5 recognize the advantage of having an adherent
6 catheter at the spot you are burning or freezing in
7 this case, because, especially if you are burning
8 during tachycardia --

9 DR. FRIEDMAN: Yes.

10 DR. PAGE: -- then it will stay put when
11 the geometry and the motion of the heart changes as
12 you break the tachycardia.

13 Let me flip that around. I have spent
14 the last 10 years doing ablations in Texas, and
15 every once in a while a patient would get up off
16 the table in the middle of a burn or grab or move a
17 leg. What data do we have in terms of, if a
18 catheter is pulled when adherent to the tissue --
19 you understand my question?

20 DR. FRIEDMAN: I do.

21 DR. PAGE: We've all been through this,
22 being in a busy lab, and suddenly a patient moves,

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1 and your catheter might move with him. With the
2 standard RF catheter, it may perforate or it may
3 more likely pull away from where you are burning.

4 But if you are attached and someone took
5 a tug at that catheter, what happens to the tissue?

6 DR. FRIEDMAN: Well, there are some
7 animal studies that we could cite, but I would
8 follow up just by saying that, if the patient
9 moved, injection can be halted within a matter of
10 seconds.

11 DR. PAGE: I understand that, but this
12 happens so fast, and we have already agreed that it
13 sticks for a couple of seconds. This happens in
14 less than half a second, as we all -- anybody who
15 has been in an EP lab recognizes sometimes the
16 patient will suddenly come up off the table.

17 DR. FRIEDMAN: Yes.

18 DR. PAGE: So if that does occur with
19 adherence, what happens to the underlying tissue?

20 DR. DUBUC: I mean, if the range of
21 motion you are talking about is rather small, I
22 mean I don't think that the patient would start

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1 running from the table.

2 DR. PAGE: No, but imagine -- let me put
3 it clearly because it happens.

4 DR. DUBUC: Yes, I know.

5 DR. PAGE: Imagine someone in the middle
6 of the burn tugs it forcefully. I mean, what comes
7 with the tip?

8 DR. DUBUC: Okay. If the patient moves,
9 nothing will --

10 DR. PAGE: That's not my question.

11 DR. DUBUC: Okay. If somebody tugs
12 really just a little --

13 DR. PAGE: No, I'm saying a good, strong
14 tug.

15 DR. DUBUC: Well, you can do damage to
16 the tissue underlying the --

17 DR. PAGE: The underlying tissue?

18 DR. DUBUC: Yes.

19 DR. PAGE: Okay. And my only caution
20 being, you know, we have had physician experts
21 talking about looking forward -- I should just
22 mention, first of all, that at the AV node slow

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1 pathway area, this probably would not be a major
2 catastrophe. If someone is taking this to other
3 places -- we have talked about parahisian. What if
4 we wanted to outflow track ablations, something
5 like this, where the tissue is thin, atrial
6 tachycardias where the tissue is thin, do we have
7 any data on what would happen then?

8 DR. DUBUC: Well, something wrong can
9 happen because, you know, we made animal studies on
10 that or on purpose we pulled --

11 DR. PAGE: Sure.

12 DR. DUBUC: -- you know, strongly on the
13 catheter. Actually, if you pull a lot, you can
14 bring part of the heart inside the IVC and even
15 have avulsion of the tissue. Really, if you have
16 two people on the -- we did that testing.

17 DR. PAGE: Sure. It doesn't happen
18 often, but it does happen rarely.

19 DR. DUBUC: Yes.

20 DR. PAGE: Okay, thank you.

21 One question I had, and I just have one
22 other question after this: We seem to agree that

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1 there were no catheter-related complications, but
2 there were a number of complications that I think
3 related to procedure time and DVT, atrial clots,
4 and bladder infection related to a Foley that you
5 don't need for an hour-and-a-half procedure, but
6 you might need for a 260 average minute procedure,
7 the average number of burns is 7.5, and those were
8 four-minute burns? Is that right?

9 DR. FRIEDMAN: Four-minute freezes, yes.

10 DR. PAGE: Thank you.

11 (Laughter.)

12 I am so old-fashioned.

13 So four-minute ablations, if you will.
14 So that is about 30 minutes of actual ablating
15 time. So this is, indeed, a longer procedure,
16 related to whether it is the experimental condition
17 or not, it is a longer procedure. I think the
18 length of the procedure related to the experimental
19 protocol, indeed, was responsible for increased
20 complications.

21 I would mention that the European data
22 you showed us, which I never had a chance to see

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1 before today, was reassuring in terms of number of
2 lesions as well as duration of the procedure. So I
3 could presume that those wouldn't be ongoing
4 complications, and the procedure time would,
5 indeed, shorten.

6 My last question was, in terms of the
7 comment on parahisian pacing, which, as I
8 mentioned, concerns me because we are talking about
9 a very limited indication here, and with approval,
10 I am already hearing that people are looking
11 forward to using off-label use of the device and
12 potentially in tissues where we have already
13 discussed could be a problem if the catheter
14 weren't handled properly.

15 But if I saw the data properly, when you
16 have a failed cryomap, that still translated to a
17 67 burn success at that site?

18 DR. KRUCOFF: Ablation.

19 DR. PAGE: Ablation. The slide, it was
20 like 90 percent ablation when you have a successful
21 cryomap, but even a failed cryomap, you ended up
22 getting successful ablation 67 percent of the time.

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1 So my only caution is, with these 20-year-olds
2 that are waiting to have their parahisian pathways
3 ablated, a negative test pulse, cryomap, will not
4 necessarily translate to failure to ablate the his
5 bundle. Am I interpreting the data correctly?

6 DR. LEHMANN: I would make one minor
7 correction. The figures that you are quoting that
8 were recently up there were on a per-patient basis.

9 The distinction between a subject with one or more
10 effective cryomaps versus subjects who were
11 attempted but had not effective cryomaps, versus
12 the group that was never attempted.

13 So that isn't on a --

14 DR. PAGE: So on a per-burn basis, it is
15 lower than that?

16 DR. LEHMANN: Well, the overall is -- we
17 would have to go back and look. I don't have that
18 on the tip of my tongue.

19 DR. PAGE: I think you're right, it's
20 significantly lower.

21 DR. LEHMANN: Yes.

22 DR. PAGE: My only caution being that I

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1 don't know what comfort I have that the test pulse,
2 indeed, will not result in true ablation of the
3 normal conduction system.

4 And my last question is, the
5 reversibility of the heart block that you have
6 seen, that wasn't just with cryomapping; that was
7 also during an attempted ablation, is that right?
8 And then you turned off in time and, indeed,
9 conduction returned?

10 DR. LEHMANN: There are two aspects to
11 this. One is the straight cryomapping where we had
12 162 effective cryomaps, of which only around 64 of
13 them, 62 of them were warmed for reassessment.
14 That is where we got the 90-plus percent
15 reversibility of an individual intended cryomap
16 effect.

17 Then we had 11 adverse events, these
18 device-related transient AV block, of which one was
19 related to cryomapping and led to a death. It was
20 intended. It wasn't the therapy, they contend.
21 They were trying to go after one of the slow
22 pathways, and that subject had unintended AV block

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1 that lasted 20 seconds. So that was an adverse
2 event.

3 DR. PAGE: But in terms of when you are
4 therapeutically ablating, those do also, if you see
5 heart block, they tend to get better?

6 DR. LEHMANN: Those, we had the 14
7 instances in 11 subjects all reverted.

8 DR. PAGE: And that is reassuring. Thank
9 you very much.

10 CHAIRMAN LASKEY: Nobody in this room is
11 more sensitized to the off-label use of the
12 material that we're discussing. So could we please
13 restrict our comments to the material at hand and
14 not encourage off-label use? But thank you very
15 much.

16 Dr. Aziz?

17 DR. AZIZ: I, too, enjoyed the
18 presentation, and I must say I learned a little
19 more electrophysiology today.

20 Let me just address a few questions.
21 Looking at the number of patients who actually
22 developed either arterial or a venous clot, I guess

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1 part of that may be related to the time that the
2 catheters were in place, and it seems that the
3 times with experience do decrease.

4 Do you put these patients on any anti-
5 platelet agents or anything that you suggest that
6 that should be done?

7 DR. FRIEDMAN: In the study protocol,
8 decisions about anticoagulation during and after
9 the procedure were left to the investigator based
10 on the practice in that laboratory and, as you
11 might imagine, varied widely from one institution
12 to another.

13 For example, the one case of a pulmonary
14 embolism that I mentioned as an AMC was a woman who
15 actually had a fairly short procedure and did not
16 get heparin during her procedure, but she went home
17 and spent two days in bed and developed a deep
18 venous thrombosis that embolized, undoubtedly
19 related to the catheter insertion site, but in a
20 sedentary, bed-ridden person.

21 These other procedures that I showed you,
22 one of them I mentioned specifically was a very,

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1 very long procedure where no heparin had been given
2 for some eight hours.

3 So our own practice at our institution is
4 that patients get anti-coagulation during right-
5 and left-sided ablations, and they all get sent
6 home on aspirin, but I think that that is going to
7 vary from investigator to investigator.

8 DR. AZIZ: And you have seen the
9 histological slides of the difference in damage
10 done with cryoablation versus RF. In clinical
11 usage, did you see that translate into better or
12 less CPK leakage with cryoablation versus RF, or
13 you didn't think about that?

14 DR. LEHMANN: We did see some CPK rise
15 and we didn't compare it to any RF experience, but
16 there is some CPK rise with --

17 DR. AZIZ: In somebody who had a prior,
18 let's say, tricuspid valve repair or a tricuspid
19 valve replacement, could you still use this
20 technology, depending on, obviously, the type of --

21 DR. LEHMANN: These subjects were
22 excluded from this trial.

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1 DR. AZIZ: I guess, when it does come
2 out, could you see it being used in somebody who
3 has had prior tricuspid valve surgical procedures
4 done?

5 DR. FRIEDMAN: That's a problem even with
6 radiofrequency ablation. I don't know the answer
7 to that. As I think about the biophysics of this
8 technology, nothing occurs to me right away that
9 would make me think that it would be
10 contraindicated. If there is a sewing ring in the
11 tricuspid valve and you are trying to ablate
12 beneath that, I am not sure how effectively the
13 cryo energy would be transmitted. It might not be
14 that effective, but I don't think there would be
15 any particular safety concern.

16 DR. AZIZ: Let me just go over -- there
17 were one or two patients. On page 85, Subject
18 0917, could you just have a look at that? This was
19 actually a 76-year-old male who had the procedure
20 performed. Echo post-procedure showed that his EF
21 had increased and he had quite significant mitral
22 regurgitation, and that the left atrial size had

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1 actually also increased. The dimensions had
2 increased by 9 millimeters.

3 DR. LEHMANN: Which document?

4 DR. AZIZ: Page 85, Subject 0917.

5 CHAIRMAN LASKEY: In the general packet
6 itself, the patient descriptions.

7 DR. LEHMANN: I can't find the reference.

8 DR. AZIZ: The patient was 0917.

9 DR. FRIEDMAN: I'm reading here from the
10 report. I don't know this patient, but let me just
11 read the details of what we know.

12 DR. AZIZ: Okay.

13 DR. FRIEDMAN: An 89-year-old female had
14 a baseline echo which showed aortic stenosis, mild
15 tricuspid, and mitral regurgitation and inject --

16 DR. AZIZ: Actually, it is the next one.

17 DR. FRIEDMAN: Okay. Seventy-six-year-
18 old male, baseline echo showed thickened aortic
19 valve leaflets, mild MR, mild TR, and an injection
20 fracture of 63 percent, underwent successful AV
21 node ablation for rate control and permanent
22 pacemaker without adverse event. Post-procedure

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1 echo demonstrated dilated left atrium; the
2 pacemaker in the right ventricle.

3 I think it is difficult to compare those
4 two echoes for a couple of reasons. No. 1,
5 baseline, the patient had a very rapid ventricular
6 response and, presumably, a normal QRS because of
7 rapid conduction through the AV conduction system.

8 Post-ablation, clearly, had a much slower
9 heart rate, which by itself would increase cardiac
10 dimensions by any measure, and, in addition, had a
11 right ventricular pacemaker, because there was no
12 intrinsic AV conduction. Pacemaker implantation
13 alone in someone with AV block could lead to
14 ventricular dilation and even some degree of mitral
15 regurgitation.

16 My guess is that that is related to the
17 pacemaker implant and the presence of AV block
18 post-procedure as compared to pre-, not a function
19 specifically of cryoablation.

20 DR. AZIZ: Thanks.

21 DR. WALDO: I just had a few short
22 questions. The histology that you showed us, the

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1 iced lesions looked like ventricle. Am I correct?
2 Have you done that at atrium? Is there any more
3 of the same, because --

4 DR. DUBUC: For the purpose of
5 presentation, we showed mainly ventricle lesions.
6 Those lesions are all ventricular, the lesions you
7 saw this morning in the presentation, but we did
8 the same in the atrium. Naturally, all these
9 lesions were transmural.

10 DR. WALDO: That was my point; they are
11 transmural?

12 DR. DUBUC: Yes.

13 DR. WALDO: And no other problems? Okay.
14 How do you decide on 4 millimeters being necessary
15 duration of the application of freezing? For
16 minutes? I'm sorry.

17 DR. DUBUC: The four minutes, yes. Well,
18 we -- and this work is already published, but we
19 demonstrated with the ultrasound we can monitor the
20 ice ball growth within the tissue, and we can
21 monitor the size and it is growing for about three
22 minutes, and then you reach a plateau after three

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1 minutes.

2 So we decided that four minutes was okay.

3 This, as I said previously, the size of the ice
4 ball correlated very well with the coefficient, the
5 correlation coefficient of .95, when we compare
6 histology to the size we found by ultrasound.

7 DR. WALDO: Okay, two other very brief
8 questions: Peter, when you answered an earlier
9 question, you didn't address the issue of the
10 relatively surprising to me poor success rate for
11 his cryoablation.

12 DR. FRIEDMAN: Yes, that does stand out,
13 Dr. Waldo, though I am not sure why. The numbers
14 are small, and those confidence intervals are
15 fairly wide. I think it is hard to make any
16 definite conclusions.

17 DR. WALDO: Okay, now just a little
18 heresy from me: I don't know, I think this is a
19 philosophical point I would like to make in
20 considering this. I think the statistics here have
21 been very well presented. I am not a statistician.

22 We are going to hear a lot of more, and I think if

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1 you just took a statistic, there are some real
2 questions, and Mitch addressed some of them.

3 But, for me, that is why it is heresy,
4 because I hope -- I have been a scientist in my
5 time, and I think data are very important, but I
6 look at this, do look at this in part as a
7 clinician. I think one of the things I look upon
8 this as another option. There are not a lot of
9 secrets about AV nodal ablation. We know the
10 mechanism. We know how to go about it. There are
11 not a lot of secrets about hisp ablation, even
12 about getting accessory AV connections.

13 I just see that there are times when one
14 would want to have an alternative technique. And
15 what becomes important there is safety. And if I
16 understand the data, I think we have seen that it
17 is remarkably safe.

18 I think efficacy is always important, but
19 I haven't seen a terrible efficacy really. I have
20 seen quite a good efficacy, maybe not as good as
21 some of us would like to see, especially
22 statistically or if you look at ITT and a lot of

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1 other things. I understand that thing.

2 But I think that we shouldn't lose sight
3 of the fact that this provides the clinician with
4 an alternative therapy that may be very important
5 sometimes, and it is safe. I would just like to
6 leave it at that.

7 CHAIRMAN LASKEY: Not heretical at all,
8 Dr. Waldo.

9 Dr. Bailey?

10 DR. BAILEY: Well, I feel like everyone's
11 waiting for my remarks here.

12 (Laughter.)

13 As a statistician, I guess I belong to
14 the group that we don't allow second chances; we
15 don't allow rescue procedures for analysis. If you
16 miss it on your first shot, we don't bail you out,
17 although I think the sponsors were well motivated
18 to try because it certainly looks like a very
19 interesting device.

20 However, as a patient or as a consumer, I
21 am certainly interested in rescue procedures. I
22 guess most of my remarks tend to be on the

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1 philosophical.

2 I agree, if you accept the design of the
3 study, the OPC pretty much ropes you in and you
4 don't even need to think about it. I agree, I
5 thought both the sponsor and the FDA made
6 excellent, clear presentations of the data, with
7 obviously some differences in interpretation.

8 Of course, the subgroups, you know, we
9 don't let you look at subgroups, but, of course,
10 you have to look at subgroups. You have to; they
11 are interesting.

12 I guess, what does it mean to have an
13 overall OPC if, indeed, the efficacy is intimately
14 linked to the composition of the study population?

15 Now I don't know how much of the variability would
16 have been known ahead of time, but I understand in
17 the radiofrequency literature there's also
18 variability of efficacy of ablating these three
19 different entities.

20 So I guess from a philosophical point of
21 view, how do you come up with an overall OPC when
22 you have heterogeneity that may influence what the

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1 result is in any given population?

2 There was a little bit of vagueness in
3 the way the protocol was written, but I think, to
4 be hard-nosed, you have to accept that the overall
5 results are what count. However, this thing about
6 the rescue procedures, I mean, as a consumer, you
7 know, if I am being offered a procedure that has
8 much better safety in some sense, but I agree with
9 the comment that that's not necessarily been shown,
10 then I might be willing to have a lower efficacy,
11 initial efficacy rate, if I can also, then, get the
12 RF procedure as a backup.

13 I guess it has sort of surprised me that
14 we weren't looking at the overall success rate of
15 the strategy. Now the RF procedure, is it done in
16 the same catheterization or do you have to come
17 back later for it?

18 DR. FRIEDMAN: It was done at the time of
19 the same procedure.

20 DR. BAILEY: I presume it adds quite a
21 bit of time though to the overall procedure.

22 DR. FRIEDMAN: It depended on the

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1 patient. Some patients who failed cryo also failed
2 RF. They, obviously, tended to be longer
3 procedures. Some had a successful RF very quickly,
4 and it was a short procedure.

5 DR. BAILEY: I had thought that the
6 complications weren't related, but, as I
7 understand, they could be related to the length,
8 overall length, of the procedure. So it would be
9 important to know whether the complication rate
10 was, indeed, related to the length of the procedure
11 and, indeed, to the performance of the back-up
12 procedure or two procedures rather than just one.

13 But, subject to that, I would think that,
14 from the point of view of seeing where this fits in
15 or if it fits in, it is not really fair to compare
16 the initial efficacy to the efficacy of
17 radiofrequency ablation, unless you are proposing
18 this procedure as a substitute for it without the
19 opportunity to perform RF ablation.

20 But if you are proposing a strategy, then
21 now that may imply that we need a higher limit than
22 85 percent, but I think that, as a consumer, not a

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1 statistician but a consumer who happens to have a
2 Ph.D. in statistics, that is what I would be
3 looking at, is, you know, what's the efficacy,
4 given that I am going to be able to have a rescue
5 procedure, if necessary? Not rescue, a back-up
6 procedure.

7 That is why I would have been interested
8 in -- well, we were given that initial success
9 rate, and it was well over 90 percent. I would
10 have been interested in the success rate at three
11 months, and so forth.

12 In terms of the safety issue, it is also
13 amazing how different, again, the OPC is from the
14 way the data seem to be that are most relevant, in
15 that although -- again, that was probably from
16 naivety -- I didn't realize that it is possible
17 that it may be somewhat actually difficult to
18 determine which complications are related to the
19 procedure versus just the device.

20 But the one thing that stands out is
21 that, in order to achieve your OPC, you had to have
22 four events -- I'm sorry -- you needed to have a

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1 rate such that you were expecting four events, four
2 complications, five was the limit, and then you
3 actually observed seven.

4 I guess what is striking is how little
5 tolerance there is between those numbers. So I
6 think this gets at the point that this is a very
7 small study on which to base safety, given the
8 vagaries of what causes these complications, and
9 the extent to which they are dependent on the
10 devices is unknown. That is why either large
11 numbers or a comparison group or something.

12 In terms of the randomized trial, I
13 didn't follow the argument why the cryomapping
14 prevents you from doing a randomization. You can
15 still look at the efficacy and safety of the
16 strategy of cryoablation. You could even randomize
17 the use of cryomapping or not, if you wanted to,
18 versus radiofrequency without the alternative of --
19 of course, on the cryoablation side, you would have
20 the opportunity to use radiofrequency, if
21 necessary. Then you would be comparing efficacy
22 immediately at three months and, of course,

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1 complications.

2 But I didn't follow the -- I heard you
3 say that the cryomapping made it impossible, but I
4 didn't follow the logic of that.

5 And I agree with all the comments that
6 have been said, that the cryomapping really, in
7 order to understand it, you really have to compare
8 the groups that get cryomapping versus groups that
9 don't, if you are trying to look at the efficacy of
10 it from a strategy point of view, and probably even
11 in this study, even doing that analysis is very
12 fraught with the usual observational biases.

13 So those are my questions.

14 CHAIRMAN LASKEY: If they were questions,
15 do you want comments or questions or more thoughts?

16 DR. BAILEY: They are comments that are
17 questions.

18 CHAIRMAN LASKEY: Oh, I see.

19 DR. BAILEY: We should give the sponsors
20 an opportunity to respond then, starting with --

21 CHAIRMAN LASKEY: Why couldn't you do a
22 trial?

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1 DR. LEHMANN: Well, it could be possible
2 to do that. I rose to just respond to a few of the
3 numbers, if I could address those.

4 Just to the overall strategy of cryo and
5 then RF, if cryo failed, resulted in a rate of 97
6 percent for every study subject, and in each
7 instance RF was undertaken in the same procedure.

8 Any measure of adverse events was not
9 correlated with either the number of
10 cryoapplications, the number of cryomaps, the
11 number of cryoablations, nor procedure duration.

12 In descending order of certainty, we have
13 151 IDE subjects in this trial with no AV block.
14 In a prior IDE trial of a 9 French device,
15 otherwise essentially identical to this one in its
16 mode of action, and two trials done in Canada under
17 essentially the identical protocol, using the same
18 monitoring group and submitted to the TPT, and
19 filed with the FDA in the PMA.

20 So we have almost 300 very-carefully-
21 observed patients followed for many months, and the
22 number AV block in that population was zero. Zero

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1 out of 300 is, back of the envelope, is about 1
2 percent upper limit.

3 Now with lesser degree of certainty,
4 there's another 300 AV node reentrant tachycardia,
5 AV reentrant tachycardia subjects in a European
6 registry, where they do get more attention than
7 normal. It is not carefully monitored in a classic
8 sense, and that is about 600 no AV block. Then, of
9 course, there is the commercial experience, which,
10 as we all know, has its issues on reporting. So
11 those are some numbers in relationship to some of
12 the remarks you make.

13 CHAIRMAN LASKEY: Thank you. Dr. White?

14 DR. WHITE: You're not going to take a
15 turn?

16 CHAIRMAN LASKEY: I'm not allowed to
17 speak.

18 (Laughter.)

19 DR. WHITE: I would like to echo, without
20 repeating the words, what Dr. Krucoff said. I
21 think we hold very similar opinions about
22 understanding the magic or the theoretic nice

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1 pieces of this procedure, but wondering why the
2 device didn't actually perform.

3 Could I just ask a specific question
4 about the IFU, about the instructions for use?
5 Could you clarify for me whether it is possible for
6 this device to be connected to an RF generator?

7 DR. DESMARAIS: The answer is no.

8 DR. WHITE: Then why did you take the
9 time to write it in here?

10 DR. DESMARAIS: I think, you know, you
11 want to address from when we do a risk hazard
12 analysis, which is a technique used in the industry
13 when you look at all the potential hazards. By
14 design we've mitigated that, but it's always there
15 and a good practice to put all kinds of warnings
16 and precautions to address the risk analysis that
17 you conduct.

18 DR. WHITE: Is the criteria for LV
19 ejection fraction being greater than 35 percent, I
20 think, in your protocol, is that necessary for
21 clinical practice?

22 DR. DESMARAIS: I will ask Dr. Friedman.

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1 DR. FRIEDMAN: As a practicing
2 electrophysiologist, I wouldn't see that as an
3 exclusion. I think for the purposes of the trial,
4 the intent was to identify healthy patients who
5 were less likely to have co-morbid conditions.

6 DR. WHITE: How do you feel about IVC
7 filters and working through them?

8 DR. DESMARAIS: Dr. Friedman?

9 DR. WHITE: Is that a problem or no
10 problem for this device?

11 DR. FRIEDMAN: With other catheters,
12 radiofrequency catheters, we traverse IVC filters
13 without difficulty. The average dimension in this
14 catheter is really 7 French, the same size. I
15 don't foresee a problem.

16 DR. WHITE: And for aortic valves
17 retrograde, do you mean mechanical valves or do you
18 mean a pig valve as well?

19 DR. FRIEDMAN: No, we don't think we
20 would advocate traversing retrograde a mechanical
21 aortic valve. Those patients would have to be done
22 transeptally. But for a porcine prosthetic valve

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1 or a native valve, this catheter could be used
2 retrograde.

3 DR. WHITE: Because the contraindication
4 simply says any aortic valve replacement, you may
5 want to be more specific about that.

6 In the demographics, in slide No. 46 that
7 you showed, it struck me that you had excess of
8 women in the trial. Is it that women have more of
9 these arrhythmias than men?

10 DR. FRIEDMAN: That's a very good
11 question actually, but that mirrors clinical
12 practice. Women present with AVNRT and AVRT more
13 commonly than men. I don't know whether it is a
14 genetic difference or there is a difference in
15 diagnosis. Maybe men don't complain of palpitation
16 or are less troubled by the palpitation. There
17 could be a host of explanations, but --

18 DR. WHITE: But you would agree that
19 percentage would be representative of the clinical
20 practice.

21 DR. FRIEDMAN: I think that is
22 representative of clinical practice.

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1 DR. WHITE: And the minorities were not
2 represented in an adequate fashion here. I mean,
3 is there a reason why American Indians, Blacks,
4 Hispanics were not represented in percentages that
5 are reflected in our population?

6 DR. FRIEDMAN: I don't have an
7 explanation for that, but I would point out that
8 overall it was a fairly small trial, and you might
9 not expect to see it reflected in those small
10 numbers.

11 DR. WHITE: We have heard today, I think,
12 a lot of reasons to think that, because the device
13 attaches and because the device has a smaller
14 footprint, that there may be some theoretical
15 safety benefits, but I am not sure I am convinced
16 that the device has been proven to be safer because
17 it has not been directly compared.

18 As I think Dr. Page mentioned, I think
19 some of the complications which are not catheter-
20 related certainly appear to be procedure-related.
21 And I think that if, as you are comparing the
22 patient who is going to have one or the other of

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1 these procedures, those complications need to be
2 taken into account.

3 The other issue is that I am not an
4 electrophysiologist, so I am hearing so much about
5 AV block and how terrible this is with RF, but in
6 the paper that you provided us in the Panel pack,
7 the Calkins paper that looked at the thousand
8 patients with radiofrequency ablation, the
9 incidence of heart block was only 1 percent in that
10 population.

11 So I guess I am not being struck with --
12 I am not convinced that in 151 patients that you
13 have actually convinced me that AV block will
14 happen in less than 1 percent of your patients.

15 DR. FRIEDMAN: I think there are a couple
16 of points to mention there. First of all, if one
17 actually does a careful literature search, the
18 incidence ranges from 1 percent even to as high as
19 14 percent in some series actually reported from
20 fairly busy laboratories with experienced
21 investigators. So 1 percent is probably the lower
22 bound, if you will. It is the best that you would

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1 expect.

2 The other point I would mention is that
3 it does not include patients who were referred for
4 AVNRT ablation, who may get one or two ablation
5 attempts, and then because of proximity to the
6 compact AV node, the procedure is stopped. I have
7 seen patients, like every one of us who does these
8 procedures have patients like that. They don't
9 develop AV block, but they also don't have a
10 successful procedure, and they're not reflected in
11 those data.

12 DR. WHITE: The other thing I would like
13 to ask you about is in slide 64 and 66, which were
14 the Kaplan-Meier curves for long-term success. It
15 appears that the patients drop out of your Kaplan-
16 Meier curve, and it is not clear to me why you
17 haven't retained the patients in the Kaplan-Meier
18 curve.

19 You've got at six months, for the long-
20 term success of all subjects, 77 patients being
21 measured in the Kaplan-Meier curve, whereas your
22 flow sheet at six months you've got, I believe, 119

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1 patients who were available. It is slide 64.

2 DR. FRIEDMAN: Well, I will see if we can
3 find the slide. Sixty-four.

4 DR. WHITE: Actually, 64 and 66 both show
5 it.

6 DR. FRIEDMAN: Right. So just bring that
7 one up.

8 DR. WHITE: You see at six months you
9 have 77 patients when in your flow sheet here you
10 have accounted for 119.

11 DR. LEHMANN: First of all, here's the
12 three-month point, starting here, and the effect is
13 stable. This six-month telephone followup, here is
14 a dispersion, because there was a window of
15 following the subjects. The software, of course,
16 takes the exact number as of the exact point. When
17 you do a live table, you take the inferred
18 endpoints. So you've got all of these subjects
19 with the nominal six months, but in this subject
20 attrition line it stops dead right there, losing --
21 so that is why you do both of the assessments.

22 But really with this curve you can see

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1 that there has been absolutely no change, and all
2 of the six-month follows are represented, although
3 they don't come to that number.

4 Have I addressed the question? No?

5 DR. WHITE: Am I dumb as a rock or what?

6 (Laughter.)

7 I mean, how many patients got measured at
8 six months?

9 DR. LEHMANN: A hundred and twenty
10 something.

11 DR. WHITE: Then how come it says 77 at
12 the bottom?

13 DR. LEHMANN: Because if the phone call
14 occurred at six months and one day, then it doesn't
15 show up in that six-month number in the Kaplan-
16 Meier; in the survival analysis it measures every
17 day as a distinct event. In the life table
18 analysis it measures the increment, the normal
19 increment.

20 DR. WHITE: All right.

21 DR. BAILEY: So, technically, it shows
22 the status of that patient.

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1 DR. WHITE: That is not the way I do my
2 Kaplan-Meier curves. I don't understand them, I
3 guess. Are you telling me that's right?

4 CHAIRMAN LASKEY: Dr. Bailey?

5 DR. BAILEY: No, in a way, I think you
6 might want to consider interval censoring there.
7 If you assume that you don't get recurrence that
8 goes away, if you just assume that the later time
9 point is representative of the earlier time point,
10 you could sort of back it --

11 DR. WHITE: I guess I would like to be
12 assured that all of the patients have been followed
13 and that their events are being accounted for. So
14 when I see 40 percent of the patients not being
15 accounted for, I am concerned that you are not
16 seeing them.

17 DR. LEHMANN: No, I forget the exact
18 number, but over 95 percent of the subjects with
19 acute procedural success were followed.

20 DR. WHITE: Right. Well, no, they are
21 here in your flow sheet.

22 DR. LEHMANN: Yes.

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1 DR. WHITE: And they are identified here.
2 So I am just wondering why they are not showing
3 up.

4 DR. LEHMANN: Well, go back to the live
5 table. Go up to the live table. I think if you
6 look at the life table, here you see we start with
7 136, and these are the subjects that are lost. So
8 by month six we have lost three out of 136 from
9 analysis. There's 122 who remain successful --

10 DR. WHITE: So does it strike you as
11 strange that your graph doesn't show 122 at six
12 months?

13 DR. LEHMANN: It doesn't strike me as
14 strange at all. That is just the way it works in
15 the two different analyses.

16 DR. WHITE: Okay. What do I know? I'm
17 dumb.

18 CHAIRMAN LASKEY: No, Chris, you're just
19 rebelling against how computers constrain our
20 thinking.

21 (Laughter.)

22 That's the output of the tests. Thanks.

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1 DR. WHITE: Yes.

2 CHAIRMAN LASKEY: George?

3 DR. VETROVEC: Very briefly, was there
4 any evidence that procedure time got shorter by the
5 number of procedures done? In other words, in the
6 second half of the study, is the average procedure
7 length less?

8 DR. LEHMANN: We haven't assessed that.

9 DR. VETROVEC: And then in terms of
10 training, the observation was made that, "I learned
11 to do a hundred of them and then I could teach the
12 other fellows in four or five procedures." What is
13 it that you have to teach them that is unique about
14 this, because this is going to be important, if you
15 come down to, what do you specify as a training
16 issue? What is it that's different?

17 Even if you couldn't document a learning
18 curve, there was something, it sounds like, you had
19 to train the other personnel in doing. What was
20 it?

21 DR. DESMARAIS: I will let Dr. Dubuc
22 answer that, specifically what has to be done for

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1 training of the person.

2 DR. DUBUC: I think you can call it
3 training or teaching. People doing this procedure
4 with this new technology, they have to acknowledge
5 that it is different from RF, and that is the only
6 point here.

7 The thing is, like I said previously,
8 when you do AV nodal reentry ablation and you are
9 going into a slow pathway area, you expect the
10 technology to produce, when you are successful, to
11 do rapid junctional rhythm. This you don't have
12 with cryo. So this is different. So the operator
13 has to know more than that; their catheter will
14 stick to the wall, adheres to the endocardial
15 surface. So during that time you can do pacing or
16 program stimulation, which you cannot do with
17 radiofrequency. So this is different.

18 And, third, you have the attachments. So
19 you cannot move the catheter during the position,
20 and the catheter is very, very stable. It will
21 stay there, not like RF, when you have this
22 slippage from the area.

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1 So those are the three main reasons, and
2 the people doing the procedures, they have to
3 acknowledge that it is different from RF from the
4 beginning. So it takes time because you change the
5 way you ablate and you make your procedure.

6 DR. VETROVEC: I don't disagree with you,
7 but it just is an issue in terms of, how has this
8 been disseminated into the practicing population?

9 DR. DESMARAIS: In that respect, I will
10 put up just a few slides. I don't even need that.

11 But we believe that through instruction
12 for use, operator manual, and we believe that there
13 is a need for didactic training, as Dr. Dubuc just
14 alluded.

15 We will utilize skilled physicians
16 experienced with Freezor to train and initiate at
17 new sites. We have learned that from our
18 experience in Europe, and we will provide ongoing
19 support with clinical support specialists, which we
20 are doing in Europe as well. We are convinced that
21 this is a need.

22 DR. VETROVEC: Are you talking about

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1 physicians proctoring this or are you talking
2 about --

3 DR. DESMARAIS: Yes, yes.

4 DR. VETROVEC: And how many procedures do
5 you anticipate as necessary?

6 DR. DESMARAIS: That is very difficult.
7 It depends on the site in terms of the volume, the
8 number of physicians. So it is a very difficult to
9 estimate at this point in time.

10 DR. VETROVEC: I don't have anything
11 else.

12 DR. DULLUM: You said that in the ice
13 ball you saw after three minutes stayed stable, so
14 that is why you chose four minutes. In surgery
15 there is usually a dry field in this aspect that a
16 little bit was talked about, that there is going to
17 be warm blood going by. So that was monitored, and
18 you still know that at three minutes with warm
19 blood that it stays the same?

20 DR. DUBUC: Well, we know in a beating
21 heart, which could be different from surgery
22 sometimes, in a beating heart we know that it is

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1 very stable after two minutes. Even if you keep
2 the catheter there for six, seven, or eight
3 minutes, there will be no change. But if you go in
4 the preparation, like a fine muscle preparation,
5 you will see that the ice ball will still grow
6 after three minutes. The longer you will keep the
7 catheter there, the bigger will get the lesion,
8 which does not happen, actually, in a beating
9 heart.

10 DR. DULLUM: So you basically have a cool
11 sink.

12 So did I understand that it took an
13 average of seven-and-a-half cryoablation procedure
14 times with your catheter? Is that the same with
15 RF?

16
17 DR. DUBUC: I would say it is about the
18 same, yes. It is the same range.

19 DR. DULLUM: So are you going to
20 recommend that in clinical practice then, when do
21 you know when to stop? Do you say, okay, after
22 seven-and-a-half or do you just keep going until

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1 you get tired or the patient gets tired?

2 DR. DUBUC: I think it is like our effort
3 goes with the clinical judgment. I mean, you are
4 doing the procedure and sometimes you know that on
5 the average it will take, four, five, six lesions,
6 but sometimes it takes more. I mean, even with RF,
7 I have seen cases you do 30, 40 applications. So
8 that can happen also with cryo, I imagine. I mean,
9 that goes with the clinical judgment.

10 DR. DULLUM: And my last question: Are
11 you going to recommend that if you go with cryo and
12 you don't ablate, then you switch to RF, or vice
13 versa? I think, as someone said, there was an RF
14 that was not successful and then you used cryo.

15 DR. DUBUC: I think we had no safety
16 problems with that in this clinical trial, doing RF
17 after cryo.

18 DR. DULLUM: And vice versa?

19 DR. DUBUC: Well, we did not -- just to
20 correct, there were no subjects in the study who
21 got RF first. Everyone, out of 166, 164 had cryo
22 first. Some failed; some succeeded, and some of

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1 the failures were RF. Two of the subjects did not
2 have a cryoapplication; they had RF alone without
3 any cryo following.

4 We did look at the complications, any
5 measure of adverse events in the group of cryo and
6 followed with RF, and there was no difference
7 between those two groups.

8 Furthermore, in terms of the number of
9 cryoapplications, either mapping or ablation, they
10 had no relationship with measures of adverse events
11 as well. So that bears a little bit on some of
12 your questions.

13 CHAIRMAN LASKEY: Thank you. Mark?

14 DR. HAIGNEY: Okay, I will be brief.

15 I am still confused about your
16 indication. You are asking for an indication for
17 parahisian pathways? You're not? Just AV node?

18 DR. DESMARAIS: As presented today, the
19 indications for it --

20 DR. HAIGNEY: AV node --

21 DR. DESMARAIS: Correct, AVRT indication.

22 DR. HAIGNEY: Okay, so not mid-septal

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1 pathways?

2 DR. DESMARAIS: Correct.

3 DR. HAIGNEY: Okay. On page 62 of the
4 final report, there is something that really
5 confused me. It said, under adverse events, it
6 says, "Thirty-one of 42 Canadian subjects and eight
7 of 124 United States subjects were reported with
8 these AEs." Is that what I think it is saying?

9 DR. LEHMANN: We believe that the three
10 Canadian sites had a very different view of what
11 constituted an adverse event. No, we don't feel
12 there was any -- other than sequelae that would
13 indicate they had had a much different means of
14 accessing the circulation, and I know it was quite
15 consistent across the Canadian sites. So we think
16 it is a reporting anomaly.

17 DR. HAIGNEY: Well, it is a reporting
18 anomaly with somebody. Whether it is with the
19 Canadians or the Americans, they're not going to
20 say.

21 Finally, I have one more weird comment to
22 make. Have you considered as a possible

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1 contraindication patients with known
2 cryoglobulinemia anemia? It just occurred to me
3 over breakfast, and it seems to me that that would
4 probably be -- if you had a patient who had known
5 cryoglobulinemia, that it is probably not the
6 technique you would want to use. So I would
7 suggest putting that in as a contraindication.

8 On the whole, I think the device
9 represents an important contribution potentially to
10 the progress of EP. It's a niche device, and it
11 doesn't replace RF ablation. So I am not as
12 bothered by the fact that you didn't make your
13 OPCs. I agree that there are no clear device-
14 associated complications. So given the fact that
15 this is not replacing RF ablation, I think I'm
16 inclined to be a little more lenient than perhaps
17 Dr. Krucoff. I usually am.

18 (Laughter.)

19 CHAIRMAN LASKEY: You're not supposed to
20 spill the beans until after the break.

21 (Laughter.)

22 We're about to take a short break,

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1 following which we will reconvene and do the
2 voting. However, I would like to raise one point
3 here in my prerogative.

4 I think in the future -- and I think it
5 is unfortunate in this trial, but in the future
6 when we have these sorts of interventional trials
7 requiring prolonged fluoroscopy, we should have
8 some measure of dose. I think all of the agencies
9 around, there's none that I can think of that
10 should be more aware of patient dose. Procedures
11 that have up to whatever the estimate is, many,
12 many minutes of fluoro time, that is not a
13 surrogate for dose. I think we should require that
14 of the studies down the road, because we are going
15 to see more and more prolonged laboratory time. So
16 let's build that into the protocol. It might even
17 be a measure of safety as well.

18 Thank you. So let's take a 10-minute
19 break. Let's reconvene. Then we will go over the
20 questions to the Panel and the Panel's preferences.

21 Thank you again, Panelists, for sticking
22 to the schedule.

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1 (Whereupon, the foregoing matter went off
2 the record at 3:48 p.m. and went back on the record
3 at 4:05 p.m.)

4 CHAIRMAN LASKEY: Good, thank you.

5 At this point I would like to proceed
6 with reviewing the questions put to the Panel, if
7 we can have them up.

8 As we go through these, I will do my best
9 to summarize points of agreement and disagreement
10 amongst the Panel members.

11 "The results of this clinical trial were
12 compared to objective performance criteria, OPCs,
13 established for the study for both safety and
14 effectiveness. The OPCs were determined from the
15 radiofrequency ablation medical literature."

16 The first question to the Panel with
17 respect to safety: "The safety endpoint was the
18 occurrence of major complications, as defined in
19 the study protocol. The FDA interprets the
20 definition of major complications to include all
21 adverse events requiring treatment which occurred
22 within seven days of the procedure. The upper 95

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1 percent confidence bound for the major complication
2 rate was 8.5 percent.

3 "This exceeded the safety OPC, which
4 specified an upper 95 percent confidence bound of
5 less than 7 percent. Please comment on the
6 following:

7 "a. Please discuss whether the results
8 of the clinical study provide a reasonable
9 assurance of device safety for the intended patient
10 population."

11 To paraphrase Dr. Bailey, I think that
12 you certainly were roped into these constraints by
13 the OPCs in that there is not a lot of wiggle room
14 in a small study. One patient either way could
15 have made the difference, and, unfortunately, it
16 didn't work in your favor.

17 "b. Please discuss the applicability of
18 a safety OPC for cryoablation which was based on
19 reported clinical experience with radiofrequency
20 ablation."

21 I think that the Panel alluded to this in
22 some of their comments. That is basically all we

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1 have to fall back on as a benchmark. It may or may
2 not be appropriate, but that serves as a benchmark
3 and it is a not unreasonable benchmark.

4 Question 2, with respect to effectiveness
5 of ablation: "The device did not meet the
6 effectiveness OPC for the overall study population
7 or for any patient subgroup. The lower 95 percent
8 confidence bound for acute success for the entire
9 study population was 76 percent. The OPC for acute
10 success specified a lower 95 percent confidence
11 bound greater than 85 percent.

12 "a. Please discuss whether the results
13 of the clinical study provide a reasonable
14 assurance of effectiveness in (a) the overall
15 patient population or (b) in any individual patient
16 subgroup."

17 I think that both statisticians have
18 spoken cogently to this point. Again, you are
19 constrained by your boundaries. One patient either
20 way could have made the difference. Again, it's an
21 awfully small study to allow for that kind of non-
22 leeway.

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1 With respect to the individual patient
2 subgroups, I think that the Panel has done a good
3 job, as well as the FDA statistician, at pointing
4 out the foibles of doing post-hoc subgroup
5 analysis. It's really treacherous, and you really
6 live or die by the limitations of this technique.

7 "b. If the clinical trial does not
8 provide enough evidence of effectiveness, please
9 discuss what would be needed."

10 I think we need to hear really how people
11 are voting before we can give you an answer to
12 that.

13 DR. ZUCKERMAN: Could we, for Question 2,
14 which really gets to the heart of the matter, could
15 we hear from several other Panel members? Is there
16 a consensus on this summary as you presented it?

17 CHAIRMAN LASKEY: Let's go back to a and
18 b with -- both parts, a and b?

19 DR. ZUCKERMAN: Yes.

20 CHAIRMAN LASKEY: Okay, well, feel free
21 to chime in, Panelists, if I didn't quote you
22 correctly. Cindy?

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1 DR. TRACY: I would like to jump in,
2 because this is sort of the crux of the struggle
3 with this thing: What would it take -- can you
4 construct a study that would look at AVNRT or do
5 the data that we have -- how close are we to
6 defining safety and effectiveness in AVNRT?

7 I have whole issues with the safety,
8 given the way there is such a variance in reporting
9 between the Canadian side, just the variance in
10 reporting in this study.

11 But, anyway, in terms of effectiveness,
12 what has to be done? I mean, are we close?

13 CHAIRMAN LASKEY: So this is "b"? This
14 is really 2b?

15 DR. TRACY: "Or not to be."

16 (Laughter.)

17 CHAIRMAN LASKEY: Please discuss what
18 would be needed, because we have before us a
19 negative trial.

20 DR. TRACY: Dr. Bailey was struggling
21 with this. Maybe he can struggle some more for me.

22 DR. BAILEY: Well, yes, as a true/false

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1 question, the answer is false, but if it's an open-
2 ended question, I mean the data do seem to support
3 efficacy, but only if you look at the strategy of
4 cryoablation with the possibility of RF as a
5 backup. That's to say nothing of the safety, but
6 in terms of efficacy, you get 161 successes out of
7 a 166, which seems pretty reasonable.

8 DR. WHITE: Well, but the problem,
9 though, Ken, is that's not what we were being asked
10 to judge because you have no comparer.

11 DR. BAILEY: Right, but that's why I say,
12 if it is a true/false question, the answer is
13 false.

14 DR. WHITE: The question is, what Cynthia
15 is asking is, what would it take to make us say
16 that they have satisfied efficacy? Is it because
17 there were so few patients that the margins were so
18 narrow and the lower bounds were not met? If there
19 were another hundred patients enrolled, would the
20 bounds narrow?

21 DR. BAILEY: No, no, I think the OPC as
22 stated doomed them to the result because that was

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1 not a quirk of sample size. You can't get that
2 high an efficacy with this technique. But in terms
3 of the overall clinical application, it's pretty
4 high.

5 DR. KRUCOFF: I think that is a really
6 key point. I think we have actually heard it
7 stated several times, but it seems like when this
8 trial was first designed, that the catheter
9 behavior and performance was expected to be the
10 same as an RF catheter. Yet, it sounds more like
11 the actual experience that's evolved out of the
12 trial is that the catheter performance may be a
13 little inferior to an RF catheter.

14 When it is, you can bail out with an RF
15 catheter, but the other safety elements and the
16 potential to pre-map and to protect more vulnerable
17 areas, that's what gets actually into an area where
18 you're suggesting a trial design that would look at
19 a potentially slightly inferior efficacy from the
20 device, but at least an equivalent behavior in an
21 intention to treat, which includes the RF backup,
22 where overall the safety would be better. I don't

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1 see that it would be very complicated to design
2 that kind of a trial.

3 The trouble is that that's not how that
4 OPC was designed. That's, unfortunately, I guess
5 the question that we're going to be asked today in
6 2a, and then in the 2, bottom "b," I think it would
7 be pretty straightforward, based on this
8 experience, to see a design where you would do an
9 intention-to-treat analysis for efficacy and really
10 concentrate on safety, and whether these are
11 catheter or dwell time or radiation time safety
12 issues or not.

13 DR. WHITE: But without a comparison
14 group, I have a hard time understanding the
15 safety --

16 DR. KRUCOFF: No, not in a randomized
17 trial.

18 DR. WHITE: Because I don't see the
19 safety in 151 patients.

20 DR. GILLIAM: I don't think you can see
21 the safety in 150 patients, but I also don't think
22 it would change if they had 650 patients or a

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1 thousand patients, because the comparison that we
2 really are talking about is looking at, for
3 instance, use of radiofrequency in an AV nodal
4 reentry group and skilled operators today. I mean
5 your heart block risk, if you will, is something
6 less than 1 percent. I mean it is.

7 If we start looking at the comp. we're
8 seeing, no one is saying that there is something
9 intrinsically not safe with this catheter. I mean
10 we are getting complications because they only had
11 150 patients, and if we probably take 150 patients
12 from any of the procedures, we may have like
13 complications. These are procedure-related but not
14 catheter-related. It may very well have been RF
15 cases we were looking at to get the same type of
16 complications.

17 I think the reality is that this is a
18 procedure that potentially may be less likelihood
19 of creating complete heart block in an AV node
20 reentry population, and, ultimately, the overall
21 efficacy of this one alone may not be as good, but
22 taken with the option of using RF, it may provide

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1 an additional tool.

2 That's saying a clinical trial -- I'm not
3 sure what we're going to compare it with. I think
4 it would be very difficult to provide such a study.
5 I don't see how it could be done easily.

6 DR. WHITE: Well, I don't understand why
7 you say that because there is a standard clinical
8 procedure now to treat these patients. So you take
9 the experimental procedure, you compare it to the
10 standard clinical procedure, you get a comparison.

11 DR. GILLIAM: If we were going to replace
12 the procedure, I would agree with you. But I don't
13 think that anyone would suggest that cryoablation
14 is intent to replace radiofrequency ablation. I
15 think that that's where I think it would be
16 difficult because it may very well be that you can
17 go in and just look at RF, you know, first or
18 second.

19 You may go in with cryo first, and if you
20 find an easy point, you map and you get it right
21 away, then fine, you may just go with it. If you
22 need a bigger lesion, if you will, or you just use

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1 RF, I just don't think that you are going to be
2 able to compare one to the other because they're
3 not going to be used the same.

4 I don't think you're going to replace RF
5 with cryo. It's a smaller, more discrete lesion.
6 That means that you're likely to have less
7 efficacy, I mean all things being even. But, on
8 the other hand, potentially that one or two people
9 that surprise the heck out of you, that when you
10 step on the pedal, they all of a sudden develop
11 heart block, and you jump off the pedal real quick,
12 you know, if you're lucky, as we most of the time,
13 frankly, are -- I mean that we don't get permanent
14 heart block.

15 But every now and then you look at it
16 happen, and you say, "Oh, my God, I wish it was
17 reversible." Maybe this is reversible. You know,
18 I don't think they've proved that, but I don't
19 think they've proved that it is any more dangerous.

20 CHAIRMAN LASKEY: But, again, we're not
21 here to talk about replacement. We have heard the
22 word "supplement" and "adjunct to." Whether that

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1 lends itself to non-inferiority versus class RCT
2 is, I guess, what Dr. Zuckerman needs to know here
3 in Question 2b.

4 DR. VETROVEC: But let me ask you, if the
5 goal, based on what you say, is to look at this as
6 something to prevent it, then it will become your
7 first choice. Otherwise, you're going to have
8 heart block the whole time.

9 So now you're suddenly substituting this
10 as a first choice, and RF is becoming second
11 choice, and do you know that that's a fair trade?
12 That's what you're suggesting, if you're going to
13 use a hundred times to prevent one or two heart
14 blocks.

15 DR. TRACY: Do we have data that -- is
16 there a way to look at this data for non-
17 inferiority?

18 CHAIRMAN LASKEY: Which data?

19 DR. TRACY: The effectiveness data.

20 CHAIRMAN LASKEY: The way I look at this
21 trial, this was a non-inferiority trial. That's
22 the study design to me.

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1 DR. KRUCOFF: Well, it didn't make its
2 boundaries on --

3 CHAIRMAN LASKEY: No, exactly, but --

4 DR. KRUCOFF: It is a negative non-
5 inferiority on a safety compared to an historical.
6 So a classic non-inferiority, this is not a
7 randomized dataset.

8 DR. TRACY: Effectiveness, not
9 inferiority.

10 DR. GILLIAM: But if we're looking at
11 heart block, let's just look at just heart block.
12 Then, in effect, this study doesn't --

13 CHAIRMAN LASKEY: We need numbers. We
14 don't have numbers here. There's no precision of
15 the estimate, and maybe I guess, Dr. Page, you said
16 something during the break about adding some
17 precision to the number. We know it's not zero.
18 Nothing is zero. But could it conceivably be on
19 the same order of magnitude as RF and is it,
20 therefore, as safe from that standpoint?

21 DR. PAGE: Yes, I would just like to
22 comment that, first of all, I think in all

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1 fairness, as Rosie Gilliam said, in good hands the
2 risk of heart block, and I would say there are a
3 number of good EPs in this room, and please speak
4 up if your heart block is over 1 percent, but most
5 of us are less than that, I believe.

6 That being said, I believe that the cryo
7 is probably as low or lower in terms of heart
8 block. I see this as another arrow in the quiver,
9 if you will, as being supplemental.

10 In addition, one thing that has to be
11 mentioned is we've focused on the specific
12 indication for AV nodal reentry, but, in addition,
13 to have this other tool in terms of cryomapping is
14 going to be valuable in a number of circumstances.

15 If I understand the indication as it is
16 written, we are not limited to the device being
17 used in the AV node reentry for the cryomapping, is
18 that correct?

19 DR. ZUCKERMAN: No. Dr. Page, your
20 comments are well-founded, but I think you're
21 getting into Question 3. Perhaps if we could go
22 back to Question 2 and take it in an ordered

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1 fashion, it will help us decide what the trial
2 showed and what can be done with this device.

3 I would like, Dr. Laskey, first of all,
4 to know, for Question 2a, the overall patient
5 population. Is there a Panel consensus as to
6 whether there's reasonable assurance of
7 effectiveness?

8 DR. PAGE: Just so I'm clear, is
9 effectiveness only in successful ablation, having
10 nothing to do with the second indication,
11 effectiveness as a mapping tool?

12 DR. ZUCKERMAN: That's correct. Right.
13 For acute procedure success; we would all agree
14 that they didn't meet it for the overall patient
15 population.

16 CHAIRMAN LASKEY: I think we all agree
17 with that.

18 DR. ZUCKERMAN: Good. Okay.

19 CHAIRMAN LASKEY: It would be hard to say
20 otherwise, yes.

21 DR. ZUCKERMAN: Now Question 2b asks -- a
22 subgroup analysis was done. You've heard multiple

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1 comments as to whether or not the subgroup analysis
2 is valid for AVNRT. It's important for the agency
3 to get a consensus, if there is one, or just a
4 response from the Panel as to the validity of the
5 result, of the effectiveness results for the AVNRT
6 population.

7 DR. BAILEY: I thought your statistician
8 made the excellent point that the OPC was for the
9 overall mixed population, and we don't know what
10 would have been specified, had it been this one
11 subgroup that was recruited.

12 CHAIRMAN LASKEY: As a non-expert in this
13 area, though, it did look as though the AVNRT group
14 is the group most likely to do well of the three
15 groups anyway. So, therefore, the bar would be
16 even higher. So that we would expect this
17 procedure to do better in that group which tends to
18 do better.

19 So I think that you need to sit down with
20 the applicant and go over the applicability of
21 OPCs. There must be data in the literature on the
22 success rate of AVNRT only rather than all-comers,

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1 and that may be helpful, although retrospective
2 still.

3 DR. ZUCKERMAN: Okay, that's one way to
4 look at it, but the electrophysiologists here in
5 the Panel have offered the suggestion that these
6 two devices, cryoablation plus RF ablation, could
7 be used in a treatment strategy approach because of
8 a comfort level associated with cryoablation.

9 So another approach which is similar, Dr.
10 Laskey, to what we do with guide wires to cross-
11 total occlusions is, if we do believe the first
12 device has some intrinsic merit, might be safer, we
13 may accept a lower success rate with a first
14 device, and then if it doesn't work, you go to your
15 next device.

16 So I'm not sure I have heard from the
17 electrophysiologists that for the subpopulation
18 called AVNRT we necessarily need a higher bar,
19 given the risk/benefit profile. Can the
20 electrophysiologists comment?

21 CHAIRMAN LASKEY: You don't need a higher
22 bar.

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1 DR. TRACY: I'll speak now as an
2 electrophysiologist, and I would be happy with this
3 level of success, knowing that there are certain
4 patients with very narrow -- there are some people
5 with very narrow anatomic windows between the slow
6 and fast pathway, that this would be a very nice
7 thing, very stable catheters used.

8 There would be certain circumstances
9 where I would use this as a first line, and I would
10 be very comfortable knowing that I had a backup of
11 RF, and in my lab the chance of heart block is less
12 than one-half of 1 percent. So it's not high, but
13 in those patients that have the funky windows,
14 those are the ones that, if they are going to get
15 into trouble, those would be the ones that would
16 have the problems with heart block. So there's a
17 group of people where this device would have a
18 distinct advantage to use.

19 So if it is a 91 percent success rate
20 with this device, that's not that far off from
21 reported data on other AVNRT studies, although our
22 success rate is 98 percent. If I took this

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1 catheter and put it in a heart, what my success
2 rate would be -- presumably, it would be better
3 after the tenth case than on the first two or
4 three.

5 To me, it's in shooting range of what
6 would be acceptable for any device.

7 DR. WHITE: But the problem I have is
8 that there is one option to approve this device for
9 -- what is it called when there is a very narrow
10 indication for this, like we use for the atrial
11 septal closure devices?

12 MR. MORTON: Those are HDEs, and the
13 population is way --

14 DR. WHITE: Right. Well, you're talking
15 about a very small population that you would choose
16 this device for. So it would be a very narrow
17 window. But when this device fails, the OPC, the
18 lower bound, then I don't understand how we can say
19 that we're in the neighborhood and we ought to let
20 that go.

21 I don't see the purpose of the OPC if
22 you're going to ignore the OPC's lower bound. I

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1 mean, once it is set, once it is agreed and we
2 proceed with that, then I find it a specious
3 argument to work around the number, if the device
4 fails the lower bound.

5 MR. MORTON: I think that's the hardest
6 thing about this, is that, obviously, there's a
7 patient population who it seems to be a real
8 consensus would benefit from doing cryos first, but
9 if, as a plumber, I'm understanding what I'm
10 hearing, that patient population isn't identifiable
11 upfront.

12 DR. TRACY: It is. In short order it is.

13 MR. MORTON: It is? So when you get into
14 the lab, you can see when the window's --

15 DR. TRACY: It is. Once you have the
16 catheters in place and you've done your baseline
17 study, then you know who you would pull which
18 catheter out for. And if you had both available in
19 your lab, you would have a very clear distinction
20 which catheter would be appropriate to use.

21 In terms of the OPC, I think that the OPC
22 is not appropriate.

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1 DR. GILLIAM: I agree. I think that the
2 question isn't -- I think the OPC is a high
3 standard, which is good.

4 DR. WHITE: A high standard?

5 DR. GILLIAM: I think it's very high.

6 DR. WHITE: For AVR? I mean, I don't
7 think you can -- that's not true. I don't know how
8 you came to that conclusion.

9 DR. WALDO: You know, I think if you're
10 introducing a brand-new concept -- ablation is not
11 a new concept. I mean if you're introducing a
12 brand-new concept, if you're doing a mated one, or
13 maybe if suddenly you're taking a new technology
14 and introducing it to a new treatment mode, you
15 have to be extremely -- well, you should be
16 rigorous always, but this is something very
17 different. This is ablation.

18 We have several tools for ablation.
19 There is not just one RF ablation technique. There
20 are many RF ablation techniques, from the size of
21 the catheter to cool tip, to, you know, saline
22 irrigation. There are all kinds of ways to do

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1 these sorts of things, but the concept is clear.
2 This is a concept of ablation. It's another way to
3 do ablation.

4 I think we can even get some information
5 from Dr. Dubuc, because what if your laboratory
6 switched to only --

7 DR. WHITE: Well, I don't think that's
8 relevant.

9 DR. WALDO: I'm going to suggest an
10 answer then. If you don't think it is relevant,
11 I'm going to think that they decided in their group
12 -- I'm guessing because I haven't talked about it,
13 but they decided in their group that it was worth
14 doing the cryo technique because they found it
15 very, very effective and they found it safe.

16 DR. WHITE: I disagree. He's conflicted.
17 He's a paid consultant for that company.

18 DR. KRUCOFF: I think we've got to
19 recognize that there's a difference between what
20 these numbers are from the study and what these
21 numbers potentially mean when they are applied to a
22 population. Kent, please correct me if this wrong,

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1 but I think that's really what boundaries are
2 about.

3 The OPC historical control creates a non-
4 randomized clinical trial venue. What that means
5 is that the 91 percent doesn't mean -- I mean it's
6 91 percent for this 130 patients; when you get to
7 136,000 patients, the boundary is what you may see.

8 You may see that's 97 percent or the upper
9 boundary or you may see that it's 83 percent or the
10 lower boundary, and that 83 percent, if that's what
11 happens in 136,000 patients compared to your 98
12 percent with radiofrequency ablation, that is my
13 understanding of what an historical boundary
14 branded number is telling us for application of
15 population.

16 That's, to me, what is so difficult and
17 what we seem to be wrestling with. Ninety-one
18 percent sounds really good, and certainly if it's
19 safer and there's a population who would benefit
20 from it, you know, that's where the consumer side
21 of a Kent Bailey steps up and says, "Maybe that's
22 what I would like to have used." But 91 percent is

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1 what happens in this 130-ish patients. The
2 boundaries tell us what might happen at 136,000
3 patients, and that's why if the trial design pays
4 attention to the boundaries rather than to the
5 number -- and somewhere we've got to figure out how
6 to digest that into whether this is just another
7 neat arrow for the quiver or whether what this
8 trial may be telling us by failing its boundaries
9 both in safety and efficacy is that, when you
10 really get out there and start using this thing,
11 compared to what you're already getting with
12 radiofrequency ablation in your lab, there's going
13 to be a bigger gap than the 91 percent kind of
14 number indicates. That seems to me to be what we
15 are wrestling with.

16 So we've come full circle. We basically
17 all agree that they failed to meet all their pre-
18 specified endpoints, and we're not being terribly
19 helpful here to the agency or to the vendor. But I
20 would have to say, if we did 136,000 or million,
21 the confidence limits would shrink. They wouldn't
22 stay that way. They would be awfully tight. Is

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1 that right? They wouldn't stay where they are?

2 DR. BAILEY: The learning curve.

3 CHAIRMAN LASKEY: But to get back to what
4 your needs are, you know, the Panel is torn. We
5 have a body of scientific evidence before us which
6 meets the null hypothesis, which has not been
7 rejected. Yet, as clinicians we have a gut feeling
8 that this probably is safe. If you take out the
9 prosthetist and you take out a few other weird
10 things that can happen, it probably is safe and it
11 probably is effective.

12 But you're asking us, and we need to
13 qualify that again and again and again, that we
14 vote as clinicians and not as methodologists or
15 statisticians. If you want a positive study, it
16 needs to redone in some manner with a larger
17 sample.

18 Does that reflect --

19 DR. ZUCKERMAN: That's helpful as a start
20 because it helps us through 2a. We have a
21 difference of opinion as to what the data show in
22 terms of effectiveness right now.

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1 So then we go to 2b. Given this
2 difference of opinion, is there any consensus on
3 what would be required in terms of replication of
4 results or new dataset that could help everyone
5 here concerned?

6 DR. WALDO: Well, you're not going to get
7 a trial of a thousand patients. I mean you know
8 that.

9 DR. ZUCKERMAN: No, but I don't think the
10 agency would require a trial of a thousand patients
11 for RF ablation. I think we have to go through the
12 usual panoply.

13 One is you always start with a randomized
14 trial. There's a difference of opinion there. But
15 at the other end of the spectrum, do we need
16 another registry experience where we can replicate
17 a number that was developed in a post-hoc analysis
18 to make everyone feel that we've reached a bar
19 that's acceptable? I mean there's always a wide
20 range of designs when we're talking about device
21 trials.

22 CHAIRMAN LASKEY: And I, for one, would

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1 suggest that. I think that if post-hoc analysis is
2 all about hypothesis-generating, then certainly
3 registry of AVNRT only, which is what the
4 indication here -- it looks like that's the
5 indication they're going for. If that's the
6 indication, then a registry of some reasonable
7 number of patients, less than a thousand but
8 greater than a hundred, would answer the question
9 as to the safety and efficacy track record.

10 I think that we're sort of jumping the
11 gun here.

12 DR. TRACY: What registry are we talking
13 about?

14 CHAIRMAN LASKEY: A registry such as has
15 been suggested to add to the qualifications of a
16 vote, for example.

17 DR. TRACY: You're talking about a
18 registry that this catheter would be entered -- or
19 patients would be entered into who had their
20 ablations performed with a cryocatheter versus a
21 registry that we would pull out of the shelf in the
22 library and say, let's compare this data to a bunch

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1 of AVNRTs?

2 CHAIRMAN LASKEY: Prospective.

3 DR. TRACY: We're talking about a
4 prospective though.

5 DR. ZUCKERMAN: I would just take a step
6 back. I'm looking at the screen, and we've dealt
7 with Question 2a, which suggests that there's a
8 difference of opinion as to effectiveness. So then
9 we go to 2b, which is, how much more might be
10 necessary to go to the goal line?

11 I think it's important for folks on this
12 Panel to understand that it doesn't imply that
13 needs to be a randomized trial. It doesn't imply
14 that needs to be a single-arm registry. We're just
15 looking for ideas here for those who feel
16 uncomfortable with the present dataset, realistic
17 ideas.

18 DR. KRUCOFF: I think one thing that has
19 been said a couple of times is that the size of the
20 current dataset plus or minus one or two patients
21 flirts source. One way to consider going forward,
22 it would seem to me, would be to focus on your

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1 indication population and sit down with a
2 calculator and see how many patients enrolled in
3 the identical protocol, but with just that one
4 indication, treated in the same way, could be
5 potentially appended to take away some of the
6 flirtation with the boundaries and really find out
7 whether you're at or better than the boundary or
8 whether you're not.

9 DR. WALDO: Can I ask a point of
10 information? In terms of safety, we heard that the
11 events, when they adjudicated all the cases, that
12 none of these things were device-related. Isn't
13 that my understanding?

14 Now I understand that there are
15 procedure-related problems in all things, and the
16 real issue, then, if I understand it correctly, is
17 that, is the device indirectly the cause of some of
18 the problems? That's what you're struggling with,
19 is that right?

20 Because I read through. I pulled it out
21 a couple of times, and I read through all the
22 things. I don't know how to answer that because

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1 I'm not a statistician, but as a clinician I
2 thought a lot of those things, the countings we see
3 anyway, most people don't look that hard.

4 I recently sat on an events committee
5 where we found some things that were newly-
6 recognized because they were looking very hard.
7 When we started looking at other patients who were
8 not in this kind of study, they found the same
9 thing these other patients had, a very, very good
10 laboratory.

11 So I don't know, I would not like to -- I
12 mean, what I hear a couple of things, and I think
13 our Chairman has stated them very well earlier -- I
14 really think there is a comfort level for me, and
15 I'll speak only for myself, about the safety of
16 this device. I think it has a utility.

17 Then the question is, do we want to just
18 disregard that at this point because it is a small
19 study and there are -- I don't know if I'm using
20 the right term -- secondary concerns because it's
21 not the device per se that has been associated with
22 the safety concerns; it's the procedure, and we

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1 don't know if the procedure of the use of the
2 device or if there is something unique about the
3 device and the procedure. My suspicion is that it
4 isn't, but I don't know that I can say.

5 I don't know if I have made myself clear,
6 but I think we're focusing on numbers, and we're
7 not focusing on what I think is the substance of
8 something that we in electrophysiology deal with a
9 whole lot, and that's ablation. I think the
10 ablation, the results of ablation are clear.

11 For me, a 91 percent and 97 percent and
12 96 percent, it's still an option for a physician
13 and there are times you want to use it. That's why
14 I made that remark earlier. I think that it's an
15 option that I think is legitimate, and I think the
16 data are sufficient to me to suggest that there's
17 an adequate efficacy, and the safety problems that
18 I see here are not the kind problems -- I haven't
19 seen life-threatening things. I've seen things --
20 you've proselytized the most obvious, but someone
21 had a problem with a sheath in a diagnostic
22 catheter. I mean those things happen from time to

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1 time. There are a bunch of other things like that.

2 So I think the forest and the trees thing
3 here is what I'm talking about. I think seeing the
4 forest, I think this is something useful. If you
5 look at all the trees, then you haven't got a sense
6 of what the forest is about here. That's what I
7 see.

8 DR. WHITE: I guess my problem is that
9 they failed on every single boundary. They failed
10 every one. It wasn't like two were good and one
11 was bad, and shouldn't we overlook that? I mean,
12 we're talking about rescuing the --

13 DR. WALDO: But you're focusing on
14 efficacy. I mean, I don't think 91 percent and 97
15 percent is to be ignored, but we're not talking
16 about life-threatening rhythms. We're not talking
17 about something terrible.

18 I think Dr. Bailey really had a very --
19 he saw it immediately, and he called it as a
20 consumer, but I think really the approach, if you
21 take the approach if you want to start with cryo,
22 and if it doesn't work, go on to RF, you've got an

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1 enormously good success rate. I think that is how
2 we think as clinicians. That's how they did it in
3 the study.

4 You have to ask yourself then, why do OPC
5 trials at all if you're not going to accept the
6 data?

7 DR. WHITE: I haven't thought about it
8 forever, but just off the top of my head, I mean if
9 you're breaking new ground, if you bringing in a
10 whole new direction of therapy, if you're
11 introducing your first implantable defibrillator or
12 your first bimitricular pacemaker, talking in my own
13 area of devices, I think you're breaking new
14 ground. But we're not really breaking new ground
15 in terms of ablation. We're playing with the
16 technology of ablation; that's all. That's how I
17 see it.

18 CHAIRMAN LASKEY: Well, but this is not a
19 510(k) either. This is a new --

20 DR. WALDO: Well, it's not 510(k).

21 CHAIRMAN LASKEY: This is a new energy
22 source.

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1 DR. WALDO: I mean, the safety issues to
2 me are not safety issues that are out of my cage;
3 put it that way.

4 CHAIRMAN LASKEY: No, I would agree with
5 you that these are procedure-related complications,
6 but these are the chances you take when you do a
7 study. You roll the dice and that's it. If you
8 win, great, but in this case they didn't.

9 But they're procedure-related and they're
10 often hard to disassociate from any device. It's
11 in the hands of the operator, and there's seven or
12 so variables that go into procedural complications.

13 Nevertheless, I tend to agree with you that I
14 think we do see the forest through the trees, but
15 the trees are awfully big.

16 DR. TRACY: Does anybody have a rough
17 estimate of what it would take to achieve an
18 effectiveness endpoint? Is it five patients or is
19 it 5,000 patients?

20 DR. PAGE: If I may just ask, I think it
21 troubles the heck out of me that an OPC trial was
22 done and it failed, but in retrospect I don't think

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1 it was the right trial. I think it was too small,
2 and given what I believe the safety is of this
3 device, then I think the bar was set too high in
4 terms of efficacy.

5 Then we're looking back at the safety
6 issue. When we dissect out the safety issue, which
7 I think is fair in this case, because one or two
8 going the other direction changes the whole result,
9 when we dissect out the safety, then it doesn't
10 look like it is the catheter that's responsible for
11 it.

12 So I feel like I'm totally schizophrenic
13 here because, as a statistician, if I were one, I
14 would not accept what I just said, but as a
15 clinician I think we would be wasting our time to
16 do another pre-approval trial because I don't know
17 if this Committee could even figure out what our
18 endpoint was, then much less go through all the
19 time of running a trial.

20 I think a registry afterwards of this
21 type of patient would be very valuable, the first
22 thousand cases, and really look at it.

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1 DR. ZUCKERMAN: Right, but the problem is
2 you need the data before approval to label a device
3 for a certain indication. So to respond to Dr.
4 Tracy's question, though, I think we need to
5 remember that with the approximate number of AVNRT
6 patients that were in this trial, the lower bound
7 was about 82 percent. So if you were going to do a
8 subsequent trial, where you could accept a lower
9 OPC, for some of the reasons alluded to, you're in
10 the same ball park, not as exactly, as to what was
11 studied, what was retrospectively determined to
12 AVNRT patients, around a hundred or so.

13 MR. MORTON: Dr. Laskey, just a quick
14 comment: I know that we're all looking at the same
15 screen, but one thing that I would emphasize that
16 the agency and the sponsor have come before the
17 Panel to ask is, is there proof of reasonable
18 safety and effectiveness? And that is exactly what
19 I'm hearing you wrestle with.

20 DR. GILLIAM: My concern is, just looking
21 at the OPC, I mean I'm not so certain that if we
22 were to do this study with 5,000 patients and it

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1 didn't meet the OPC, does it mean that we should
2 not approve the device? I guess at the end of the
3 day we have to take a vote.

4 As Dr. Waldo said, I sort of feel that,
5 if you were to say, "Is this device as effective as
6 RF for ablation," then I would probably say RF is
7 probably a little bit better. I mean, it's a
8 bigger lesion maybe, and maybe that's why it's
9 better or maybe quicker, whatever.

10 But is this an effective treatment? I
11 would have to say, yes, it's effective. Maybe it's
12 not as good as RF, but it's different. It's not
13 the same thing.

14 So I think using the OPC standards we
15 have for RF may not fully be applicable to this
16 type of therapy. I mean it's an ablation, but it's
17 different. I mean, maybe the efficacy is not as
18 good, but it doesn't mean that it is still not
19 effective. I think that's the distinction that I
20 make.

21 DR. HAIGNEY: Would it be possible to
22 have a registry that would be aiming at safety? I

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1 think it's quite possible that this isn't as good
2 as RF, but RF is darn good and it has been
3 developed over 10-11 years. If it turned out,
4 after looking at a thousand patients, it had an 85
5 percent success rate, I would say fine, that
6 doesn't bother me because there are certain
7 patients who I want to use it in.

8 It would bother me, however, if we did a
9 registry and we started getting more heart blocks.

10 Then I would say, well, wait a minute, maybe this
11 isn't the thing I want to try in the area of the AV
12 node. In a registry, couldn't we design a registry
13 that was a couple hundred patients with the express
14 purpose of being sensitive to detecting AV node
15 block and other -- the sort of device-related
16 complications that we're all --

17 DR. WHITE: If we haven't seen heart
18 blocking in over 600 patients I heard, how are you
19 going to find it? This is going to be very hard to
20 find.

21 DR. WALDO: Well, that's terrific. I
22 don't want to find it.

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1 DR. WHITE: No, no, no, but I mean for
2 pre-approval. We already have 600 --

3 DR. WALDO: You've only had 150 patients
4 to look at. You've had 150 European experience.

5 DR. WHITE: Well, I would love to see
6 that data. I would love to see it, but it wasn't
7 presented to us. So I have 150 patients with a 1
8 percent incidence.

9 DR. WALDO: If the prevalence is zero,
10 the confidence is because the numbers are small, is
11 what we're talking about.

12 DR. WHITE: But it would only take one or
13 two patients. The next two patients have heart
14 block, and all of a sudden --

15 DR. WALDO: AVNRT has fewer patients than
16 that, but I think we have to decide what the agenda
17 of the Panel is. If, ultimately, there's a
18 regulatory process that's asking a question about
19 an indication based on data, then that's one
20 conversation.

21 I think you could probably put this
22 catheter in the hands of any of the EP people

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1 sitting here, and in about five or ten cases they
2 would know 99 percent of what we have been talking
3 about today, but that's not data.

4 I think ultimately we have to decide
5 whether there is information here sufficient to
6 support a regulatory approval and/or indication or
7 not, and if not, then what would provide that, I
8 think is what I interpret to be the part of this
9 question to allude to.

10 DR. WHITE: I may be confused, but what
11 I'm hearing from the EP group here is that this may
12 not be as good as RF, but it has a niche. But, on
13 the other hand, what the sponsor, I think, asked
14 the FDA was, how could we have this approved that
15 it's at least equivalent to using the guidelines of
16 RF ablation?

17 We didn't quite hit that, and that is the
18 problem we are struggling with. I have sat on a
19 number of these panels, and I'm always startled by
20 the fact that somehow the studies really never have
21 the power to answer the question you would really
22 like. I think when you go back and look at these

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1 in the future, you hope that people will do the
2 studies that are going to answers the questions you
3 want or design the question, design the trial to
4 answer the question.

5 Maybe it should have been designed as a
6 niche device trial in some way rather than the way
7 it is being presented, but somehow the position of
8 the product needs to fit the study that's done, and
9 an adequate study ought to be done to answer that
10 question.

11 DR. KRUCOFF: Well, the OPC questions are
12 on the safety side that the boundary established
13 tells us that the use of this catheter is not going
14 to do more harm than radiofrequency.

15 And on the effectiveness side, the other
16 boundary basically tells us that this catheter is
17 at least as good as, within a range, the point of
18 comparison. The reality is I think what we are
19 hearing is that clinicians who do these procedures
20 would be happy to have this instrument in their
21 lab, even if it was not as good as. The trouble is
22 that's not what this trial addresses.

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1 Either we have an approval process based
2 on the trial or we have an approval process based
3 on what, unfortunately, may or may not be some
4 degree of bias, having looked at the data as to
5 where you think, in fact, the right trial design
6 might have been, if you were to go backwards. It's
7 a little head spin.

8 CHAIRMAN LASKEY: Does it help the agency
9 at all for the Panel to at least say with some
10 unanimity, I think, that the OPC criteria, these
11 criteria chosen are not applicable, and, therefore,
12 need to be evaluated in that context?

13 That gives us the room in which to make a
14 clinically-driven decision rather than the one that
15 we're agonizing over, which is our clinical horse
16 sense says one thing, but our methodologic rigor
17 says another. But if we were all willing to
18 discount or to freely acknowledge the known
19 limitations of the OPC criteria as to another
20 device, to this device, that would make us all feel
21 better in terms of our final recommendations.

22 DR. WHITE: I'm not sure I feel guilty

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1 about this. I mean, I'm not the one who choose to
2 do the OPC trial.

3 CHAIRMAN LASKEY: No, but having done it,
4 you know, we're trying to be fair here to everyone,
5 and it is fair, I think, to acknowledge the
6 limitations of somewhat arbitrary criteria that act
7 as a benchmark, which is a moving target, and
8 perhaps if done in 2003, and not in 1990, would be
9 different.

10 DR. BAILEY: But I think the
11 considerations that make people think that it has a
12 niche are the heart block issue and things like
13 that. It seems it might theoretically have a
14 better safety profile, but we don't have data --

15 CHAIRMAN LASKEY: There are no numbers to
16 support that.

17 DR. BAILEY: We don't have enough
18 precision on the thing that gives it the niche that
19 it needs. It has to be better at something.

20 CHAIRMAN LASKEY: You keep putting us
21 back in the hole. We need to get out of the hole.

22 DR. ZUCKERMAN: Oh, but that's fair. I

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1 think it's fair to summarize there's a difference
2 of opinion on Question 2a and b regarding the
3 effectiveness shown presently. We'll get into it
4 later with the Panel voting, but I'm not sure
5 there's more to say about this question more.

6 CHAIRMAN LASKEY: Thank you. Agreed.

7 (Laughter.)

8 There are so many ways to rephrase it.

9 Question 3, effectiveness in the
10 cryomapping area: "The submission describes the
11 use of cryomapping technology and effectiveness
12 evaluation. Please discuss whether the study
13 results show that the cryomapping technology is
14 effective for use in the intended patient
15 population."

16 First of all, the intended patient
17 population is now AVNRT. So to answer that
18 question, we need to delimit the Panel's response
19 to AVNRT, not to AVRT or AF, is that correct?

20 DR. HAIGNEY: No, I don't think so.

21 CHAIRMAN LASKEY: No?

22 DR. HAIGNEY: I believe the indication is

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1 for cryomapping around the AV node for accessory
2 pathways, as well as AV node reentry. Isn't that
3 correct?

4 DR. WALDO: No, it says, essentially,
5 says for AV-conducting tissues. That would
6 include --

7 DR. ZUCKERMAN: Dr. Haigney, do you have
8 Section 3 of the label?

9 DR. HAIGNEY: Yes. It says, "Cryomapping
10 of conducting tissue near the AV node."

11 CHAIRMAN LASKEY: You're correct. That's
12 absolutely correct. That's my misread, uh-hum.

13 DR. TRACY: I think that is, in fact,
14 what that says, but when it was asked earlier of
15 the sponsor, maybe that would need to be clarified,
16 but their answer was pertaining to the AV node.
17 You could say, well, that is anterioseptal pathways
18 conducting tissue near the AV node. So that it's
19 not -- if you want to limit this specifically to AV
20 nodes, you have AV nodes or peri-AV nodal tissue,
21 something to more specifically state that.

22 MR. MORTON: I have a question.

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1 Shouldn't we be looking at the slides that were
2 presented today by the sponsor and the agency,
3 rather than what was in the labeling, because this
4 labeling was presented or actually was what was
5 used to start the study, as I understand? Is that
6 not correct, when we're talking about the
7 indications for use?

8 CHAIRMAN LASKEY: I suppose that's a good
9 point, Mike. We need to make sure we're on the
10 same page.

11 DR. TRACY: It's actually on page 4 of
12 the sponsor's -- the identification of a variant
13 conducting tissue responsible for SVT using
14 reversible electrophysiologic cryomapping of
15 conducting tissue near the AV node. It doesn't
16 really narrow it down any further. In fact, it
17 broadens it if you consider aberrant conduction to
18 mean accessory pathway.

19 DR. HUGHES: To me, that means that you
20 could use it to cryomap accessory pathways where
21 you think there's danger of causing AV block, but
22 not ablate those accessory pathways with the

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1 cryoablation catheter. Just a little bit odd. I
2 guess you would pull the catheter out at that
3 point.

4 CHAIRMAN LASKEY: Well, that's right. I
5 mean that's the problem with the semantics here,
6 and it does need to be reworded. You can't reword
7 it on the fly? Can we reword it on the fly,
8 because as it is it's not --

9 DR. GILLIAM: Did they show that
10 cryomapping was successful at any point for
11 anything?

12 CHAIRMAN LASKEY: No, the results were
13 the same with and without.

14 DR. GILLIAM: My question, really to be
15 on the other hand, I think I'm kind of liberal with
16 the first area. As a clinician, I want to go that
17 way. But the second area, I think I might be the
18 guy with the dagger to put into it because I think
19 at that point -- I mean, I haven't seen anything in
20 any of the study, in any subgroup, in any way that
21 suggests that cryomapping has been effective in any
22 way.

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1 DR. HAIGNEY: Didn't they show that they
2 had a higher percentage of successful burn for
3 efficacy in the sites with positive cryomaps? Is
4 that correct, the 95 compared to 67, which they had
5 positive or negative in the seventies if they
6 didn't do a cryomap?

7 DR. TRACY: I think the problem was it
8 was more effective than a negative cryomap, but it
9 was particularly more effective than if you had not
10 done a map. But if you had done a map in the
11 places where you had not done a map, you might have
12 had further data in one direction or another.

13 So it was only a piece of the data that
14 was collected, and it was not mandatory to collect
15 cryomapping. So it makes it a little hard to say
16 too much definitive about it.

17 DR. WALDO: But having more rigorous and
18 selective -- I mean savvy, it would have been
19 really nice to focus specifically on the patient
20 groups of interest, but I think we all know why we
21 would love to have this, if it really works, which
22 theoretically it ought to.

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1 CHAIRMAN LASKEY: But just to remind
2 everybody, it was P equals NS. I think it was .59
3 or something from the chi square result, that was
4 just not even close, the efficacy with and without
5 mapping. So they chose to do the analysis and it
6 was way off.

7 All right, can we move on?

8 This study did not show it's effective,
9 at least if we talk about the intended patient
10 population, which was the chi square that they gave
11 us.

12 No. 4 -- oh, sorry. I will read on.
13 With respect to the training and learning curve,
14 "Acute success rate varied per institution in this
15 study," albeit the numbers were also variable.
16 "Acute success rate per institution ranged between
17 zero and 100 percent.

18 "a. Please discuss the concept of the
19 site-based and physician-based learning curves."
20 Can you go back to A? Thank you.

21 DR. WHITE: You know, in our world there
22 are roll-ins, and that's how we take care of

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1 learning curves with plumbing devices, is we decide
2 how many you need to get comfortable with this, and
3 then you have roll-ins and then you start your
4 pivotal trial. So I think that's the way that you
5 handle a learning curve with any new device, which
6 we all agree is there.

7 The only question is, how many roll-ins
8 do you need to feel comfortable? Three? Five?
9 Seven?

10 DR. WALDO: But maybe to demonstrate
11 this, I thought that they admitted that they didn't
12 demonstrate any learning curve. The numbers are so
13 small.

14 DR. WHITE: But I think it was because
15 they had multiple operators at the sites, and so
16 they didn't have numbers -- it kept changing over
17 time, too.

18 DR. WALDO: But I don't think there's any
19 question among us that a new device requires some
20 training and some comfortability, and that you
21 don't want to hit the deck with the first time that
22 it ever touches your hand, impacting the safety and

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1 efficacy pivotal trial, and that's the purpose of a
2 roll-in. So you get to try it and it doesn't count
3 you if you have a problem until you get
4 comfortable.

5 CHAIRMAN LASKEY: So the Panel agrees
6 with the concept of physician-based learning
7 curves. What the number is is up for grabs. I
8 think we all espouse that.

9 "b. All new devices inherently involve a
10 learning curve in their evaluation. Please discuss
11 whether the concept of a learning curve, either per
12 site or per physician, may be considered in the
13 evaluation of device safety and effectiveness."

14 Yes, it may be considered. Some trials
15 actually do allow for that in terms of looking at
16 roll-in patients and not counting them in a
17 randomized but still analyzing them in the same
18 way. So I think we all would agree that they may
19 be considered in the evaluation, and, in fact,
20 should be. Roll-in patients should be followed in
21 every detail the same way as the rest of the trial.

22 "c. Please discuss whether and/or what

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1 type of physician training should be required for
2 this device if approved."

3 Here I think there was lots of
4 discussion. So, Cindy, do you want to lead off
5 whatever consensus you took away from the
6 recommendations for training?

7 DR. TRACY: I think there has to be some
8 physician training. I don't know whether that has
9 to be a visitor come to your lab and show you how
10 to use the equipment versus you go and observe the
11 use of the equipment someplace else.

12 I think it would be preferable to have
13 somebody come and train onsite. I'm not sure it
14 needs to be a physician. It could be a well-
15 trained clinical field engineer or something like
16 that. But I think there should be some specific
17 individual physician training as well as training
18 of the staff in the laboratory on how to use the
19 device correctly.

20 I think I would hesitate to mandate the
21 specific number of cases that would have to be
22 performed with an observer in the lab with you. I

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1 think it would depend on the individual expertise
2 of the person learning.

3 CHAIRMAN LASKEY: It sounds reasonable.

4 DR. PAGE: Will you forgive my addressing
5 Question No. 3 one more time, and just to point
6 out, because I think what we just agreed on wasn't
7 what I remembered and isn't supported by the FDA
8 slide series?

9 If I can just draw your attention to
10 slide No. 70, which shows a p-value of .0001 in
11 terms of the analysis of cryomap. The overall
12 group -- so the prospectively-defined, overall, no
13 subanalysis group is .001.

14 The next slide, 71, points out that it's
15 driven by the AVRT patients, but, in fact, that's
16 where I see the mapping as being useful. Actually,
17 that's where the proposed indication is. The
18 second proposed indication reads, to my
19 interpretation, and maybe it needs to be clarified,
20 but reads to my interpretation exactly the issue of
21 mapping AVRT around the AV node.

22 So it seems to me that, at least my

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1 impression was, we dismissed the idea of
2 cryomapping showing any efficacy, and it seems to
3 me we have both an indication of efficacy on slide
4 70 and a request for indication for that exact
5 purpose on slide four.

6 CHAIRMAN LASKEY: The request for the
7 indication calls for the identification of tissue.

8 DR. PAGE: Right, for mapping.

9 CHAIRMAN LASKEY: Period, right.

10 DR. PAGE: But, as I interpret that,
11 aren't they talking about parahisian conduction in
12 and around the AV node?

13 CHAIRMAN LASKEY: They didn't specify.

14 DR. TRACY: It's not specified, and it's
15 inconceivable that somebody would put in a
16 catheter, map an anterioseptal accessory pathway
17 successfully, pull that catheter out, and put
18 another catheter in and try to get it in the same
19 place. I mean it's a can of worms that you open
20 there.

21 DR. PAGE: Well, I didn't open it.

22 (Laughter.)

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1 But that's the request that they have.
2 Indeed, the data are the data.

3 CHAIRMAN LASKEY: Lilly, could you help
4 me out here? What was the results of your analysis
5 in the 2-by-2 table of the outcomes by mapping or
6 no mapping?

7 DR. YUE: Okay. Now please remember we
8 have three subgroups: effective, ineffective, and
9 no attempts. The sponsor combined effective --
10 sorry, the sponsor combined "ineffective" with "no
11 attempts," correlated without cryomapping, then
12 compared this without effective cryomapping with
13 effective cryomapping.

14 Okay, now here the overall p-value, the
15 p-value for the overall analysis is less than
16 .0001, but you'll see it is driven by 49 AVRT
17 patients. This subgroup is not the group that the
18 sponsor is, it is occurring to me, claiming for.
19 Instead, the AVNRT group is the only group they are
20 claiming for. We have a concern about this
21 grouping.

22 DR. GILLIAM: I think you're asking what

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1 ablation --

2 DR. YUE: What is the meaning of the
3 comparison? Why are they grouping "ineffective"
4 with "no attempts"? Is the subgroup classification
5 "effective" versus "without effective" biologically
6 plausible?

7 It seems if we try to test the impact of
8 effective cryomatching ablation with success, we
9 could compare the effective group with the
10 ineffective group, then use "no attempts" as a
11 control.

12 Now from here, we can see the acute
13 success rate is 94 percent for effective group. It
14 is much better than 50-65 percent for the
15 ineffective group, but the chance of having an
16 effective cryomatching is only 64 percent. On the
17 other side, if we try to test the impact of our
18 attempt cryomatching on ablation with success, we
19 could compare attempts with no attempts. Attempts
20 include effective and ineffective here.

21 We performed this study. Then we found
22 there's no significant difference in ablation acute

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1 success between attempt and no attempts.

2 Now here the p-value is .59 here.

3 DR. BAILEY: The point is, if you were
4 doing a randomized trial, it would be use of
5 cryomapping or not using cryomapping. You can't
6 just take the people that are positive and say,
7 because their success rate is high, that shows that
8 cryomapping is a good thing to do.

9 DR. WALDO: You know, this is the
10 problem. We understand the statistic very clearly,
11 and there's no challenge to that. But the specific
12 thing that we are talking about is very unique.
13 What you are trying to do is avoid the his bundle,
14 and I'm not sure they presented that specific data.

15 We are not talking about ablating -- this
16 is very, very unique, and you can't apply it the
17 same as looking at pathway on the left side with a
18 his bundle. This is a very unique application
19 where we have nothing at the moment to help us,
20 and, fortunately, it is not the most common type of
21 Wolf Parkinson-wide or accessory AV connection
22 problem, but it's very, very real.

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1 The hope is, and maybe we heard some of
2 it anecdotal, unfortunately, here, but the hope is
3 that you can use this cryomapping technique to find
4 the sweet spot and avoid the his bundle and help
5 the patient effectively and safely. That is as
6 simple as that.

7 That's not going to come out of anything
8 we say about the statistics here because it is just
9 not going to. It's not there.

10 DR. TRACY: It's also not necessarily
11 something that needs regulating. This is something
12 that people over time can find out: If I attempt,
13 I'm successful, I ablate; what is my success at
14 ablation at that spot?

15 So I think this is something that you can
16 do with this catheter that is unique. You can't do
17 it with anything else, but it doesn't seem to be
18 the make or break whether this catheter is useful
19 or not.

20 DR. KRUCOFF: I think this is also a good
21 illustration of the difference between the data we
22 actually have to discuss and the questions that go

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1 through your mind. In fact, I think the sponsors
2 during their presentation came up with a discussion
3 that actually the inability to show any effect may
4 be a great way to show that it's safe to ablate in
5 certain patients, but while it's a great concept,
6 you know, this trial doesn't give us the basis to
7 address it with data. I mean it's a great concept.

8 CHAIRMAN LASKEY: Frankly, all bets are
9 off with the cryomapping because there was an
10 arbitrary selection criteria that we were not privy
11 to as to who were mapped and who were not. It is
12 really difficult to take any lessons home from
13 that. I just wish it weren't here, but it's the
14 second bullet in their IFU. So sorry.

15 Labeling: "Labeling for a new device
16 should indicate which patients are appropriate for
17 treatment, should identify potential device-related
18 adverse events, and should explain how the device
19 should be used to optimize its risk/benefit
20 profile. If you recommend device approval, please
21 address the following:

22 "a. Please discuss whether the proposed

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1 warnings, precautions, and contraindications are
2 acceptable, based on the study results."

3 Let's be clear about one thing: We're
4 now back to the AVNRT group, is that right, Panel
5 members? Right.

6 Are the warnings, precautions, and
7 contraindications acceptable, based on the study
8 results?

9 DR. GILLIAM: I'm going to go back to my
10 electrocution question still. I still have real
11 issues with that, and maybe I'm not electrocuting a
12 dead horse. But it is not clear to me how this
13 device can electrocute a patient if it were hooked
14 to an RF generator. I think if it is possible,
15 then maybe a little sterner warning needs to be
16 connected, because I can't see how you can avoid or
17 prevent me from hooking this device to an RF
18 generator.

19 DR. TRACY: I don't think it fits.

20 DR. WHITE: I asked them specifically
21 that.

22 DR. GILLIAM: You said they can't do it,

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1 but if you're going to be able to record, I assume
2 at some point you record an electrogram from the
3 end of this catheter some way. That means it's got
4 to plug into your recording machinery you have. So
5 at some point there's a pin that gets to my, if you
6 will, Pruca or whatever system you have.

7 So that would suggest to me that I could
8 plug it into an RF generator, because all I need is
9 one pin. If that is a significant risk, it may
10 need to be a little bit higher.

11 I mean I've never seen anything like this
12 in anything we've done other than plugging the pin
13 directly into the shield, when we went to hooded
14 pins --

15 DR. TRACY: Well, but I'm not sure,
16 Rosie. You might, then, carry it to the extreme of
17 saying: Don't plug this into the wall because that
18 could be dangerous.

19 I think the connectors are simply not
20 meant -- they don't fit into an RF generator.

21 DR. GILLIAM: Okay. I think that's how
22 we ended up with the hooded pins, by the way, so

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1 people didn't plug them into the wall. But I'm
2 maybe getting a little bit overboard here. I just
3 find it very curious. I have never seen that
4 specific thing written out in any way.

5 CHAIRMAN LASKEY: Well, it's certainly a
6 red flag, but can we settle this one more time from
7 the engineer? Can you explain the physical basis
8 for the inability to make this hazardous
9 connection?

10 MR. ABOUD: Actually, technically, you
11 can connect anything to an RF generator, right?
12 You can take any wire and connect it to the RF
13 generator.

14 The catheter has a tip, a metal tip, and
15 has a wire on it. And like you said, you can take
16 that wire and put an adapter and put it on the RF
17 generator, but no electrocution can happen. That
18 catheter is not designed to deliver enough energy,
19 and there is no reference electrode first to
20 connect it. That means someone has to take that
21 catheter, that second end wire, make all the
22 adaptation and put it to the right pin to an RF

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1 generator and make it work, right?

2 CHAIRMAN LASKEY: Okay. All right, and
3 we do have a big warning with a box around it, is
4 that right, in the IFU?

5 Let me just go back to identify potential
6 device-related adverse events. I think Dr. Waldo,
7 in the lead, explained it is very difficult to
8 pinpoint specific device-related AEs when they are
9 procedure-related. So I might suggest modifying
10 that language to get us off the hook. We can't
11 look at device-related AEs unless it's heart block,
12 and that didn't occur.

13 So other than Rosie's concern --

14 DR. ZUCKERMAN: Okay, Dr. Laskey, maybe I
15 can take you and the Panel through the labeling
16 because we do need some comment on the big ticket
17 items. I'm looking at the label which is in
18 Section 3, "Indications for Use," Mr. Morton, which
19 is the same as on our slide.

20 This is the key point. The first bullet
21 regarding cryoablation, is that still acceptable to
22 the Panel, and the second bullet should be removed?

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1 CHAIRMAN LASKEY: What page are you on?

2 DR. ZUCKERMAN: I'm in Section 3,
3 "Labeling of the Panel Pack," and page 2 starts
4 with, "Device description" and then "Indications
5 for Use."

6 The "Indications for Use" somehow got
7 deleted from Question 5, but is our major question
8 here: Is the device appropriately labeled?

9 DR. TRACY: I think it would save a lot
10 of angst simply to remove that second bullet.

11 DR. ZUCKERMAN: Okay. Part "b" would be:
12 "Is the Panel satisfied with the current
13 contraindications? Should some be removed? Are
14 there others that are important?"

15 DR. TRACY: Didn't we decide that we
16 could put it through a bioprosthetic aortic valve,
17 so that that slight change in the wording in the
18 retrograde -- but then again, why are you going
19 retrograde for the AV node? I suppose you could,
20 if you were ablating it on the left side.

21 I mean, it's there. It's not pertaining
22 to this population, but --

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1 DR. VETROVEC: If I'm correct, if one
2 reads the package insert for a porcine
3 bioprosthesis valve, it says it should not be
4 crossed by a catheter, not to say that we haven't,
5 most of us in this room, done that, but --

6 MR. MORTON: I think the valve
7 manufacturers would definitely not want you
8 crossing anything across prosthetic valves.

9 DR. GILLIAM: Do we have guidance from
10 other like RF catheters and their ablation systems?
11 The contraindications, are these substantively
12 different from that in any way? I guess I'm asking
13 FDA.

14 DR. EWING: The indications for all the
15 non-generic-indicated RF catheters include
16 accessory pathway and adrophobe.

17 DR. GILLIAM: I was thinking more of the
18 contraindication, not the indications. I mean, the
19 indications I will grant here a specific
20 arrhythmia, but are there any specific
21 contraindications to RF systems?

22 DR. DESMARAIS: I can answer that. We

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1 based the contraindication of this indication for
2 use based on prior RF ablation safety and
3 effectiveness data that we lifted from the FDA
4 website, and this is the model we used to create
5 this impression for use and this labeling.

6 DR. WALDO: By eliminating your angst, we
7 eliminated the one potential advantage of this
8 because we haven't had data, and we've made our
9 peace with that, is that what we're saying,
10 unhappily, but that's the way it is? Is that we're
11 saying?

12 DR. TRACY: Yes, that's what that means.

13 DR. PAGE: Does everybody agree with
14 that? I personally think that having this as a
15 mapping device for cryomapping is a potentially
16 useful indication.

17 DR. HAIGNEY: I agree with that. I think
18 it does require us to have certain amount of faith
19 in our fellow man that they will map and then pull
20 the catheter out, but I don't think -- I think it
21 depends on whether you have a Hobbesian view of man
22 or not.

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1 CHAIRMAN LASKEY: Again, we're straying
2 from the data. I think it always helps to go back
3 to homeplate, and I think we all understand its
4 attractiveness, but we're straying from the data to
5 support that. We all know that you're going to do
6 it anyway.

7 DR. WALDO: That's an easy thing to
8 recommend, a recommendation on how to focus them on
9 identifying a bunch of patients like this --

10 CHAIRMAN LASKEY: Yes.

11 DR. WALDO: -- and giving us the data.
12 That's the one easy thing I think of all the things
13 we talked about so far.

14 CHAIRMAN LASKEY: Well, we'll get to
15 that.

16 Brian, do you want to lead us through the
17 wilderness some more?

18 DR. ZUCKERMAN: Okay, now we're dealing
19 with warnings. Dr. Gilliam has expressed an
20 opinion on one warning. Are there any other
21 warnings that are of concern here for the
22 precaution section?

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1 DR. HAIGNEY: The cryoglobulinemia
2 contraindication I think should be included.

3 CHAIRMAN LASKEY: I think we're all in
4 agreement about what not to do. There's confusion
5 about what to do, but I think Part a is pretty easy
6 here for the labeling. Do you agree? Yes?

7 Do we feel the IFU described how the
8 device should be used? From a technical
9 standpoint, I think so, yes. Agree? Good.

10 Are we awake?

11 No. 6, from a post-marketing standpoint:
12 "If you recommend approval, please discuss whether
13 a post-market study should be performed to address
14 any issues that are unresolved, but not essential
15 to the pre-market approval of the device."

16 DR. KRUCOFF: Were one to approve the
17 device, then one might append a post-market look at
18 the value of mapping, for instance, if it's built
19 into the same device. That might be --

20 DR. WALDO: Specifically, the parahisian
21 mapping.

22 CHAIRMAN LASKEY: One might, agreed.

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1 What else one might recommend?

2 DR. VETROVEC: Can you look for things
3 that aren't necessarily indicated? If we talked
4 about removing one of the indications, then that
5 wouldn't be a legitimate question to ask someone to
6 do.

7 DR. ZUCKERMAN: I think Dr. Vetrovec's
8 viewpoint is correct. The parahisian question is
9 an important one, but that could be studied in a
10 new IDE study with the intent to get that on the
11 label. We're really talking about some issues for
12 the intended indication which are not show-stoppers
13 for making a decision today, but would be nice
14 subsequently to study because there would be
15 utility for having that additional data.

16 DR. TRACY: This is a dreadful suggestion
17 because it just goes full circle to where we were
18 earlier in terms of our registry on effectiveness.

19 DR. AZIZ: What about monitoring the
20 instance of heart block that people have spoken
21 about?

22 CHAIRMAN LASKEY: Sorry?

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1 DR. AZIZ: The instance of heart block
2 that people have spoken about?

3 CHAIRMAN LASKEY: Yes, I couldn't agree
4 more. I am very enthusiastic about -- I would go
5 further than one might. I would strongly suggest a
6 prospectively-designed registry, designed for a
7 safety outcome analysis. I think the efficacy is
8 believed by most, but safety is the issue, if this
9 is a complementary or an alternative technique.

10 DR. ZUCKERMAN: I think, again, in
11 understanding the nature and intent of post-market
12 surveillance for a problem like complete heart
13 block, which has an extremely low incidence, while
14 that information might be interesting to
15 clinicians, it would really require several
16 thousand patients perhaps to make a definitive
17 determination. That's not the intent usually of
18 post-market surveillance.

19 What we are asking here is for the
20 intended use indication under study, are there some
21 additional points where we still feel very
22 uncomfortable, not where we still want to dot an

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1 "i" rather than get an A-plus-plus on a paper?

2 DR. GILLIAM: I think the utilization of
3 cryomapping even in the AVNRT patients could be
4 effectively shown. I mean, you could show, when
5 you achieve an effective cryomap in a specific
6 place, I mean in the study here it suggests that it
7 wasn't particularly useful, but I think the data
8 are really suspect because we don't know how those
9 patients were selected or, you know, in any way. I
10 think that is something post-market could be
11 handled within the study population.

12 DR. BAILEY: I don't see how you could
13 learn about the efficacy unless you design a study
14 to look at it. I mean, post-marketing, some people
15 will get cryomapping and some won't, but how do you
16 know, what does that show?

17 DR. GILLIAM: I mean specifically design
18 a study to look at that.

19 DR. BAILEY: But that's not post-
20 marketing.

21 DR. ZUCKERMAN: Right. Again, that's a
22 traditional IDE study for a new indication on the

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1 label. Perhaps to put this in perspective and
2 allow the Panel to better appreciate what we're
3 getting at here, if this was a traditional RF
4 ablation catheter, there wouldn't be any post-
5 market study required because, as several people
6 have pointed out, this is a tried-and-true
7 technology.

8 Is there something unusual here that has
9 been indicated in the dataset about a safety issue
10 that would make you really want post-market data?

11 CHAIRMAN LASKEY: The consensus seems to
12 be no, but --

13 DR. VETROVEC: Heart block seems to be
14 the obvious.

15 CHAIRMAN LASKEY: Heart block seems to be
16 the obvious one, yes.

17 DR. BAILEY: Yes, I think heart block
18 would be --

19 CHAIRMAN LASKEY: With due respect to the
20 precision of the estimate, I would think that a
21 thousand cases could be done across the country in
22 a reasonable period of time.

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1 DR. BAILEY: And if the incidence is
2 zero, the estimate will be quite precise?

3 CHAIRMAN LASKEY: Yes.

4 DR. KRUCOFF: The other part of this is
5 the premise of approval based on current data,
6 because while device-related safety looks pretty
7 good, procedure-related safety, if a significant
8 percentage of these procedures end up being bailout
9 RF ablations, you're going to have catheters in the
10 blood -- I mean the safety, the potential safety
11 issues from a procedural point of view, if this was
12 approved for use, might well be worth tracking in
13 the post-market, but that begs the question of
14 whether you see the safety issues as sufficient to
15 approve the device in the first place.

16 So the way this question is stated, it's
17 a little hard to --

18 DR. TRACY: Does it make any sense to
19 look at how the catheter is used, how many times it
20 is a bailout for RF versus how many times RF is
21 used to bail out from a cryo? Is that something
22 that would be -- I know it would be interesting.

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1 Is it something that's worthwhile?

2 CHAIRMAN LASKEY: Or easy to do. I mean,
3 recording that kind of stuff is just one more thing
4 to record. Generally, the surveillance studies are
5 just do it and we'll look at the outcomes, but this
6 is yet another iteration. So it's one more thing
7 to do. It's getting closer to a study than just an
8 observational kind of thing. I would think it's a
9 good idea, but it just requires one more thing to
10 do and puts the sponsor on the hook for paying for
11 that information.

12 DR. KRUCOFF: I think what we are
13 wrestling are ideas for actually it would just be
14 better studies to do. Maybe pertinent to the
15 agency's interest, I haven't heard anyone suggest
16 that there's anything about the lesion in animals
17 or the behavior of the catheter, or whatever, that
18 ought to spook us in some way that would make you
19 want to keep watching longer.

20 I would suggest that the real question
21 here is approval, not sort of unique post-market
22 kind of issues.

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1 CHAIRMAN LASKEY: So as we get ever
2 closer -- at this point I would like to ask the
3 sponsor -- at this point I would like to ask the
4 agency and then the sponsor if they have any
5 additional comments or questions before the vote.
6 So the agency first?

7 DR. ZUCKERMAN: The agency doesn't have
8 any additional comments.

9 CHAIRMAN LASKEY: Again, on behalf of the
10 Panel members, I thank the various contributors who
11 have helped us out significantly.

12 Any final comments from the sponsor?

13 DR. DESMARAIS: Yes.

14 CHAIRMAN LASKEY: Brief?

15 DR. DESMARAIS: Very brief.

16 CHAIRMAN LASKEY: Thank you.

17 DR. DESMARAIS: We really appreciate and
18 are fortunate to be here and to present our
19 technology to the Panel. We are very grateful to
20 the Panel and FDA for their thoughtful comments.

21 We believe that the risk/benefit profile
22 for this product for this profile is favorable and

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1 that the technology will play an important role in
2 the patient care.

3 Once again, on behalf of CryoCath, I
4 would like to thank the Chairman, Panel members,
5 and ladies and gentlemen for letting us present our
6 technology. Thank you.

7 CHAIRMAN LASKEY: Thank you, sir.

8 Before we proceed with the motion, I
9 would like to ask our industry and consumer
10 representatives if they have any final thoughts,
11 beginning with Mr. Morton.

12 MR. MORTON: Just to thank the sponsor
13 for a clear and good presentation of data and
14 clinical utility of the device, and thank the
15 Panel. This is exactly the sort of decision that
16 the agency needs Panel input on, new technology and
17 the outcomes not being crystal-clear. So thanks
18 very much.

19 CHAIRMAN LASKEY: Mr. Hughes?

20 DR. HUGHES: Thank you Dr. Laskey. Let's
21 see, I know it's late in the day and I would like
22 to be brief, should be brief. If it wasn't for

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1 spring break, I would have done a three-hour
2 lecture at my institution.

3 I think that, first of all, I appreciate
4 the presentation by the manufacturer and the FDA,
5 as well as the comments and discussion by my
6 colleagues. I think that there were a couple of
7 points that I really would like to highlight some
8 that have come around.

9 That is one with regards to learning
10 curves and being able to translate whatever level
11 of success the device has to other physicians,
12 other surgeons, and certainly a concern when it
13 comes to the consumer. The consumer I think of as
14 being the patient, as opposed to his or her learned
15 agent; that is, the surgeon or physician.

16 I also appreciate the comments of Dr.
17 White having to do with labeling and mechanical
18 valves; that is, making sure that the labeling does
19 not say specifically or does not indicate that it
20 might be okay to traverse mechanical valves, as
21 well as representativeness of any studies, minority
22 representation, gender representation, things like

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1 that.

2 I think overall, though, this particular
3 device does need in some form more study, more
4 statistical study to assure its efficacy for the
5 patient. This particular kind of study or set of
6 studies I would think could take the form of
7 perhaps post-approval studies. But, otherwise, I
8 think that from the perspective of alternatives,
9 the consumer/the patient should have alternatives,
10 and in that regard the physician, of course, should
11 have alternatives at his or her disposal.

12 I think that this device conceptually
13 theoretically looks very, very promising, but I
14 think that there are additional studies more
15 specific to the intent as opposed to taking the
16 OPCs and applying them. Anyway, more specific
17 studies would be nice and they could take the form
18 of post-approval studies.

19 Thank you.

20 CHAIRMAN LASKEY: Thank you, sir.

21 I would like to quickly, hopefully, open
22 the public hearing. Anyone in the audience who

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1 wishes to address the Panel on today's topic before
2 we vote?

3 (No response.)

4 Thank you. If not, we will close the
5 open public hearing.

6 I would like to ask Geretta to read the
7 voting options.

8 MS. WOOD: "The medical device amendments
9 to the Federal Food, Drug, and Cosmetic Act, as
10 amended by the Safe Medical Devices Act of 1999,
11 allows the Food and Drug Administration to obtain a
12 recommendation from an expert advisory panel on
13 designated medical device Pre-Market Approval
14 Applications, PMAs, that are filed with the agency.

15 "The PMA must stand on its own merits,
16 and your recommendation must be supported by safety
17 and effectiveness data in the application or by
18 applicable publicly-available information.

19 "Safety is defined in the Act as
20 reasonable assurance, based on valid, scientific
21 evidence, that the probable benefits to health
22 under conditions on intended use outweigh any

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1 probable risks.

2 "Effectiveness is defined as reasonable
3 assurance that in a significant portion of the
4 population the use of the device for its intended
5 uses and conditions of use, when labeled, will
6 provide clinically-significant results.

7 "Your recommendation options for the vote
8 are as follows: approval if there are no
9 conditions attached, approvable with conditions.
10 The Panel may recommend that the PMA be found
11 approvable subject to specified conditions such as
12 physician or patient education, labeling changes,
13 or a further analysis of existing data. Prior to
14 voting, all of the conditions should be discussed
15 by the Panel.

16 "Not approvable. The Panel may recommend
17 that the PMA is not approvable if the data do not
18 provide a reasonable assurance that the device is
19 safe, or if a reasonable assurance has not been
20 given that the device is effective, under the
21 conditions of use prescribed, recommended, or
22 suggested in the proposed labeling.

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1 "Following the voting, the Chair will ask
2 each Panel member to present a brief statement
3 outlining the reasons for their vote."

4 CHAIRMAN LASKEY: I now ask for a motion
5 on the PMA. Anyone? I now ask for a motion on the
6 PMA. May I have a motion?

7 DR. TRACY: I am making this motion as an
8 electrophysiologist with the understanding that the
9 reasonable safety and effectiveness of this device
10 has been shown. I move to approve with conditions.

11 CHAIRMAN LASKEY: Is there a second?

12 DR. GILLIAM: I second.

13 CHAIRMAN LASKEY: It has been moved and
14 seconded that the motion to approve with conditions
15 move forward. May I have condition one for the
16 PMA?

17 DR. TRACY: The first condition would be
18 some minor modification in the labeling to include
19 cryoglobulinemia as a contraindication to
20 cryoablation.

21 CHAIRMAN LASKEY: Do we have a second?

22 DR. GILLIAM: Second.

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1 CHAIRMAN LASKEY: Do you need a count for
2 these? Can we have a hand-raising response to the
3 second, the seconding of the first condition that
4 Cindy just raised?

5 All members in agreement with
6 cryoglobulinemia to be added to the labeling,
7 please raise hands.

8 (Show of hands.)

9 It looks like unanimous.

10 This is new for me, too, Rosie.

11 DR. KRUCOFF: Can I ask a clarification,
12 Mr. Chairman?

13 CHAIRMAN LASKEY: Yes, I was just about
14 to invite the Panel discussion on this condition.

15 DR. KRUCOFF: Oh, it isn't about the
16 condition.

17 CHAIRMAN LASKEY: Oh.

18 DR. KRUCOFF: I am trying to understand
19 what we have moved in terms of the indication for
20 ablation and/or the indication for mapping.

21 DR. TRACY: That's a condition. We have
22 moved for, what I was moving to approve was for the

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1 condition of ablation in patients with AVNRT.

2 DR. KRUCOFF: And the other one was in
3 the --

4 CHAIRMAN LASKEY: We had previously
5 agreed, before we got to this point, to strike the
6 second bullet. Is that correct?

7 DR. ZUCKERMAN: Right, but right now we
8 are voting to discuss each condition. You're going
9 to vote on each condition of approval, and you're
10 going to put the package together.

11 So you have started with labeling
12 Condition No. 1, which refers back to
13 cryoglobulinemia. You want to discuss that and
14 have a vote.

15 DR. TRACY: We had the vote. We did vote
16 on that, yes.

17 CHAIRMAN LASKEY: We had the vote.

18 DR. ZUCKERMAN: Fine.

19 CHAIRMAN LASKEY: There didn't seem to be
20 a lot of discussion.

21 DR. ZUCKERMAN: Then, Dr. Tracy,
22 Condition No. 2?

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1 DR. TRACY: Condition No. 2 is that we
2 strike the cryomapping from the indication.

3 CHAIRMAN LASKEY: Discuss first or
4 before? Yes. Do we have a second?

5 DR. GILLIAM: Second.

6 CHAIRMAN LASKEY: We do.

7 DR. PAGE: I would just like to state
8 that I think it's useful to have that in there.

9 CHAIRMAN LASKEY: Okay, there's the
10 discussion. Okay, let's vote on the second
11 condition then.

12 All in favor of striking the second
13 bullet from the current IFU?

14 (Show of hands.)

15 One, two, three, four, five in favor.

16 All against?

17 (Show of hands.)

18 One, two, three, four, five against.

19 DR. ZUCKERMAN: Okay, it's important to
20 state who is in favor and who is against the vote
21 for the record.

22 CHAIRMAN LASKEY: I have to name my

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1 colleagues in public?

2 DR. ZUCKERMAN: Yes.

3 (Laughter.)

4 CHAIRMAN LASKEY: How about we do it
5 henceforth or do you want another vote? Let's do
6 this procedurally correct then. Let's just do the
7 hand vote again.

8 All in favor of Cindy's second condition,
9 which is the elimination of the second bullet?

10 (Show of hands.)

11 In favor are Cindy, Dr. Dullum, Kent
12 Bailey, Mitch Krucoff, and Dr. Gilliam.

13 Okay, and those against this condition?

14 (Show of hands.)

15 Drs. Haigney, Vetrovec, Waldo, Aziz, and
16 Page.

17 I've never had to do that. All right.
18 It's five/five.

19 MS. WOOD: If you voted against the
20 condition, could you please raise your hand again?

21 I missed -- okay.

22 CHAIRMAN LASKEY: One, two, three, four,

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1 five.

2 MS. WOOD: Okay.

3 CHAIRMAN LASKEY: It's five/five.

4 Okay, is there a third condition?

5 DR. TRACY: Yes, a third condition --

6 DR. ZUCKERMAN: Well, we need to decide
7 what's going on with this condition.

8 CHAIRMAN LASKEY: Of course.

9 (Laughter.)

10 You need a tie-breaker?

11 DR. ZUCKERMAN: Yes.

12 CHAIRMAN LASKEY: Well, I vote with the
13 group that recommends striking it.

14 The third?

15 DR. TRACY: I move that a formal training
16 program, the details of which can be worked out at
17 a later date, be part of the approval.

18 CHAIRMAN LASKEY: A second?

19 DR. GILLIAM: Second.

20 CHAIRMAN LASKEY: Thank you. Do we have
21 any discussion on this one?

22 (No response.)

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1 Let's have a hand vote for all in favor
2 of the training criteria to be elaborated
3 subsequently, articulated subsequently.

4 (Show of hands.)

5 Drs. Haigney, Cindy, Dullum, Vetovec --
6 we have unanimous agreement on this, and I would
7 agree with that, too. That's the third condition.

8 Is there a fourth?

9 DR. TRACY: Maybe. I move that there be
10 post-market surveillance to monitor for the
11 incidence of AV block.

12 CHAIRMAN LASKEY: May I have a second?

13 DR. HAIGNEY: Second.

14 CHAIRMAN LASKEY: And a vote?

15 DR. DULLUM: Can we have discussion?

16 CHAIRMAN LASKEY: Oh, I'm sorry.

17 DR. DULLUM: Yes. I just want to go back
18 to, is that going to require a thousand patients,
19 do we think, and how is that going to be trackable
20 and relevant, the less than 1 percent incidence
21 most places?

22 CHAIRMAN LASKEY: It depends on what

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1 happens, I guess. All right, surveillance for a
2 relatively-rare event, although not astonishingly
3 rare, if we think it is on the order of 1 percent?

4 Kent, what would be a reasonable --

5 DR. BAILEY: Well, if it's really 1
6 percent, then you can never show that it's less
7 than 1 percent. If it's really very low, like one
8 in a thousand, then you should be able to show it
9 in a few hundred patients.

10 CHAIRMAN LASKEY: And that would be the
11 goal?

12 DR. BAILEY: But if it is a percent, then
13 it sounds like what I'm hearing is that it's not
14 necessarily any advantage over RF. So I think
15 you're really trying to show that it's better,
16 which would lead to, presumably, a lower sample
17 size.

18 CHAIRMAN LASKEY: Than the equivalent,
19 yes.

20 MR. MORTON: I have a question on this to
21 the agency, Dr. Zuckerman. Is post-market
22 surveillance actually not an early-warning system,

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1 something that we would look for for an event that
2 we suspect could happen, an adverse event that we
3 suspect could happen? In this case, we actually
4 suspect just the opposite?

5 DR. ZUCKERMAN: Right. Again, I think
6 there are two issues. One, we want to distinguish
7 the need for post-market surveillance versus the
8 need for addressing interesting scientific
9 questions. Certainly, if someone wants to go out
10 and organize this registry of "X" thousand patients
11 to definitively prove that the incidence of heart
12 block is less with one form of therapy than the
13 other, that's a very interesting scientific
14 question, but it's not necessarily in the purview
15 of the FDA's post-market authority.

16 The agency would be more interested in
17 perhaps the following question: Perhaps if you add
18 a certain delta to that 1 percent level, and
19 proposed a registry and the incidence of heart
20 block is unexpectedly a safety problem because it
21 is coming in at 3, 4, 5 percent, but I think one
22 needs to pose the right post-market question here

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1 initially: What is the question?

2 DR. HAIGNEY: Yes, I think the question
3 is not, is it better than RF ablation? I think it
4 is, is it worse than RF ablation? So I would be
5 interested if the incidents maybe blocked were 2
6 percent. I would consider that an important factor
7 that I would want to know before I used the
8 catheter.

9 DR. DULLUM: Well, wouldn't it be a
10 reportable event anyway, MDR, or not, AV block?

11 CHAIRMAN LASKEY: But, Mark, doesn't that
12 presuppose some kind of simultaneous or concurrent
13 control or would you resort back to the literature
14 for comparison?

15 DR. HAIGNEY: I would resort to the
16 literature.

17 CHAIRMAN LASKEY: I mean, I personally
18 don't see what's wrong with a surveillance that
19 looks for the incidence of complete heart block in
20 "X" consecutive patients undergoing this procedure.
21 I'm not allowed to -- right, but that's my concept
22 of the surveillance; it's not necessarily a study,

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1 but it's an observational approach to event-
2 collecting.

3 DR. HAIGNEY: We were having trouble
4 trying to find a number of patients that we want in
5 the registry, and I'm saying that I don't think we
6 need to look for the high standard of less than 1
7 percent incidence. Do you see what I'm saying?
8 I'm proposing a more liberal --

9 CHAIRMAN LASKEY: Yes, but my point is we
10 can do better than 150 patients. I think we can
11 come up with a better estimate with more than 150
12 patients, which is exactly what a post-marketing
13 survey would do for us.

14 DR. HAIGNEY: If I have learned anything
15 today, Dr. Laskey, it's that we need more than 150
16 patients.

17 DR. WALDO: Would it be permissible to
18 use people in other countries or would it only be
19 people in the United States? My question is, in
20 this surveillance, would it only be post-marketing
21 in the United States or could they use worldwide
22 information?

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1 CHAIRMAN LASKEY: You would have to ask
2 the agency for how they would receive that data.

3 DR. ZUCKERMAN: Again, what is the
4 question --

5 DR. WALDO: But you get it much faster
6 with worldwide, the numbers anyway.

7 DR. ZUCKERMAN: Right, but what is the
8 question being asked? The question that we would
9 like to ask is, for the label indication, is there
10 an unusual safety problem that produces heart
11 blocks, say, in 3 percent of patients?

12 So if you were convinced that outside
13 U.S. data was being utilized, was being obtained in
14 that intended patient population, then, yes, a
15 large simple registry, both U.S. and OUS patients,
16 might be applicable. On the other hand, if the OUS
17 data contains patients who are being treated
18 multiple other indications, it's not going to help
19 us answer the question.

20 DR. TRACY: I think that the intent of
21 the condition is to identify an unusually large
22 number of AV blocks, an unanticipated number of AV

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1 blocks. I think that right now I'm not certainly
2 prepared to say what that number of patients would
3 be required, but I think we could statistically
4 come up with something that would be a reasonable
5 number of patients to survey for that phenomenon.

6 CHAIRMAN LASKEY: Yes, I agree. I don't
7 think we should be on the hook for the study design
8 and the sample size, but I think we're simply
9 recommending that this be an additional condition.

10 I think it is designable. This is a study which
11 is designable.

12 DR. WALDO: So can we move the question?

13 CHAIRMAN LASKEY: So, therefore, we need
14 to vote on the fourth condition, which calls for
15 the configuration of a post-marketing surveillance
16 for the event of complete heart block in a sample
17 size to be defined.

18 May I see all in favor?

19 (Show of hands.)

20 Drs. Haigney, Cindy, Dullum, Kent, Waldo,
21 Aziz, Page, and Gilliam.

22 And those against?

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1 (Show of hands.)

2 Dr. Vetovec. Okay.

3 DR. VETROVEC: I guess I am supposed to
4 state why. My position would be, I think,
5 reflecting the industry comment, which is we're
6 really doing this because of our interest. We
7 don't think there is a problem with heart block.
8 We think there's not a problem with heart block,
9 but that's not sort of the spirit of a post-
10 marketing surveillance.

11 DR. GILLIAM: But we don't know that
12 there's not, and I think that's why the post-
13 marketing is necessary. We haven't been presented
14 enough data to show that this is, in fact --

15 DR. VETROVEC: I would suggest you not
16 suggest that when you're trying to convince some of
17 us that, because you're already off the beam, that
18 may be one of its advantages.

19 CHAIRMAN LASKEY: Okay. Any further
20 conditions, Cindy?

21 DR. TRACY: Not for me.

22 CHAIRMAN LASKEY: So we have a motion.

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1 We have conditions.

2 DR. ZUCKERMAN: Okay, so now you're going
3 to --

4 CHAIRMAN LASKEY: Do we need to raise any
5 other conditions? Are there any other conditions
6 that any other members of the Panel want to raise
7 besides Cindy?

8 (No response.)

9 Good. All right, and I think at this
10 point we're ready to vote on the motion presented,
11 which is to move to approve with the following five
12 conditions:

13 To add the contraindication that patients
14 with cryoglobulinemia be excluded from
15 consideration for this treatment.

16 The second condition being that we strike
17 the second bullet on the IFU pertaining to the
18 mapping.

19 The third condition being the
20 establishment of a better-articulated and more-
21 specific training criteria, perhaps including the
22 number of cases for a learning curve.

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1 The fourth condition being -- there's
2 only four conditions here -- being the post-market
3 surveillance for heart block as a measure of safety
4 of the procedure.

5 So the one motion with four conditions.

6 DR. KRUCOFF: Do we discuss the motion
7 itself?

8 DR. ZUCKERMAN: Sure.

9 CHAIRMAN LASKEY: Yes, we can, as is.
10 That's en bloc now, yes, before we vote. Sir?

11 DR. KRUCOFF: I would just like, before
12 we vote, to encourage everybody to think about what
13 this vote means beyond just this product, but with
14 regard to the process of designing a trial
15 prospectively between a sponsor and the agency, and
16 then having to expend this kind of energy to really
17 salvage what amounts to the wrong trial or a trial
18 whose pivotal data suggests the opposite of what
19 you're intuitively inclined to do.

20 That may well be the right decision for
21 this device, but what it will stop is any ability
22 to answer that question, and whether it will roll

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1 over to then, as a precedent, for future studies to
2 leave it to this body to bail out trial designs
3 that don't answer the questions that actually are
4 brought forward as an indication question, and I'm
5 really concerned about that.

6 It's really not an issue of whether --
7 you know, I don't think there's any question about
8 the diligence with which this trial was done, about
9 the interest of the sponsor of bringing this device
10 forward, or about the interest and the passion of
11 the investigators who have had their hands on it.
12 In fact, we're looking at a very similar situation
13 upcoming with a coronary device.

14 But I really do think that the process of
15 prospectively designing a clinical trial that
16 actually addresses a question that has to do with
17 an indication is a vital process. If we decide to
18 vote around that today, that there's a bigger issue
19 that impacts by setting that precedent that
20 ultimately this body would be put in a position to
21 suggest to the FDA or for a sponsor to rely on to
22 bail out having done the wrong trial, or whatever,

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1 to bring a device forward. So I'm really concerned
2 about where we go with this.

3 CHAIRMAN LASKEY: I think we all
4 appreciate that. The reason we're here until six
5 o'clock is because we were giving due diligence to
6 the process and realizing how the serious the task
7 is.

8 So it being six o'clock and with those
9 reminders, let's vote. May I see, by a show of
10 hands, all in favor for approval with the
11 conditions as enumerated?

12 (Show of hands.)

13 In favor for: Drs. Haigney, Tracy,
14 Dullum, Waldo, Aziz, Page, and Gilliam.

15 And those against?

16 Drs. Vetovec, Bailey, and Krucoff.

17 How did Dr. White vote?

18 DR. ZUCKERMAN: He didn't vote.

19 CHAIRMAN LASKEY: He didn't? He did, but
20 he didn't.

21 DR. ZUCKERMAN: But you could guess.

22 (Laughter.)

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1 CHAIRMAN LASKEY: Okay.

2 DR. ZUCKERMAN: Dr. White, for the
3 record, is no longer present.

4 CHAIRMAN LASKEY: So the motion passes by
5 a vote of six to three.

6 I would like to spend 60 seconds or less
7 for each member of the Panel to please state your
8 name and the reason for your vote, please. Dr.
9 Haigney?

10 DR. HAIGNEY: Mark Haigney. I thought
11 the sponsor showed that the device is safe. I
12 think that the clinical trial, as it was designed,
13 it was entirely appropriate because of the way this
14 device is going to be used. I think I'll stop at
15 that point.

16 DR. TRACY: Cindy Tracy, and I voted for
17 approval because I think the sponsor has shown
18 reasonable safety and effectiveness for the device.

19 DR. DULLUM: Mercedes Dullum. I voted
20 for approval because of showing the reasonable
21 safety and efficacy.

22 DR. VETROVEC: I voted against because I

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1 think that every time we say something is
2 reasonable but it didn't hit the target that the
3 sponsors said they would hit, we're really leaving
4 ourselves open for question as to why we made that
5 decision. I'm not comfortable in this
6 circumstance, and would almost like to encourage
7 this as a reason that people really should answer
8 the question that they set out to or set up studies
9 that approach that.

10 CHAIRMAN LASKEY: Yes, I think that today
11 this has probably been one of the more difficult
12 sharp edges to sit on. We didn't have with support
13 what our clinical intuition suggested.

14 I would strongly recommend, just as a
15 personal opinion, that we relook at the concept of
16 OPCs. They're moving targets, particularly in the
17 technologic arena, where things move awfully
18 dramatically and they can be better or worse within
19 a six-month period of time as the numbers
20 accumulate. So I would be wary of those kinds of
21 strawmen basically to design a study, and there's
22 nothing like a good, old, randomized, controlled

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1 trial that, hopefully, will answer the question
2 with more statistical rigor.

3 DR. BAILEY: Kent Bailey. I voted
4 against approval based on the evidence that was
5 presented today. Although I think the sponsor
6 demonstrated reasonable efficacy, that is not --
7 although the device works in a vacuum, you can't
8 look at that in a vacuum.

9 It's probably not as efficacious as the
10 other conventional approach. So, well, maybe it's
11 safer. Well, it didn't met the safety standard
12 either. So we can't really say that it's safer.

13 But, well, it has less heart block, but
14 we don't have the evidence to show that either.
15 So, potentially it's not as good in any of those
16 three categories.

17 I also agree with the process question,
18 that this is a bad precedent to set, although I
19 think it is a very promising device and I would
20 have liked to have seen data presented that showed
21 that it was as good or superior in at least one
22 category.

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1 DR. WALDO: Dr. Waldo. I voted for. I
2 would like to just second what Dr. Laskey said. I
3 think he said it succinctly and well after a long
4 afternoon.

5 I voted for it because I thought that the
6 efficacy and safety was reasonably presented and
7 reasonably demonstrated. I really think that it
8 would serve us well to relook at some of the
9 criteria that were the strawmen in this target, the
10 strawmen targets in this study. Thanks.

11 DR. AZIZ: Salim Aziz. I voted in favor
12 of the device because I think, firstly, it showed
13 relative safety and efficacy. I think it adds a
14 new way of dealing with a somewhat difficult
15 problem for the EP and people, and, hopefully, with
16 the surveillance the evidence will bear out the
17 fact that it has a low incidence of problem.

18 DR. PAGE: Rick Page. I was convinced by
19 the evidence that there is reasonable assuredness
20 that this device is efficacious and safe, and I
21 think it will be a useful tool to the clinical
22 electrophysiologist.

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1 DR. KRUCOFF: Mitch Krucoff. I voted
2 against because, while it is obvious that from the
3 user's point of view, this really does look like a
4 promising device, that the lesson we have is that
5 intuition in medicine is a very dangerous direction
6 to follow exclusively, and that's why we do
7 clinical trials. In this particular clinical
8 trial, neither the safety or the efficacy data
9 landmarks were hit.

10 An OPC trial, by and large, we consider
11 to be an easier target to hit than a randomized
12 trial, and that's why I voted against it.

13 DR. GILLIAM: Roosevelt Gilliam. I voted
14 for the motion, aware that it did not meet the OPC
15 trials of radiofrequency device, a device that has
16 an extraordinarily high standard of success and
17 safety that's been proven over years.

18 I recognize that this device, I felt,
19 demonstrated it has a reasonable degree of safety
20 and efficacy, although both may be close to, or at
21 least falling short of, the accepted
22 radiofrequency, it provides a different approach to

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1 a very difficult problem. So it provides an
2 additional tool.

3 I think that insofar as this is not to
4 replace radiofrequency ablation, I think the data
5 so we can have a relative appreciation of its
6 safety was there, and I was comfortable with that
7 level of safety. Thus, I voted for the device.

8 CHAIRMAN LASKEY: Mr. Morton, Mr. Hughes,
9 any final words? No?

10 DR. HUGHES: Yes, I have just a quick
11 comment to send out to the manufacturer, and that
12 is, with regards to the post-market surveillance, I
13 feel like in the long run that it will be a good
14 thing for the manufacturer.

15 In fact, I think we have been, or the
16 Panel has been, somewhat mild with regards to those
17 recommendations with regards to post-market
18 surveillance. A very thorough kind of post-
19 approval study I think would be in order, including
20 such things as the potential for cryomapping. I
21 think that, once again, in the long run this would
22 be beneficial not only to the consumer, to the

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1 patient, but also to the manufacturer overall.

2 There are regulatory kinds of issues that
3 have to be taken care of by the FDA, but that does
4 not preclude the manufacturer from taking
5 additional steps voluntarily, and I want to urge
6 the manufacturer to consider that as it goes
7 forward.

8 Thank you.

9 CHAIRMAN LASKEY: Okay, on behalf of the
10 Panel members, I want to thank the sponsor for a
11 superb presentation and for sitting here with us
12 until this late hour. Thank you again.

13 This concludes the report and
14 recommendations of the Panel on PMA P020045 from
15 CryoCath Technologies for the Freezor Cardiac
16 Cryoablation Catheter for cryoablation of cardiac
17 tissue to treat patients with AV tachycardia.

18 Thank you again, and good evening.

19 (Whereupon, the foregoing matter was
20 concluded at 6:06 p.m.)

21

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