

UNITED STATES OF AMERICA
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

* * *

MEDICAL DEVICE DISPUTE RESOLUTION PANEL

* * *

Thursday, April 19, 2007

The meeting came to order at 8:30
am in the Grand Ballroom of the Holiday Inn
Gaithersburg, 2 Montgomery Village Avenue,
Gaithersburg, Maryland.

PRESENT:

SCOTT D. RAMSEY, M.D., Ph.D., CHAIRPERSON
WARREN S. BROWNER, M.D., MPH, VOTING MEMBER
JONATHAN D. SACKNER-BERNSTEIN, M.D., VOTING
MEMBER
JOHN W. HIRSHFELD, M.D., TEMPORARY VOTING
MEMBER
CHRISTOPHER H. SCHMID, Ph.D., TEMPORARY VOTING
MEMBER
DAVID J. SLOTWINER, M.D., TEMPORARY VOTING
MEMBER
CONNIE F. WHITTINGTON, NSN, RN, CONSUMER
REPRESENTATIVE
MELISSA WALKER, MS, RAC, INDUSTRY
REPRESENTATIVE
NANCY COLLAZO-BRAIER, Ph.D., EXECUTIVE
SECRETARY
LES S. WEINSTEIN, ESQ., CDRH OMBUDSMAN

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

C O N T E N T S

PAGE

Introductions 3

Deputization of Voting Members and Conflict of
Interest Statements 11

Open Public Hearing 16

Cardima Presentation 17

ODE Presentation 111

Cardima Follow Up/Rebuttal..... 185

ODE Follow Up/Rebuttal..... 199

Public Hearing..... 213

Open Committee Discussion..... 235

ODE Summation..... 311

Cardima Summation..... 315

Panel Deliberation and Vote..... 321

Adjourn

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

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

2 (8:54 a.m.)

3 CHAIRPERSON RAMSEY: I would like
4 to call this meeting of the Medical Devices
5 Dispute Resolution to order.

6 I'm Scott Ramsey. I'm the
7 Chairperson of the Medical Devices Dispute
8 Resolution Panel. My expertise is that I am
9 an internist, and I have expertise in
10 technology assessment of medical devices.

11 If any of you haven't already done
12 so, please sign the attendance sheets that are
13 on the tables by the doors. Also, if you wish
14 to address this panel during one of the open
15 sessions, please provide your name to Ms. Ann
16 Marie Williams at the registration table.

17 Is she out front? Could you raise
18 your hand? Okay. Thank you.

19 I note for the record that the
20 voting members present constitute a quorum as
21 required by 21 CFR Part 14. I would also like
22 to add that the panel participating in this
23 meeting today has received training in FDA
24 device law and regulations.

25 So I'll now have the panel members

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 introduce themselves, and I would ask that
2 they start by stating their name, area of
3 expertise, position and affiliation, and we'll
4 start on the left.

5 MS. WHITTINGTON: Yes, my name is
6 Connie Whittington. I'm the Director of
7 Nursing Systems at Piedmont Hospital in
8 Atlanta, Georgia. My position on this panel
9 is as the consumer representative. I serve in
10 that capacity as an advocate for those people
11 in the public who would receive these devices
12 implanted.

13 I am a clinical researcher. My
14 clinical expertise is orthopedics, but I can
15 use and translate those same techniques and
16 approaches to science and data, whichever
17 device it's related to.

18 DR. SACKNER-BERNSTEIN: Jonathan
19 Sackner-Bernstein. I'm trained as a
20 cardiologist largely with a focus in heart
21 failure and heart failure devices; currently
22 the chief medical officer at CLINLABS in New
23 York City.

24 DR. BROWNER: I'm Warren Browner.
25 I'm an internist and an epidemiologist and

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 currently the Vice President and Scientific
2 Director of the Research Institute at
3 California Pacific Medical Center and an
4 adjunct professor of medicine and epidemiology
5 and biostatistics at the University of
6 California, San Francisco.

7 DR. SLOTWINER: I am David
8 Slotwiner. I'm a cardiac electrophysiologist
9 practicing at North Shore and Long Island
10 Jewish Medical Centers and Albert Einstein
11 College of Medicine. I've primarily practiced
12 clinical electrophysiology and performed
13 clinical research as well as education.

14 DR. HIRSHFELD: I'm John Hirshfeld.
15 I'm an interventional cardiologist at the
16 University of Pennsylvania at Philadelphia.

17 DR. SCHMID: I'm Chris Schmid.
18 I'm a statistician, and I'm a professor at
19 Tufts University School of Medicine and
20 Director of the Biostatistics Research Center
21 at Tufts New England Medical Center.

22 MS. WALKER: I'm Melissa Walker.
23 I'm a zoologist by education and a regulatory
24 professional by vocation. I am the Senior
25 Vice President for Regulatory Quality and

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 Clinical for Stereotaxis.

2 CHAIRPERSON RAMSEY: Thank you all.

3 Now I'll ask the ombudsman and the
4 Executive Secretary to introduce themselves.

5 MR. WEINSTEIN: Good morning. I'm
6 Les Weinstein. I'm the ombudsman in FDA
7 Center for Devices and Radiological Health,
8 and one of my roles is to facilitate the
9 equitable resolution of disputes between
10 offices in CDRH and device sponsors,
11 applicants, and manufacturers.

12 I convened today's dispute
13 resolution panel meeting at the request of
14 Cardima, Incorporated, to resolve a scientific
15 dispute between Cardima and the Office of
16 Device Evaluation, ODE.

17 I want to publicly thank the panel
18 members for agreeing to participate in this
19 important meeting and to wish them well in
20 their deliberations.

21 Thank you.

22 DR. COLLAZO-BRAIER: Good morning.

23 I'm Nancy Collazo-Braier, and I'm the
24 Executive Secretary of this panel.

25 CHAIRPERSON RAMSEY: Thank you

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 both.

2 I'd also like to identify the FDA's
3 press contact, who is Karen Riley.

4 Karen, can you? There she is right
5 there in the back.

6 Also, if you all could do us a
7 favor and silence your cell phones, we'd be
8 grateful about that. I'm now going to read
9 the summary of the scientific issues under
10 dispute as summarized by the ombudsman.

11 This meeting is being held at the
12 request of Cardima, Incorporated to resolve
13 the scientific dispute between Cardima, the
14 sponsor of premarket approval Application
15 P020039, as amended, for the Revelation Tx
16 Microcatheter Ablation System and the Office
17 of Device Evaluation, ODE, in FDA's Center for
18 Devices and Radiological Health.

19 The Revelation Tx Microcatheter
20 system is the subject of this PMA application.

21 The system consists of a single use,
22 steerable, multi-electrode ablation
23 microcatheter with an automatic flexible, non-
24 electrically active tip, and a single use
25 deflectable NavAblator hot tip ablation

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 catheter, 8-French, with an electrically
2 active tip.

3 Accessories to the system include
4 Cardima's support catheter, NaviPort, cleared
5 under K-974683; the select switchbox and
6 associated connecting cables.

7 The Phase 3 study protocol
8 specified that the NavAblator catheter was
9 optionally available for the ablation of the
10 isthmus after first attempting to create a
11 linear burn with the Revelation Tx.

12 The Revelation Tx Microcatheter
13 Ablation System manufactured by Cardima,
14 Incorporated, has as its proposed indication
15 for use the treatment of atrial fibrillation
16 in patients with drug refractory paroxysmal
17 AF.

18 The Office of Device Evaluation, or
19 ODE, has determined that the Cardima premarket
20 approval application, P-020039, is not
21 approvable because the clinical study design
22 and results were inadequate to demonstrate a
23 reasonable assurance of safety and
24 effectiveness of the Revelation Tx
25 Microcatheter Ablation System, indicated for

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 the treatment of drug refractory paroxysmal
2 atrial fibrillation.

3 ODE believes that the safety and
4 effectiveness information collected thus far
5 provides some support for the safety and
6 effectiveness of the device, but fundamental
7 problems with the study design limit the
8 conclusions that can be drawn from these data.

9 The deficiencies outlined by ODE
10 include, but are not limited to the following:
11 the lack of a control arm made the trial
12 susceptible to placebo effects. The clinical
13 study lacked an accurate measurement of
14 effectiveness endpoints due to several
15 confounding factors, and the data provided
16 demonstrates that the NavAblator was not
17 sufficiently effective in creation of bi-
18 directional conduction block, BDB, at the
19 cavotricuspid isthmus.

20 Cardima disagrees with ODE's not
21 approvable determination and the reasons for
22 it. Cardima concludes that the data and
23 information are sufficient to support a
24 determination that there is a reasonable
25 assurance that the device is safe and

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 effective for its intended use in conformity
2 with applicable statutory and regulatory
3 requirements.

4 Specifically, Cardima asserts that
5 the PMA as amended should be approved because
6 the trial was well controlled and the primary
7 endpoint was met, and the procedure specified
8 in the study protocol, amplitude reduction, is
9 an acute procedural endpoint sufficient for a
10 trained practitioner.

11 Cardima believes that the results
12 of the single arm pivotal trial are reliable
13 and sufficient to provide reasonable assurance
14 of effectiveness for the device that's
15 labeled, and that adequate directions for use
16 can be developed for use of the device.

17 Thus, the dispute resolution panel
18 to whom Cardima has appealed the not
19 approvable decision will be charged with
20 reviewing and making a recommendation to the
21 CDRH Center Director as to the approvability
22 of the PMA, that is, does the PMA as amended
23 provide valid scientific evidence that
24 demonstrates a reasonable assurance of the
25 safety and effectiveness of the Revelation Tx

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 Microcatheter Ablation System for its intended
2 use in the specified patient population?

3 The summary of scientific issues in
4 dispute is an overview. It is not intended to
5 be a full and detailed statement of all such
6 issues and arguments that will be presented at
7 the panel meeting by ODE and the sponsor.

8 Specifically, ODE is to present
9 data and analyses to support its not
10 approvable determinations and Cardima is to
11 present its reasons for disputing the not
12 approvable determinations.

13 This was signed by Les Weinstein,
14 CDRH Ombudsman, March 21, 2007.

15 Dr. Braier.

16 DR. COLLAZO-BRAIER: I will now
17 read the deputization of temporary voting
18 members' statement and the conflict of
19 interest statement.

20 Appointment to temporary voting
21 status statement. Pursuant to the authority
22 granted under the Medical Devices Advisory
23 Committee Charter, dated October 27th, 1990,
24 and as amended August 18, 1999, I appoint the
25 following individuals as voting members to the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 Medical Devices Dispute Resolution Panel for
2 this meeting on April 19, 2007:

3 Christopher H. Schmid, Ph.D.

4 John Hirschfeld, M.D.

5 David Jan Slotwiner, M.D.

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

13 And this is signed Dan Schultz.

14 I will now read the conflict of
15 interest statement.

16 The Food and Drug Administration is
17 convening today's meeting of the Medical
18 Devices Dispute Resolution Panel of the
19 Medical Devices Advisory Committee under the
20 authority of the Federal Advisory Committee
21 Act, FACA, of 1972.

22 With the exception of the industry
23 representative, all members and consultants of
24 the panel are special government employees or
25 regular federal employees from other agencies

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 and are subject to federal conflict of
2 interest laws and regulations.

3 The following information on the
4 status of this panel compliance with federal
5 ethics and conflict of interest laws covered
6 by, but not limited to those found at 18 USC
7 208 are being provided to participants in
8 today's meeting and to the public. FDA has
9 determined that members and consultants to
10 this panel are in compliance with federal
11 ethics and conflict of interest laws.

12 Under 18 USC 208, Congress has
13 authorized FDA to grant waivers to special
14 government employees who have financial
15 conflicts when it is determined that the
16 agency's need for a particular individual's
17 services outweighs his or her potential
18 financial conflict of interest.

19 Related to the discussions of
20 today's meetings, members and consultants of
21 this panel who are special government
22 employees have been screened for potential
23 financial conflicts of interest of their own,
24 as well as those imputed to them, including
25 those of their employer, spouse or minor

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 child. This interest may include investment,
2 consulting, expert witness testimony,
3 contracts, grants, CRADAs, teaching, speaking
4 or writing, patents and royalties, and primary
5 employment.

6 Today's agenda involves a
7 scientific dispute between the agency and
8 Cardima, Inc., related to the not approvable
9 determination for the premarket approval
10 application of the Revelation Tx Microcatheter
11 with NavAblator ablation system, indicator for
12 the treatment of drug refractory paroxysmal
13 atrial fibrillation.

14 Based on the agenda for today's
15 meeting and all financial interests reported
16 by the panel members and consultants, a
17 conflict of interest waiver has been issued in
18 accordance with 18 USC Section 208(b)(3) to
19 Dr. Scott Ramsey. Dr. Ramsey's waiver
20 involves a consulting interest with a
21 competing technology firm on a topic unrelated
22 to today's agenda. He received between 10,001
23 to 50,000 for this consulting agreement. The
24 waiver allows this individual to participate
25 fully in today's deliberations.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 Copies of these waivers may be
2 obtained by visiting the agency's Website at
3 www.fda.gov/ohrms/dockets/default.htm or by
4 submitting a written request to the agency's
5 Freedom of Information Office, Room 630 of the
6 Parklawn Building.

7 A copy of this statement will be
8 available for review at the registration table
9 during this meeting and will be included as
10 part of the official transcript.

11 Melissa Walker is serving as the
12 industry representative acting on behalf of
13 all related industry and is employed by
14 Stereotaxis, Inc.

15 We would like to remind members and
16 consultants that if the discussions involve
17 any other products or firms not already on the
18 agenda for which an FDA participant has a
19 person or imputed financial interest, the
20 participants need to exclude themselves from
21 such involvement, and their exclusion will be
22 noted for the record.

23 FDA encourages other participants
24 to advise the panel of any financial
25 relationships that they have with any firms at

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 issue.

2 Thank you.

3 Before I turn the meeting back to
4 Dr. Ramsey, here are a few general
5 announcements. Transcripts of today's
6 meetings will be available from Neal Gross &
7 Company, phone number, (202) 234-4433.

8 Information on presenters of
9 today's meeting can be found at the table
10 outside the meeting room. Presenters to the
11 panel in the two open public session hearings
12 today, if they have not already done so,
13 should provide FDA with a hard copy of their
14 remarks, including overheads.

15 I will collect these from you at
16 the podium.

17 CHAIRPERSON RAMSEY: Okay. So we
18 will now proceed with the first open public
19 hearing of the meeting. Here public attendees
20 are given the opportunity to address the panel
21 to present data, information or views relevant
22 to the meeting agenda.

23 Is there anyone now who wishes to
24 speak during the open public hearing?

25 (No response.)

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 CHAIRPERSON RAMSEY: Okay. So
2 there are no requests at this time to speak, I
3 will close the open public hearing, and we
4 will now proceed to Cardima, Inc.'s
5 presentation for the Revelation Tx
6 Microcatheter system, P020039.

7 As Cardima is getting ready, I just
8 want to remind the public observers at the
9 meeting that while this meeting is open for
10 public observation, public attendees may not
11 participate except at the specific request of
12 the panel, and I understand the sponsor will
13 introduce their speakers.

14 So it's to you now.

15 DR. GASTON: Good morning. My name
16 is Richard Gaston. I'm a cardiologist who has
17 had a 25-year clinical practice in the wine
18 country north of San Francisco, Petaluma, and
19 for the past few years I've also been a
20 consultant to the company in various
21 capacities for which I receive a small
22 stipend, and I do own some stock which I paid
23 for.

24 Cardima has developed a 3.7 French
25 multi-electrode, flexible radio frequency

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 catheter, which is very much unlike the
2 standards seven and eight French stiffer radio
3 frequency catheters in use for decades.

4 This is a diagram of the catheter.
5 It shows several electrodes. There are
6 thermocouples on each end, which measures
7 temperature. The thermal injury from each
8 electrode overlaps with its neighbor so that a
9 linear lesion is created. The construction of
10 the catheter allows for a high current density
11 and a little heat sink effect, which is
12 drawing heat away from tissue when compared to
13 standard catheters so that less power is
14 needed to create the same depth of lesion.

15 This is from a canine thigh muscle
16 experiment. I draw your attention to
17 significant depth of lesion with relatively
18 low power along the entire length of the
19 catheter, and this is a picture from an early
20 animal study at Johns Hopkins showing such a
21 linear lesion.

22 Now, the standard catheters in use
23 are very effective and safe for the treatment
24 of the typical super ventricular Tach A
25 arrhythmias such as WPW and AV nodal reentry

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 tachycardia, but appear to be less than ideal
2 to create the long linear lesions required to
3 affect atrial fibrillation.

4 So the company in the late 1990s
5 initiated its pivotal trial using as its model
6 Dr. James Cox's work with the Cox-Maze
7 procedure. Several investigators had shown
8 that right atrial lines were important in
9 achieving the high success rates above 90
10 percent.

11 So the company elected to do a half
12 Maze procedure, if you will, only addressing
13 the right atrium, the thought being that this
14 would be much safer than entering in the left
15 atrium. It would also be a shorter procedure
16 and easier to learn.

17 In the ensuing years there has been
18 a lot of interest and even hype at affecting a
19 cure in the left atrium by affecting triggers
20 or doing some sort of left atrial
21 compartmentalization procedure, and when the
22 company finished its pivotal trial and came
23 before the panel in 2003, clearly right atrial
24 ablation had fallen out of favor.

25 However, results from the left

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 sided only treatments have been variable and
2 clearly, there's a need for more effective
3 technology and a better lesion set, and we
4 think the pendulum is swinging back. There
5 are several published articles recently that
6 include a step-wise approach or a hybrid
7 therapy, and most people now do believe that
8 the right atrium plays an important role in
9 atrial fibrillation and its management.

10 Today we are asking that you vote
11 to approve the system for linear ablation
12 confined to the right atrium in patients with
13 drug refractory paroxysmal atrial
14 fibrillation. The basis of this is the 84
15 patient prospective trial, the amended
16 submission which includes only the Phase 3
17 patients. The trial definitely shows
18 reduction in total AF frequency and
19 improvement in atrial fibrillation symptoms.
20 It meets the definition of valid scientific
21 evidence, and I might add this has been
22 published in the peer reviewed Journal of
23 Interventional Cardiac Electrophysiology.
24 Clearly, safety and efficacy have been
25 established.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 FDA disputes that claim and has
2 identified issues which they say impair
3 analysis of the data and even taint the trial.

4 Now, this comes from a May 2004 nonapprovable
5 letter, and I would remind you that there was
6 a nonapprovable prior to that which involved a
7 different data set and is irrelevant in
8 today's discussion.

9 We are going to address each of the
10 issues in a scientific and referenced fashion.

11 We are fully aware of FDA's concerns about
12 approvability of new products. Nevertheless,
13 protecting the public also means promoting the
14 public good.

15 Atrial fibrillation is a large and
16 growing problem. Standard of care today in
17 2007, as highlighted in a position statement
18 issued by the three major cardiology societies
19 in the United States and Europe in early 2006,
20 includes ablation for all patients after one
21 drug failure and first line for patients who
22 are unable to tolerate medications.

23 This is in spite of the fact that
24 there are no approved devices at this time for
25 atrial fibrillation and no universally

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 accepted lesion set.

2 This is our agenda, and we have
3 some prestigious speakers today, but I'm going
4 to let them introduce themselves.

5 Thank you very much.

6 DR. SAKSENA: Good morning, Dr.
7 Ramsey, members of the panel, ladies and
8 gentlemen. I have the opportunity to be here
9 to present my thoughts on the Cardima
10 application and AF ablation in general.

11 I've been a clinical cardiac
12 electrophysiologist for now three decades, and
13 I've had the privilege of being part of the
14 inflection points in the development of this
15 specialty. So to the great --

16 CHAIRPERSON RAMSEY: Excuse me.
17 I'm sorry to interrupt, but could you just
18 state your name for the record, please?

19 DR. SAKSENA: I'm Sanjeev Saksena,
20 and I'm Professor of Medicine at the Robert
21 Wood Johnson School of Medicine.

22 As I said, I'm a clinical cardiac
23 electrophysiologist for 30 years standing, and
24 I've had an opportunity to be part of the
25 development of this field at important

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 inflection points in this development of
2 treatment.

3 I believe we stand at such an
4 inflection point at this time, and I would
5 like to share with you some of my newer
6 insights and newer therapeutic directions as
7 we look at 2007 and beyond.

8 This slide is taken from a survey
9 on catheter ablation published about a year
10 and a half ago looking at the kind of ablation
11 procedures in practice at the beginning of
12 this century, and what is clearly apparent is
13 that there has been an exponential increase in
14 ablation procedures despite the unavailability
15 of approved devices in the United States.

16 In addition, what is notable is
17 that a particular type of left atrial ablation
18 procedure has dominated the experience, but
19 right atrial linear ablation starting in the
20 mid-'90s has remained at a modest level, but
21 has persisted till 2002 and beyond. And the
22 question must always be asked as to why right
23 atrial ablation has remained in the picture,
24 what it's being used for and are we taking our
25 patients in the right track by the growth of

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 one alone of the opportunities that patients
2 may have? Is this in the patient's interest?

3 Is this a procedure that has the best
4 efficacy or are we exposing our patients to a
5 direction of over sided (phonetic) efficacy
6 and greater risk by not making available other
7 options, part of that problem being the
8 availability of appropriate technology?

9 So what I'll try to share with you
10 in the next few slides is the rationale for
11 the use of right atrial ablation, which was
12 really kind of absent from the thought process
13 in previous years and perhaps in the previous
14 review, and talk a bit towards the end of my
15 presentation of the kinds of patients that
16 benefit from this.

17 In a later segment I'll talk to you
18 about the landscape of efficacy and safety of
19 these procedures, competing procedures, and
20 identification of these patients.

21 Our evolution of atrial
22 fibrillation understanding has really spanned
23 many decades, but the inflection point
24 occurred around 1990 when the long-standing
25 multiple wavelet reentry hypothesis, faster by

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 work of Moe and Alessie was the dominant
2 thought process.

3 In 1995, the bardogrow (phonetic)
4 with Michelle Haissaguerre changed our
5 thinking by the demonstration of triggered
6 focal activity in the palm remains, suggesting
7 that atrial fibrillation was not chaotic and
8 disorganized. That has been our view for over
9 a century.

10 But neither of these two models
11 explains what we see in daily clinical
12 practice, ECG recordings, EP recordings,
13 intracardiac electrograms, and other options
14 suggest that Lewis model of impure flutter
15 that suggested that AF was made up of flutters
16 in organization had fallen into disfavor.
17 This is a typical recording from the pulmonary
18 vein showing that focal activity, suggesting
19 that atrial fibrillation started on the left
20 side.

21 But this what happens in clinical
22 practice, and I can say that just about
23 everybody on the panel who has seen these
24 patients will have seen this phenomenon that
25 occurred in a single day in a patient of ours.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 Here's the start of atrial
2 fibrillation with what appears to be some kind
3 of triggering activity. Here's a termination
4 an hour and a half later with some appearance
5 of organization. Fine atrial fibrillation
6 with no suggestion of organization. What
7 looks like organized coarse atrial
8 fibrillation could even be called a flutter,
9 and another episode which could be a flutter
10 with a different morphology or a different
11 coarse atrial fibrillation.

12 You see this in practice every day,
13 and how do we explain this other than the
14 possibility that this is really a melting
15 (phonetic) part of many tachycardias. So the
16 early logic that pervaded the ablation field
17 was that if arrhythmogenesis of human AF is
18 uniform, we can empirically define the
19 ablation target whether it's the trigger or a
20 substrate. We can devise an empirical
21 ablation procedure. We'll get a high degree
22 of success.

23 The reality is that that has not
24 happened. There are persisting issues. Most
25 clinicians know that genesis of atrial

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 fibrillation varies by presentation and
2 disease state. The pulmonary vein now we know
3 is not the sole origin of even the invariable
4 source in a given patient of atrial
5 fibrillation, and the success rates for left
6 atrial ablation have been declining with
7 increasing surveillance.

8 In this process important lessons
9 from the operating room have been forgotten.
10 This is work from James Cox and his group and
11 Rick Schuesler when he published this data
12 showed that when you could map both atria and
13 the open chest, you could show organized
14 activity in the right atrium, and when Jim Cox
15 stopped operating on the right atrium and his
16 lesion set, his success rate declined and he
17 reintroduced the right atrium into his lesion
18 set.

19 You need to do on line signal
20 analysis of both atria with a high density
21 system, and you need to be able to do bi-
22 atrial mapping to understand the full spectrum
23 of atrial fibrillation. So bi-atrial and
24 regional mapping is needed and should be
25 feasible.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 We know that the surface ECG never
2 reflects the intracardiac arrhythmias. We now
3 believe that multi-focal and bi-atrial
4 triggers are present in both atria, and there
5 is organized atrial activation in atrial
6 fibrillation beyond doubt.

7 So we have combined the use of a
8 bi-atrial catheter array with a three-
9 dimensional mapping system, clearly an off-
10 label kind of combination to try and get at
11 the issue of mapping in the cath lab what Jim
12 Cox did in his operating room, and what we
13 succeed in doing is that we truly get
14 simultaneous beat-to-beat recording. Global
15 mapping is possible in a beat-to-beat basis.
16 We can see this in three dimensional
17 propagation, and we can see both atria to know
18 what we are doing is actually what is actually
19 happening in real time.

20 And as we do that, we have taken
21 down existing concepts. Here's the patient
22 with mitral valve replacement for mitral valve
23 disease who had persistent AF following that.

24 You would expect the disease in the left
25 atrium. This patient's persistent AF came

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 from the right atrium, from a right atrial
2 tachycardia, which was ablated and the patient
3 was free from atrial fibrillation for many
4 years.

5 So the novel insights we have from
6 this mapping approach is both atria are always
7 involved in atrial fibrillation. There is a
8 bi-atrial and multi-focal origin of triggers
9 and organized tachycardias. There is bi-
10 atrial involvement is paroxysmal and
11 persistent AF.

12 Structural hard disease magnifies
13 the bi-atrial origins of the arrhythmia.
14 Right atrial tachycardias often surpass left
15 atrial tachycardias in structural hard disease
16 and persistent AF.

17 And persistent AF is the only
18 condition in which simultaneous right and left
19 atrial tachycardias can exist at the same time
20 in the same patient at the same point in time.

21 And here is the problem that occurs
22 with trigger ablation as it's being practiced.

23 This is the widest, most widely used approach
24 for treating ablation, and look at the
25 problem: multiple triggers, one breaking in

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 from the left atrium, one at the top of the
2 right atrium, one at the bottom of the right
3 atrium. This was a five-minute span in this
4 patient. It is clearly obvious why our
5 results don't match up with our expectations.

6 Another patient in the course of a
7 study over a 30 minute period of time. Three
8 distinct right atrial triggers, two distinct
9 left atrial triggers. Clearly, trigger
10 ablation is not going to solve the problem of
11 atrial fibrillation.

12 Organization in tachycardias. We
13 see organized tachycardias in drug refractory
14 atrial fibrillation, such as this woman who
15 had an organized right atrial rotor, and the
16 proof of the pudding here was that this
17 organized rotor could be terminated with
18 pacing, anti-tachycardia pacing by an
19 implanted device, and atrial fibrillation
20 terminated.

21 You can have these rotors in just
22 local regions of an atrium, and here is a
23 reentry circuit in the interatrial septum in
24 this patient's refractory AF.

25 But AF evolution typically involves

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 in a patient a cascade of these rotors or
2 tachycardias starting on the left side, moving
3 over to the right side in the course of a few
4 minutes, in fact, in a given patient with
5 atrial fib.

6 In fact, in the more advanced forms
7 of atrial fibrillation you can have semi-
8 independent tachycardias running in the right
9 atrium and the left atrium. So it is clearly
10 obvious the solution cannot be unilateral.

11 Organized tachycardias we concluded
12 in this paper have multiple unilateral bi-
13 atrial locations in human AF, and patients
14 with heart disease and persistent AF have more
15 extensive distribution of these conditions,
16 and here is just a tabulation of the data in
17 that paper by showing a multi-focal origin and
18 multiple sources.

19 Now, if you look at the rotors, the
20 rotors are common in the right atrium, and
21 here is a shaded oval here showing the right
22 atrial contribution to atrial fibrillation in
23 patients with and without heart disease. The
24 group in yellow is without heart disease.
25 Here's the group in blue, is with heart

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 disease.

2 And you can see that multiple
3 rotors are the rule rather than the exception.

4 So the mechanisms of atrial fibrillation have
5 changed in man. We have moved beyond goats
6 and dogs to what we see in human beings, which
7 are what Jim Cox saw in the operating room:
8 multiple potential rotors with fibratory
9 conduction in different parts of the two atria
10 occurring simultaneously.

11 How does it change our thinking of
12 how we treat these patients? We've now
13 concluded that trigger ablation is unlikely to
14 be effective. It's the most popular technique
15 in the United States. Since AF structural
16 heart disease is the vast group of the
17 millions of patients with atrial fibrillation,
18 these are the people who have bi-atrial
19 disease, bi-atrial genesis, and they need bi-
20 atrial interventions, and therefore, right
21 atrial ablation is increasingly necessary for
22 a complete ablative procedure.

23 The classic analogy I give is the
24 patients with advanced multi-vessel coronary
25 disease where you dilate one artery and think

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 that you have a change at an effective cure of
2 angina.

3 So what are the options in bi-
4 atrial therapy? Anti-arrhythmic drugs which
5 work on both atria? Bi-atrial ablation as
6 practiced in the operating room by Cox or by
7 catheter approaches, or a unilateral right or
8 left atrial fibrillation where you add
9 something on to take care of the other atrium,
10 whether it's a drug or a device or both.

11 And, therefore, the debate is no
12 longer trigger versus substrate. This is no
13 longer germane to the discussion. What we
14 already know is that even in the early forms
15 of paroxysmal AF, bi-atrial treatment is
16 needed, and you have the choice of hybrid
17 therapy, as was practiced in this trial, anti-
18 arrhythmic drugs with ablation and/or pacing.

19 This observations has been
20 confirmed by clinical experience. Here is
21 work from the Bordeau group. When they looked
22 at the sites of failures after the AF ablation
23 and where they went, they went to the right
24 atrial septum, to the lower part of the
25 Triangle of Carr (phonetic), the isthmus, the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 superior vena cava and sites in the right
2 atrium to get some of their failures, a
3 substantial proportion.

4 It then ran another study, which is
5 shown here, where they ablated sites in the
6 left atrium, the septum, and the right atrium,
7 and what they found was organized atrial
8 fibrillation. When they ablated it at these
9 sites it stopped, and that was the validation
10 of the belief that there are multiple rotors,
11 but this result comes at a price, and it's
12 important for the patient to know what that
13 price is. It's important for the patient in
14 this country to know what their options are,
15 and their options when they choose bi-atrial
16 ablation is a staged procedure, sometimes
17 multiple procedures, rarely one procedure.
18 These are long, demanding, and I will show you
19 data on efficacy and safety.

20 The complications and widespread
21 practice differ greatly. In fact, most
22 people's experience may differ from what is
23 reported in the literature, and in fact, in my
24 journal when we published a survey of U.S.
25 physicians, the survey, which was much more

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 realistic of what was the efficacy and safety
2 of this procedure has now been validated by
3 published literature some years later.

4 Efficacy may not be as high as was
5 originally hoped.

6 Work from Taiwan. Isolated right
7 atrial onset of atrial fibrillation being
8 treated with short lines of right atrial
9 ablation and elimination of atrial
10 fibrillation in a large group of patients.
11 These are potential candidates for right
12 atrial ablation alone.

13 Even if you look at the left atrial
14 randomized trial, the first one that was ever
15 published out of Milan, Italy, it was a right
16 atrial linear lesion done right here in that
17 trial. And despite that, they found a 60
18 percent efficacy rate, a 40 percent recurrence
19 rate at one year, and a much poorer rate for
20 drug therapy.

21 So what's the message? We need
22 ablation for treating our patients because
23 during the fourth and the fifth anti-
24 arrhythmic drug trial with today's drugs is
25 not the place to go. We know that.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 But realistically we get a modest
2 benefit with that ablative procedure, and we
3 need more choices. We need to be able to do
4 more vessels in that coronary tree than just
5 one.

6 So what did this study not do? Why
7 did they get a 40 percent recurrence rate?
8 The lesion set took care of these findings.
9 These are the rotors that it did attack, but
10 it forgot about the rotors in the right atrium
11 that are the very subject of the Cardima
12 study. Forty-four percent of our patients
13 have this rotor; seven percent have focal
14 tachycardia. That's where the recurrences can
15 come from. We need a tool to be able to deal
16 with that.

17 Here are recordings from right
18 atrial compartmentalization where your
19 technology shows that linear block is
20 conclusively achieved. The
21 compartmentalization of the right atrium is
22 achieved by these kinds of approaches, and you
23 can test that as you can see here in a three
24 dimensional map, and you can see that there is
25 a block along the line.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 This patient was done last week in
2 our laboratory, and you can see the second
3 reference stays in the posterior compartment.

4 We have done what Jimmy Cox did in the
5 operating room without opening the chest.

6 There were potential concerns
7 raised about the approach with the catheter.
8 Well, ablation orientation was the concern in
9 French Legion death. In fact, this is not a
10 problem in the atrium. The atrium is only two
11 to three millimeters thick. I don't want a
12 seven millimeter lesion. I don't want a cool
13 catheter. I only get into trouble when I do
14 that.

15 There's variable topography.
16 Transmurality of an atrial lesion is an
17 optimistic thought. The only person who gets
18 a transmurable lesion is the surgeon with the
19 knife. No lesion today has complete linear
20 block and complete transmural, and that is
21 more than adequately attested when these
22 patients who have had catheter ablation go to
23 the operating room, and the surgeon shows us
24 photographs of how we jumped around the atrium
25 and missed large chunks of tissue.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 So this is a figment of people's
2 imagination, the catheter ablation approach.
3 What we do is produce conduction block and
4 make it hard for the tachycardia to continue.

5 The right atrium is a bi-standard
6 in atrial fibrillation. This was the thought
7 process when this application was probably
8 reviewed some years ago. Nothing can be
9 further from the truth, and it is refuted by
10 human AF mapping and ablation.

11 And here's an example of conduction
12 block with the Cardima catheter system with
13 right atrial mapping showing exactly the same
14 finding I showed you in real time.

15 Now, what does that mean? It means
16 real different procedures for patients. This
17 is a procedure on a 50 year old woman who had
18 been avoiding ablation for ten years. She was
19 a classic candidate for pulmonary vein
20 ablation.

21 When we mapped this patient, we
22 found there was nothing in any pulmonary vein.

23 There were four rotors in the right atrium
24 and one rotor in the top of the left atrial
25 septum. We did what we call a tailored

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 ablation in this patient, compartmentalized
2 the right atrium, ablated the site in the left
3 atrium. We never touched the pulmonary vein,
4 and the patient has done well ever since.

5 What do these alternatives in
6 treatment offer? This is the hybrid approach
7 that we have used in persistent and permanent
8 AF, far sicker patients than patients in the
9 Cardima study. These people all get devices.

10 There's no question when they're in AF and
11 when they're not in AF. Eighty percent of
12 these patients after hybrid treatment are no
13 longer in persistent, permanent AF and most
14 have very brief runs of atrial tachycardia.

15 This translates into a real
16 reduction in AF hospitalizations by 70 percent
17 and cardioversion (phonetic) hospitalizations
18 as well. This data has just been published,
19 and it shows that there's improved rhythm
20 control and fewer hospitalization when we have
21 more tools.

22 That data compares quite favorably
23 with the kind of data that's used as a
24 standard. The, for example, linear left
25 atrial fibrillation as reported from Milan,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 except that this data which has been published
2 and we have done over 300 patients over ten
3 years with this kind of approach at our
4 center, is validated by device data logs, not
5 by intermittent ECGs, not by clinic visits.
6 This is by real device data logs. We know
7 they are in sinus rhythm all the time. We're
8 out at five years at beyond 80 percent.

9 So the point being that when we
10 have more tools, we can do better things for
11 our patients, and we have actually started
12 based on this a Euro-American trial looking at
13 a combination of this right atrial Maze with
14 pacing as an alternative to pulmonary vein
15 isolation, and the first patient in that study
16 was just done ten days ago in Rome.

17 What this result in is a single
18 state abbreviated procedure, improved safety,
19 widely applicable in patients. It's a much
20 easier procedure to do.

21 So let me conclude by saying that
22 we have learned that right atrial ablation is
23 clinically relevant to AF ablation and is
24 achieved by the system under review. Re-
25 entrant rotors initiate and maintain AF. They

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 require substrate ablation. The ablation of
2 the right atrial substrate is essential for a
3 complete ablative strategy.

4 Right atrial linear ablation of the
5 right atrial electrogram diminution is clearly
6 associated with conduction block on 3D
7 mapping, and this system under review today,
8 that Revelation NavAblative Systems produce
9 right atrial compartmentalization quicker.
10 This shortened procedure times. I can reduce
11 the long and arduous procedure of catheter
12 ablation.

13 As a training program director, I
14 know that the span of life of an
15 interventional electrophysiologist in that lab
16 doing that procedure is limited by the demand
17 of these procedures, the radiation exported to
18 the patient, as well as the physician. We
19 have to make this procedure easier. We have
20 to make it safer. We have to make it
21 available in the general EP lab, and all
22 surveys show that both physicians and patients
23 shy away from doing this on a large scale.

24 So finally, who is a candidate for
25 right atrial Maze ablation? Patients who need

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 a bi-atrial procedure, which is where we are
2 going. That's the vast majority of catheter
3 ablation that will be done in the future.

4 If you have a recurrence after a
5 left atrial ablation, you need to be able to
6 do the right side. You need a tool that's
7 approved in this country.

8 Patients with a preference for
9 hybrid therapy incorporating a Maze, drugs are
10 pacing. Let me tell you that I have patients
11 who walk into my office having been turned
12 down for rhythm control or offered left atrial
13 ablation, physicians, dentists, nurses who
14 have reviewed their literature, and when I
15 talked with them about hybrid therapy, I can
16 tell you that there's at least two or three
17 people a year who say, "Why was I never told
18 that this was an option?"

19 The inhibition of technology growth
20 and availability of procedures is part of that
21 problem.

22 And finally, patients with
23 documented right atrial onset of atrial
24 fibrillation. So let me say to you that
25 hopefully the data today will show you that

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 there's patient benefit. There is patient
2 safety, and we give our patients another
3 option that will help them in the development
4 of ablation.

5 Thank you much for your attention.

6 CHAIRPERSON RAMSEY: Just a note
7 now that you have 60 minutes remaining. I'll
8 let you know when you're at 30 and ten.

9 DR. KOCHERIL: Good morning,
10 everyone. I am Dave Kocheril. I'm a cardiac
11 electrophysiologist at the University of
12 Illinois. I served as the principal
13 investigator for the Phase 3 clinical study.
14 I am paid for my time and expenses, and it is
15 my honor to present the Phase 3 clinical study
16 and results to you.

17 I've been involved with catheter
18 ablation since 1990. I started work on
19 ablating atrial fibrillation in May of 1998.
20 It started with a single center study where I
21 developed a protocol where we delivered map
22 guides linear lesions in the right atrium.

23 This is a quick summary of that
24 study. The lesions were created during atrial
25 fibrillation, and lesions were delivered to

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 organize the rhythm either to the point of
2 sinus rhythm of adequate compartmentalization.

3 I was able to achieve long term success in 79
4 percent of the patients at an average follow-
5 up of 19 months.

6 Now, with these results showing
7 benefit to my patients, I then joined the
8 Cardima investigators in the multi-center
9 trial of the Revelation Tx Microcatheter and
10 the idea here was to look at right atrial
11 linear lesions in a multi-center study to see
12 the impact on patients.

13 The study design followed the 1998
14 panel recommendations, and these consisted of
15 doing a single arm, nonrandomized study where
16 the patients serve as their own control.
17 There was a requirement to have failed two
18 anti-arrhythmic drugs or to have failed
19 amiodarone.

20 The baseline episode count was
21 commended to be two episodes over three
22 months. In the Cardima study the requirement
23 was three episodes in one month. Long term
24 success could be measured by a 50 to 75
25 percent reduction in the frequency of

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 symptomatic atrial fibrillation episodes
2 coupled with a six month evaluation of therapy
3 effectiveness. Safety would be assessed on
4 the basis of the incidence of major
5 complications, and in this patient population,
6 the quality of life was determined to be
7 important.

8 Our primary study outcomes
9 consisted of frequency of spontaneous
10 symptomatic episodes of atrial fibrillation
11 experienced by the patient. The incidence of
12 adverse events and the secondary outcomes
13 include the quality of life measured by two
14 instruments. The SF-36 is something everyone
15 is familiar with, the standard of quality of
16 life instrument, and we also used the atrial
17 fibrillation severity scale which is an
18 instrument specific to atrial fibrillation.

19 Success was defined as a reduction
20 in the number of symptomatic AF episodes at
21 six months compared to baseline. We required
22 a reduction of 50 percent or more for subjects
23 with at least five episodes at baseline, a
24 reduction of 75 percent or more for subjects
25 with three or four episodes at baseline.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 On the secondary endpoints, we were
2 looking for a change of ten points or more in
3 the subscales of the SF-36 and the AFSS at six
4 months compared to baseline.

5 The inclusion criteria were that
6 the patients needed to have three or more
7 symptomatic AF episodes in the 30 days of
8 monitoring prior to a procedure. They had to
9 be refractory to two or more anti-arrhythmic
10 drugs or to amiodarone.

11 The protocol called for absence of
12 significant structural heart disease and a
13 left atrial size less than or equal to five
14 centimeters, and also called for absence of
15 echocardiographic evidence of interatrial
16 thrombus, patent frame in a valley (phonetic)
17 and/or atrial septal defect.

18 This was the study schema. There
19 were 14 study sites, screening 178 patients.
20 After informed consent there was a 30-day
21 period of baseline monitoring. If they had
22 three or four symptomatic AF episodes, then
23 they went on to have a trans-esophageal
24 echocardiogram. If there was no thrombus
25 present, then they were eligible for radio

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 frequency ablation. Evaluations were done
2 pre-discharge and follow-up evaluations at
3 one, three, six, 12 and 24 months, and as I'll
4 show you, there were 84 patients in the
5 effectiveness cohort.

6 The assessments were standard
7 history and physical 12-lead EKG at baseline,
8 one, three, six, 12 months post ablation.
9 There was a trans-esophageal echocardiogram at
10 baseline. Echo and stress tests were done at
11 baseline and three months.

12 Cardiac event monitors were given
13 to the patients, and they were instructed to
14 transmit weekly and with symptoms, and this
15 was required at baseline, at one, three, and
16 six months time periods.

17 Quality of life questionnaires were
18 administered at baseline, three, and six
19 months, and there was a telephone interview at
20 24 months.

21 This is the subject flow chart. As
22 I mentioned, 178 patients were screened.
23 Nineteen were withdrawn because they failed
24 monitoring or the patients withdrew prior to
25 ablation. There were 61 screen failures, and

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 many of these were due to insufficient
2 episodes of atrial fibrillation at baseline.

3 There were others that were
4 excluded because of insufficient follow-up or
5 because the patients withdrew.

6 The ablation procedure cohort was
7 93 patients. There were 88 who completed six
8 months of follow-up. We had part of our study
9 design an independent cardiologist reviewing
10 episodes at baseline, and that cardiologist
11 determined that four more patients did not
12 meet the entry criteria from having
13 insufficient episodes. So they were also
14 excluded, and that left 84 patients as our
15 effectiveness cohort.

16 These are the baseline
17 characteristics of our patients. The average
18 age was 58, 74 percent male. Importantly, the
19 average number of symptomatic episodes at the
20 30-day baseline was 9.7, and that's important
21 because this is a different patient population
22 than that studied in the affirm and other
23 trials where the frequency of atrial
24 fibrillation episode was much lower.

25 The symptom characteristics, 88

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 percent had palpitations; 58 percent had
2 fatigue; 36 percent had light headedness.

3 The other important part of our
4 study was that the average number of anti-
5 arrhythmic drugs that the patient was
6 refractory to was 2.9. So this was not a
7 group of patients who are early in atrial
8 fibrillation. You already know that they have
9 had five years of atrial fibrillation on
10 average, and they were typically failing three
11 anti-arrhythmic drugs by the time they got
12 into the study.

13 The ablation procedure consisted of
14 delivering linear lesions in the right atrium.

15 You have already heard mention of the Cox-
16 Maze procedure, which was a cut and sew
17 procedure where atrial tissue was sliced and
18 then sewn together to create lines of
19 conduction block, and the initial scheme for
20 the Cardima procedure was to replicate the
21 right side, the right atrial portion of that.

22 So what we did was deliver linear
23 lesions using the Revelation Tx in posterior
24 and lateral and septal locations. All of
25 these lateral and septal lesions are created

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 with the Revelation Tx Microcatheter. DAQ
2 procedural endpoint was an appropriate
3 published endpoint or reduction in post
4 ablation amplitude relative to pre-ablation.

5 I'm going to show you a quick
6 video. Some of our investigators felt
7 compelled to show this conduction block with
8 noncontact mapping. This is the insight
9 system. There's a lesion here, and you see
10 the waves propagate around that lesion without
11 actually crossing it.

12 The next picture is after
13 delivering two linear lesions, and this is
14 done with the Revelation Tx. So you see the
15 posterior lateral lesion, the septal lesion.
16 The electrical impulses travel in the corridor
17 and then is able to break out into the rest of
18 the atrium without crossing either of those
19 linear lesions.

20 This is another view of the same
21 thing. So once again, here's the two lesions
22 and you see the electrical activation proceeds
23 between the two lesions without actually
24 crossing them.

25 So what that shows is that the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 technique that we employed did produce conduct
2 block, and you can see in a noncontact mapping
3 setting that it did work.

4 Our acute procedural endpoint for
5 the study was adequate tissue ablation was
6 indicated by a reduction in the direction by
7 50 percent in the post ablation amplitude
8 under the recording electrode. Also
9 acceptable were an obvious widening of the
10 signal and split potentials where you started
11 out with the signal with a single potential,
12 also indicating that the tissue under the
13 electrode had been ablated.

14 There was a flutter line
15 incorporated in the procedure. Atrial flutter
16 can coexist with atrial fibrillation.
17 Patients who had not undergone prior isthmus
18 ablation received an ablation line at the
19 cavotricuspid isthmus (phonetic).

20 The thinking here was not that we
21 were treating atrial flutter, but that in
22 early work, such as the seminal work of John
23 Schwartz and even from the surgical
24 literature, what we had known is that after an
25 atrial fibrillation ablation, patients can

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 come back with atrial flutter. There is the
2 potential that the linear lesion and the
3 posterior lateral segment could set up the
4 substrate for atrial flutter. So for a number
5 of reasons, the investigators felt that a
6 flutter line was important.

7 The idea here was the prevent
8 potential flutter, not to treat atrial
9 fibrillation.

10 In the protocol, the investigator
11 should attempt flutter ablation first with the
12 Revelation Tx and second with the NavAblator.

13 Now, there's a practical reality here, that
14 the Revelation Tx was not created to address
15 the isthmus. The isthmus is a complicated
16 structure anatomically with ridges and all,
17 and many investigators felt that they could
18 get at the flutter isthmus better with the
19 hot-tipped catheter, and that's why the
20 NavAblator was developed. There were no
21 approved catheters at the time for doing a
22 flutter line.

23 If neither device created bi-
24 directionally conduction block, the
25 investigators were to use standard

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 institutional procedures to complete the line
2 because at that point doing a flutter line for
3 treating atrial flutter had become a standard
4 procedure, even without an approved catheter.

5 And I'll just point out that bi-
6 directional isthmus block was not a study
7 endpoint.

8 These are the endpoint results.
9 Forty-eight of 84 patients -- I'm sorry -- 49
10 of 84 patients, or 58 percent, achieved a
11 target level decrease in symptomatic episodes
12 of atrial fibrillation. The mean per subject,
13 six month reduction in symptomatic AF episodes
14 was 62.3 percent, with a highly significant P
15 value.

16 The average symptomatic AF episodes
17 at three and six months were at 3.7 and 3.4,
18 respectively, down from the 9.7 that I showed
19 you at baseline.

20 This is the graphic representation
21 of that data. So 9.7 episodes per month at
22 baseline, going down to 3.7 and 3.4.

23 Not only is this statistically
24 significant, but I can tell you as a clinician
25 that this is huge because aside from the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 stroke risk in these patients, the major issue
2 is symptoms with paroxysmal atrial
3 fibrillation. That's what takes a toll on
4 their quality of life, and seeing this kind of
5 result is very meaningful.

6 So here is a six month summary.
7 The mean percent reduction was 62.3 percent.
8 A target level reduction was achieved in 49 of
9 84, or 58 percent, of the patients. There was
10 some episode reduction in 66 of 84, or 78
11 percent, of the patients. Interestingly, a
12 100 percent reduction was achieved in 29 of
13 84, or 34.5 percent of the patients.

14 Now, if you think about this, these
15 are patients who are highly symptomatic at
16 baseline reporting no episodes at the six
17 month follow-up period, and this was
18 accomplished with a low risk, right atrial
19 procedure, and you'll hear more in our
20 presentations about that, but as a clinician,
21 once again, I think this is very impressive
22 that we're able to offer this kind of benefit
23 with a low risk procedure.

24 There was no reduction or an
25 increase in 11 of 84, or 13 percent.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 This is looking at quality of life.
2 You're all familiar with the SF-36. So
3 what's shown here is the population mean in
4 blue. The baseline of our patients is shown
5 in yellow, and the six month follow-up is
6 shown in orange.

7 So even from the back of the room
8 you can see that the AF patients aren't as
9 good as the population mean in quality of
10 life. That's known. That has been shown by
11 multiple studies. What's really encouraging
12 is that there is general improvement in the
13 quality of life by SF-36 in all of these
14 domains except for general health. General
15 health is a more complex measure, and it
16 incorporates other illnesses.

17 But you can see that physical
18 function improved, role physical. Bodily pain
19 improved, vitality, social function, role
20 emotional, and mental health, and they're all
21 statistically significant.

22 This correlates well with the AFSS,
23 which is a different quality of life
24 instrument, and here we see an improvement in
25 episode frequency, episode duration, episode

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 severity and the total score, and again, all
2 of these are highly statistically significant.

3 This was looking at specific
4 symptoms. With those improvements in quality
5 of life, you would expect a nice decrement in
6 these symptoms, and that's exactly what we
7 saw. So here is baseline in blue, three
8 months in yellow, and six months in orange.
9 this is palpitations. There's a steady
10 decrement in palpitations as you go out from
11 baseline to six months. Chest pain improves.

12 Shortness of breath improves, light
13 headedness, and fatigue and weakness, and
14 these are all typical symptoms of atrial
15 fibrillation.

16 So at six months we've already seen
17 that symptoms improved overall. Palpitations
18 decreased 53 percent. Fatigue decreased 54
19 percent. Light headedness decreased 62
20 percent, and all of the EPs in the room will
21 appreciate that these are very significant for
22 a highly symptomatic group of atrial
23 fibrillation.

24 We also had long term follow-up
25 built into the study. So at 12 months 26 of

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 64 patients, or 43 percent, reported no
2 symptomatic episodes of A.Fib. since their
3 last study visit. So this first speaks to the
4 durability of the result, and it's probably
5 indicative of positive HRA modeling that
6 occurs from adequate suppression of atrial
7 fibrillation over time.

8 Let's look at safety results. Six
9 adverse events were either possibly or
10 probably related to the study device. Four of
11 these were categorized as mild. One was
12 actually a reaction to sotalol. There was one
13 episode of sinoatrial block caused by the
14 ablating catheter. There were no injuries to
15 the phrenic nerve, no strokes, no deaths, and
16 no esophageal fistulas.

17 The complete list of adverse events
18 is readily available to you, but what we're
19 generally interested in is the serious adverse
20 events. There were five serious adverse
21 events in four subjects. So the rate was five
22 events in 95 procedures or five percent. Only
23 one of these was considered to be device
24 related.

25 Specifically, these events were two

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 femoral AV fistulas, one sinoatrial block that
2 I mentioned. This was treated with a
3 pacemaker. There was one pneumonia, one
4 cardiac tamponade that was addressed quickly
5 with no sequelae. Only one patient was left
6 with a permanent sequela, and that's the
7 patient here with the pacemaker.

8 Now, all of you who follow the PVI
9 literature know that this safety profile is
10 better, in general, than what we see with
11 pulmonary vein isolation procedures, and as
12 Dr. Saksena mentioned before, one of the
13 issues there is that there isn't a good tool
14 out there for doing a radical procedure as
15 yet.

16 I'm going to come back to this
17 before closing. This is, once again, the
18 symptomatic benefit, episodes at baseline
19 versus three months versus six months, and I
20 think this is a very significant benefit to
21 patients, and as a clinician, I appreciate not
22 getting phone calls about symptoms, and so,
23 again, it for managing patients is a very
24 important effect.

25 So in conclusion, there was a

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 significant reduction in symptomatic atrial
2 fibrillation events. This was correlated with
3 a significant meaningful improvement in
4 quality of life. We have seen an excellent
5 safety profile. I think there is sufficient
6 data to draw these conclusions, and the
7 benefits outweigh the risks.

8 So in summary, the Revelation Tx
9 Microcatheter Ablation System is safe and
10 effective for the treatment of patients with
11 drug refractory symptomatic atrial
12 fibrillation, paroxysmal atrial fibrillation,
13 and I hope the panel votes to allow this tool
14 to be placed into the armamentarium of the
15 electrophysiologists to treat patients.

16 Thank you very much.

17 DR. CHER: Members of the panel,
18 good morning. My name is Daniel Cher. I'm a
19 physician and part of the medical device
20 industry since 1997. I'm currently Vice
21 President of Clinical and Regulatory Affairs
22 at an unrelated device company in California.

23 I'm here today because I was
24 Medical Director between 2003 and 2004 at
25 Cardima. I was the person who was primarily

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 responsible for the submission of the PMA
2 amendment submitted to FDA in January 2004.
3 In that amendment we described the results of
4 the study that Dr. Kocheril just described to
5 you.

6 Other than being paid for my time
7 to be here today, I have no financial interest
8 in the company.

9 My goal, my job today is to review
10 with you the concerns that FDA has raised and
11 has sent to you in their package that you've
12 received regarding the clinical study. I'm
13 hoping that by the end of my talk you will see
14 the concerns that FDA has raised do not impair
15 our ability to interpret the study and that
16 the study overall provides us reasonable
17 assurance of safety and effectiveness.

18 So what I'm going to do in the next
19 series of slides is go through a number of
20 issues that FDA has raised and give you some
21 thoughts on them.

22 The first issue is placebo effect,
23 and the specific question of interest here is
24 does the placebo effect account for the
25 entirety of the effectiveness that we've seen

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 in this study. I'm hoping that you'll see
2 that the answer is no.

3 Although our study was a single arm
4 study, it was not an uncontrolled study. Each
5 patient served has his own control in a before
6 and after design, and I remind everyone that a
7 before and after design is a valid type of
8 control and is accepted by international
9 standards, but not only that. The design of
10 the study was actually done in concert with a
11 1998 expert panel convened by FDA specifically
12 to discuss the design of AF ablation trials.

13 By the time our trial was finished,
14 FDA had published a guidelines document. This
15 was January 2004, just a few weeks before we
16 submitted our PMA amendment. In that
17 guidelines document, FDA talks about
18 performing randomized trials, but at the same
19 time in their discussion of control groups,
20 they note that patients as their own controls
21 may be a valid type of design for these
22 studies.

23 I thought it would be interesting
24 to take a look at other premarket approval
25 applications for devices used for cardiac

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 ablation. There have been a total of 19
2 devices, 19 PMAs -- I'm sorry -- that have
3 been approved. Of these, only one of them did
4 a randomized trial against medical therapy.
5 So this tells you that a randomized trial for
6 ablation catheters is not required.

7 Moreover, this one trial was in a
8 catheter used for a ventricular tachycardia,
9 not for atrial fibrillation.

10 Let's get a little bit more
11 specific with respect to placebo effect.
12 Let's try to answer the following questions.

13 What is the natural history of
14 paroxysmal atrial fibrillation?

15 Does it spontaneously go away or
16 does it stay with the patient?

17 The second question is: what is
18 the short term variation in symptomatic
19 episodes? Because, after all, that's what
20 we're looking at in our clinical trial.

21 A third concern that FDA has raised
22 is whether atrial fibrillation episodes
23 cluster, and I'm going to show you that while
24 they may, it does not make any difference.

25 And finally, is there a

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 participation effect?

2 Let's take a look first at the
3 natural history of paroxysmal atrial
4 fibrillation. Obviously this is a very large
5 subject, impossible to summarize in one slide,
6 but okay. Here it is, a summary in one slide.

7 This is a study of 63 subjects with
8 paroxysmal atrial fibrillation very similar to
9 the patients that we did in our study. All of
10 these patients underwent EVNO (phonetic)
11 ablation, plus placement of a dual chamber of
12 pacemaker.

13 Of these patients when they were
14 followed forward in time, you can see that by
15 three years 56 percent of them had developed
16 permanent atrial fibrillation. What this
17 slide is trying to tell us is that this
18 disease is not one that spontaneously remits,
19 but rather one that progresses.

20 Another very interesting question
21 is what is the short term variation in AF
22 episodes. There was a very interesting study
23 published this year that I'd like to go
24 through with you briefly. This was a study of
25 250 patients with paroxysmal atrial

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 fibrillation who got a special type of
2 pacemaker that could actually record episodes.

3 The patients were observed for four
4 months with anti-tachycardia pacing off, and
5 they were on a stable anti-arrhythmic drug
6 regimen. The study authors decided to divide
7 the four month study period into two periods,
8 the first two month period and the second two
9 month period, and then they looked at atrial
10 tachycardia recurrences during those two
11 periods.

12 As you can see here, the same
13 proportion of patients experienced a
14 recurrence during the first two month period
15 and the second two month period. This tells
16 us that a paroxysmal atrial fibrillation is
17 not something that spontaneously remits.

18 This is a little bit hard to see,
19 but let me describe what this shows. On the
20 top we see the results of the Botto study, the
21 one I just described. They looked at the
22 difference in number of episodes for
23 individual patients from the first period to
24 the second period. If the number of episodes
25 got better, they were on the improvement side.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 This is the percentage of improvement, and
2 here's a histogram of the percentage of
3 improvement.

4 If you had more episodes, then you
5 were on this side of the graph, and if you had
6 the same number of episodes or zero episodes
7 during both periods, you were here right in
8 the middle.

9 Well, if you look here, there is a
10 perfect balance kind of as we expect of the
11 change in the number of AF episodes. Down
12 here I've plotted the Cardima results along
13 the same lines with the same X axis, and you
14 can see that our results very strongly
15 indicate an observed improvement, primarily an
16 improvement, and a very small number of
17 patients who worsen.

18 I would argue to you that this
19 study up here serves as a type of historical
20 control for our study in that it gives us good
21 information as to the natural history of what
22 happens to these patients.

23 Let's take a look at clustering.
24 As you may have read, AFD has expressed some
25 concern about whether AF episodes cluster and

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 whether that could impact our study.
2 Obviously, another large topic that I won't be
3 able to cover completely. Let me just
4 summarize by saying that there have been a few
5 studies that have looked at patients with
6 various methods and have found some degree of
7 clustering. The clustering has occurred over
8 the time period of hours and days, but not
9 months.

10 And as I showed you previously, if
11 we look on a month-to-month basis, the
12 frequency of atrial fibrillation is relatively
13 constant.

14 There was one more study done
15 earlier with transtelephonic monitoring that
16 actually showed interinterval event times that
17 were consistent with an exponential
18 distribution, which is a very fancy way of
19 saying that they were randomly distributed and
20 not clustered.

21 Finally, of concern, something
22 called a participation effect, that is, the
23 patient received a novel therapy for his or
24 her disease, and they report better outcomes
25 just simply having received what he thinks is

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 something new.

2 There's an interesting study that
3 FDA pointed to our attention, a study by
4 Gerstenfeld in which patients underwent left
5 atrial catheter ablation, and there were three
6 types of patients in the study. There were
7 some who after ablation had no AF recurrences.

8 When they measured quality of life changes,
9 they observed large changes.

10 They had some patients -- and I
11 think this is important for us to consider --
12 who had AF recurrence, but those patients
13 still felt better, and when they reported
14 quality of life, indeed, they reported
15 moderate changes.

16 Finally, there was a group that
17 underwent mapping only, and this group had no
18 improvement. If there were a placebo effect,
19 we might have expected some improvement from
20 this group, but in fact, the article itself
21 says that what they're observing is not a
22 placebo effect.

23 I'd like to talk a little bit more
24 about the participation effect. I think there
25 are some aspects of the study design and

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 analysis that strongly speak against a
2 participation effect.

3 First, episodes were confirmed by a
4 transtelephonic monitoring and they were also
5 confirmed by an independent cardiologist. Of
6 interest to us, about 75 percent of all
7 symptomatic episodes turned out to be atrial
8 fibrillation when looked at by the independent
9 cardiologist, and this was both at baseline
10 and at follow-up. You would think that if
11 some of this were due to placebo that that
12 proportion would vary systematically, but it
13 did not.

14 As you know, the threshold that we
15 used to call a patient a success was high.
16 You had to have a 50 percent or in some cases
17 75 percent improvement in episode frequency.
18 The placebo effect is unlikely, in my opinion,
19 to last six months or be of the largest amount
20 at six months, and I think that speaks against
21 the placebo effect.

22 The changes in episode counts that
23 we observe were correlated with the
24 improvements that we observed in quality of
25 life. I don't think this would be expected if

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 it were placebo effect, but again, I refer to
2 Table 62 of the PMA that we submitted.

3 Finally, and importantly, our
4 procedure is based on a known, effective,
5 surgical procedure called the Cox-Maze
6 procedure in which the atrium is cut and then
7 re sewn. The goal of our ablation procedure is
8 to mimic that procedure in the right atrium.

9 Let's turn next to the next
10 subject. FDA has raised some concern about
11 transtelephonic monitoring compliance and
12 whether it impacts the study results. I'd
13 like to discuss that.

14 Just as a reminder, the patients in
15 our study were told to record and transmit
16 episodes when they had symptoms and also
17 weekly independent of symptoms, and that
18 weekly maneuver was meant to enhance
19 compliance, but itself was not a study
20 outcome.

21 All of the transmissions as you
22 know were verified by an independent
23 cardiologist, and in terms of effectiveness,
24 we only counted those transmissions that
25 showed atrial fibrillation.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 So the big question is: were
2 patient compliant with TTM transmissions?

3 The data that we have presented
4 show that 88 percent of patients transmitted
5 three or more rhythm strips during the sixth
6 month of follow-up. this is a picture of a
7 patient population that's with the program and
8 not out of control.

9 Of interest, of those patients who
10 had no symptomatic episodes at three months,
11 93 percent of them transmitted at least three
12 TTMs during that period. So this is a picture
13 actually of a patient population that's highly
14 compliant.

15 It turns out that noncompliance
16 occurred mostly in those patients who were
17 already study failures, and I'll show that to
18 you in the next few slides.

19 This slide shows the proportion of
20 patients who were reporting strip -- who were
21 doing TTM transmissions at various follow-up
22 times. At month six, 88 percent of patients
23 had three or more; 77 percent had four or more
24 transmissions in total.

25 The real question is whether the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 transmission frequency affects the success
2 rate. So what we did here was take a look at
3 the total number of transmissions, and we
4 divided it into those patients with two or
5 fewer transmissions at six months versus three
6 or more, and as you can see here, those
7 patients who had fewer transmission were not
8 more likely to be successes. In fact, they
9 were more likely to be failures.

10 The overall result that we reported
11 may actually, therefore, be somewhat of an
12 underestimate.

13 Now, in this slide, I'm looking at
14 the total number of transmissions. It's also
15 of interest to look at just those
16 transmissions having to do with weekly
17 asymptomatic transmissions.

18 So here we divide it into patients
19 with two or fewer of those weekly
20 transmissions; three or four more here; four
21 or more, and you can see here an even greater
22 difference. So those patients who are highly
23 compliant with those weekly transmissions were
24 also more likely to be successes.

25 This is not a picture of a trial

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 that has non-complied its way into success.
2 Rather, this is a picture of a trial with a
3 good adherence to the protocol for a large
4 number of patients, and in those compliant
5 patients, we have high success rates.

6 Another concern that FDA has raised
7 is the difference in reporting at baseline
8 versus at follow-up. FDA has suggested that
9 patients might over report episodes at
10 baseline, and similarly, they might under
11 report episodes during the follow-up period.

12 Well, it's obviously very difficult
13 to have objective data to confirm that.
14 However, let me remind you of the following.
15 First of all, patients were not aware of the
16 number of episodes needed to qualify for the
17 study, and that was three. So there was no
18 incentive for them to over report at baseline.

19 And as you know, even if a patient
20 recorded a transmission, it was verified to be
21 atrial fibrillation by an independent
22 cardiologist. So we have no evidence that
23 patients over reported baseline episodes.

24 Well, let's ask the same thing
25 about six month follow-up. Did the patients

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 under report episodes during follow-up?
2 Primarily the question is: did patients have
3 decreased motivation to participate at six
4 months.

5 Well, I think this is directly
6 contradicted by investigator experience and by
7 the patient population we're working with.
8 The investigators have told me that their
9 patients very readily called them up when they
10 were treatment failures, and that the patients
11 themselves were highly experienced with their
12 disease and highly unlikely to be motivated to
13 get better.

14 As I showed you before, under
15 reporting when it did occur was mostly in
16 patients who were already failures. I think
17 the key point here is that the degree of under
18 reporting and a bias in under reporting from
19 baseline to follow-up would have to be
20 extremely large to produce our study's
21 results.

22 CHAIRPERSON RAMSEY: You are under
23 30 minutes.

24 DR. CHER: Thank you.

25 Another concern that FDA has raised

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 is whether episodes can occur close together,
2 and if so, did the patient record with the
3 transtelephonic monitoring multiple
4 transmissions during one single underlying run
5 of atrial fibrillation, and they've proposed
6 that this could occur more commonly at
7 baseline than at follow-up.

8 I don't think that's the case. In
9 atrial fibrillation, episodes can occur at
10 random, and I reviewed those data with you.
11 It would, therefore, not be surprising that
12 some episodes would occur close together.

13 But in our study it turns out that
14 the vast majority were separated by more than
15 a day, and we did a sensitivity analysis which
16 we shared with FDA that showed that removing
17 those episodes that occurred very close
18 together that might represent this particular
19 phenomenon here made no difference whatsoever
20 in terms of the effectiveness calculation.

21 So in summary, regarding
22 compliance, compliance itself with the weekly
23 maneuver was not a study outcome in itself. I
24 showed you data to suggest that we did not
25 non-comply our way into success, and the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 various biases that I just discussed there's
2 no evidence to support them.

3 Let's turn to another concern that
4 has been raised by FDA, which is regression to
5 the mean. Regression to the mean occurs or
6 could occur in our study if a patient with a
7 low underlying episode frequency happened to
8 get enrolled because he had a bad month. In
9 subsequent months, that patient might have low
10 counts due to regression to the mean.

11 As you heard, the baseline mean
12 number of episodes was nine, which was very
13 far away from the threshold required for
14 enrollment. So a priori at first glance, we
15 wouldn't think that this would be a big issue.

16 But let's look at this in a little
17 bit more detail. What I've done is some
18 modeling, and I've done some statistical
19 modeling very similar to what Dr. Li has done
20 and included in his slides, and I'd like to go
21 over this for you.

22 Let's imagine a patient with an
23 underlying episode frequency of one episode
24 per month. If we model the number of episodes
25 that actually occurred during a month with a

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 Poisson distribution, a standard assumption,
2 the patient might experience zero, one, two,
3 three, et cetera. This particular patient
4 would have an eight percent chance of getting
5 enrolled in our study due to random variation.

6 Let's take another look at a
7 patient with an underlying frequency of nine
8 per month. Obviously, the expected number of
9 events that this patient would experience
10 during a baseline period would most likely be
11 above the threshold, but there could also be
12 some chance that the patient actually
13 experienced a low number of episodes and,
14 therefore, might not have gotten enrolled. So
15 obviously regression to the mean can work both
16 ways.

17 Here's the actual distribution of
18 episodes per month that we observed in the
19 baseline period. You can see that there are
20 some with a low number of episodes close to
21 the threshold and a larger number with more
22 episodes, and in fact, there were 20 patients
23 who had 15 or greater episodes.

24 Obviously for the patients on the
25 right side of the graph regression to the mean

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 is going to play almost no role, but we do
2 have to be concerned on those patients on the
3 left side of the graph.

4 So I did some modeling, and this
5 modeling was actually very similar to what Dr.
6 Li did. I assumed that the patients in our
7 patient population had an underlying monthly
8 AF frequency of somewhere between one and ten,
9 and I modeled it as a uniform distribution.
10 The mean number of episodes modeled here is
11 about five and a half. It's the mean of one
12 to ten, which is actually less than what we
13 observed in our clinical study, but I thought
14 I should do a conservative model.

15 I assumed that episodes would be
16 distributed as Poisson. I assumed that there
17 would be no effective treatment whatsoever so
18 as to be able to calculate the regression to
19 the mean effect.

20 I then chose at random from the
21 distribution to represent baseline and follow-
22 up values. I calculated the percent change,
23 and then applied our study rules to figure out
24 whether these patients would be successes or
25 not.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 There's a lot of data here, but
2 let's get to the bottom line. In an
3 unrestricted model where we don't have a
4 threshold for enrollment, I calculated a
5 success rate of 18 percent. You could think
6 of this as the success rate that might occur
7 just a random variation.

8 If we apply the rules that we did
9 in our clinical trial, which is to remove
10 those patients with less than three episodes
11 at baseline, this results in removing about a
12 quarter of the patients, which is, in fact,
13 kind of what happened in our study, and the
14 success rate was about 16 percent. You can
15 see that the difference was hardly anything at
16 all, and in fact, in the opposite direction.

17 And these results are actually very
18 similar to what Dr. Li has shared with us in
19 his slides, and it suggests to me or it
20 strongly suggests to me that regression to the
21 mean in this trial is irrelevant and does not
22 play a role.

23 Let's look at pacemaker treatment.
24 Some patients in our trial received
25 pacemakers in follow-up, and the big question

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 is did pacemaker treatment result in the trial
2 being a success. There are three types of
3 pacemaker treatment. Again, i want to remind
4 everyone this is a huge topic and will be
5 difficult to summarize very briefly, but I've
6 tried to summarize here why pacemakers are
7 placed in atrial fibrillation.

8 First, we have a salvage procedure
9 in which a patient has avinode (phonetic)
10 ablation, ablation followed by a pacemaker to
11 make sure that the ventricle beats enough.
12 This is well accepted to reduce symptoms and,
13 in fact, was used in our some of our study
14 failures, and I'll show you our data.

15 There are patients who have
16 bradycardia, and bradycardia can occur very
17 commonly in patients with atrial fibrillation,
18 a syndrome called sick sinus syndrome or
19 tachybrady syndrome.

20 What we have to ask ourselves is
21 whether pacemaker placement in this study
22 population will reduce the frequency of
23 symptomatic AF episodes, and the answer is no,
24 and I'll show you that in a moment.

25 Finally, we have anti-tachycardia

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 pacemakers designed to pace the patient out of
2 atrial fibrillation. Obviously, this is for
3 getting a patient out of atrial fibrillation,
4 not preventing it. It's not accepted that
5 these pacemakers reduce atrial fibrillation
6 frequency either.

7 Don't accept my word for it. Let's
8 take a look at what the literature says. This
9 was a summary that was in the January 2004 PMA
10 amendment wherein I summarized a number of
11 trials in patients with paroxysmal atrial
12 fibrillation with bradycardia or without
13 bradycardia. All of them provide no
14 convincing evidence that pacing reduces the
15 frequency of AF episodes relevant to our
16 study.

17 But again, it's not just the
18 literature. It's actually the American Heart
19 Association and the Heart Rhythm Society.
20 They have published a guideline on pacemaker
21 treatment in atrial fibrillation. this is
22 hard to read. So I blew it up here.

23 They write there's no consistent
24 data from large randomized trials to support
25 the use of various types of pacing. Even

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 fewer data support atrial pacing in the
2 management of atrial fibrillation in patients
3 without bradycardia, and finally, permanent
4 pacing to prevent atrial fibrillation is not
5 indicated.

6 So the Heart Rhythm Society does
7 not believe that pacemakers are relevant to
8 prevent atrial fibrillation episodes.

9 Well, let's actually look at the
10 data in our clinical trial. Again, this is
11 the Phase 3 trial. There were a total of 16
12 patients who had pacemaker placement during
13 follow-up. Of these, ten had pacemaker
14 placement followed by AV node ablation. These
15 were clearly failures, although in one case
16 pacemaker placement occurred more than six
17 months after the primary endpoint -- I'm sorry
18 -- more than six months after ablation, that
19 is, after the primary endpoint was assessed.
20 So we were able to count that patient as a
21 success.

22 Six patients had pacemaker
23 treatment for bradycardia. Of these, two had
24 episode reductions consistent with success,
25 and because as I told you, pacemakers for

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 bradycardia don't prevent atrial fibrillation,
2 I thought it was reasonable to count these
3 patients as successes.

4 And as you heard, there was one
5 patient who had a pacemaker placement as a
6 complication of ablation.

7 So what do we conclude from all of
8 this? Other pacemakers in this study were
9 placed for either treatment failure, and these
10 patients were already counted as failures, or
11 bradycardia, in which pacemaker placement is
12 not effective, and therefore, I concluded, and
13 I hope you agree, that pacemaker use in our
14 trial does not impair our ability to interpret
15 the results of the study.

16 Let's turn next to another concern
17 that has been raised repeatedly by FDA.
18 That's isthmus ablation. As you heard from
19 Dr. Kocheril, the isthmus ablation is an
20 accepted for atrial flutter, but remember
21 patients in our study did not have atrial
22 flutter. They had atrial fibrillation.

23 In our trial, it was included as a
24 preventive maneuver, as a prophylactic
25 maneuver to prevent the occurrence of atrial

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 flutter. It is not a treatment for atrial
2 fibrillation, and as you heard from others, it
3 has never been proven to be useful in atrial
4 fibrillation.

5 Well, as you know, at the time the
6 Cardima study was developed, there was no
7 approved catheter for isthmus ablation. The
8 company, therefore, developed the NavAblator
9 catheter, a catheter very similar in design to
10 other catheters, and the protocol required
11 that the physician use the Revelation Tx
12 followed by the NavAblator, followed by other
13 catheters if need be to treat the isthmus line
14 to try to prevent atrial flutter.

15 The big question we have is does
16 this all matter. Does it make any difference
17 whatsoever?

18 Here's a table. This table was in
19 our January 2004 amendment. It showed that
20 roughly 30 percent of patients another
21 noninvestigational catheter was used to ablate
22 the isthmus.

23 Did it matter? That's the really
24 big question of the day. Let's take a look.
25 In isthmus ablation, the physician typically

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 tries to see bi-directional conduction block
2 as an endpoint, and so what we did was divided
3 the patients into those with bi-directional
4 conduction block and those without bi -
5 directional block to try to ask the question
6 did isthmus ablation make any difference
7 whatsoever.

8 It turns out that in those patients
9 in whom it was not achieved, the success rate
10 was actually higher. The AF success rate was
11 actually higher.

12 This means that isthmus ablation
13 did not improve AF success and, in fact, was
14 irrelevant to AF success. Another table that
15 was included in the PMA amendment but not
16 included here was that when we analyzed
17 success rates by catheter used for the
18 isthmus, it also did not make any difference.

19 So how do I summarize this? Non-
20 investigational catheters were used. They
21 were used in a small proportion of patients.
22 They were used primarily to prevent a
23 condition that the patients did not have, and
24 there was no relationship to AF success either
25 in terms of which catheter was used or

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 achievement of that particular endpoint in
2 isthmus ablation.

3 Let's take a brief look at quality
4 of life as a secondary endpoint in our study.

5 Is it important? Well, obviously you heard
6 from Dr. Kocheril that quality of life was
7 substantially impaired in patients with
8 paroxysmal atrial fibrillation, and quality of
9 life was deemed by the 1998 panel to be a very
10 important endpoint.

11 Quality of life, as you heard, was
12 measured by SF-36 and atrial fibrillation
13 symptom scale, a validated score used in other
14 trials.

15 Here's the mean change in SF-36
16 results by SF-36 subscale. As we showed you
17 previously, all of them are statistically
18 significant and clinically important except
19 for general health.

20 With respect to change in AFSS, we
21 also observed similar large, clinically
22 important improvements in episode frequency,
23 episode duration, and episode severity.

24 So I tried to put all of this into
25 perspective by looking through the literature

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 for SF-36 improvement in other settings,
2 specifically drug therapy, RF ablation, and
3 the Maze surgery. Again, a very large
4 subject, a lot of work to put all of this
5 together.

6 Here's a summary of the results.
7 Here's a snapshot of the results. These are
8 drug trials. These are changes, improvements
9 in SF-36 scores in the drug trials. What you
10 can see here is that the changes are all in
11 the single digit category. Some of them are
12 even negative. These are changes from
13 baseline to follow-up.

14 Most of these trials actually did
15 not show any difference in quality of life
16 between the treatment and the control groups.

17 Here now are the changes in SF-36
18 scores in studies of ablation, and what I've
19 put here on the right is Cardima study
20 results. You can see that these results are
21 far more consistent with the ablation
22 literature than they are with the drug
23 literature, strongly suggesting to us that
24 what we've observed is real and is due to
25 ablation.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 Let's turn next to the issue of new
2 anti-arrhythmic drugs. As you recall,
3 patients who are enrolled in our study were
4 refractory to anti-arrhythmic drugs. They
5 were refractory on average to 2.9 drugs.

6 In follow-up in our study, there
7 were 49 successes, and there were some changes
8 in anti-arrhythmic drug therapy. On the
9 whole, there were increases in three. There
10 was a decrease in 22, and there were new anti-
11 arrhythmic drugs used in 12 patients.

12 Well, obviously, a new anti-
13 arrhythmic drug is a concern for confounding.

14 Let's take a look at what those drugs were.
15 They were in two cases new amiodarone and in
16 other cases flecainide, propafenone, et
17 cetera.

18 We did not collect a reason for the
19 changes, but most of the changes, I believe,
20 were due to tolerance issues and not due to
21 effectiveness issues. As you know, these are
22 drugs with substantial side effect profiles.

23 Now, the big question is: if a
24 patient has received three anti-arrhythmic
25 drugs already, how likely is he to respond to

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 the fourth?

2 Well, there's really very little
3 information out there in the literature, but
4 as you know, the Heart Rhythm Society has
5 already recommended ablation after a single
6 drug failure. So let's ask the question: is
7 there any information out there that tells us
8 about the response of patients to yet another
9 anti-arrhythmic drug?

10 There's only one trial out there.
11 It's from 1991. They looked at serial drug
12 therapy. This was done in AAD naive patients,
13 and even in that patient population they
14 showed a minimal improvement. So in our
15 patient population, how much good is another
16 anti-arrhythmic drug going to do? Probably
17 not much.

18 I'd like to turn to the issue of
19 amplitude measurements. In your panel pack,
20 you may have seen the slide from FDA that says
21 that amplitudes were not measured in 100
22 percent of procedures. I'm here to tell you
23 that that's incorrect.

24 It's important to remember that
25 while amplitude measurement was used in our

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 trial, it was not necessary to measure at
2 every single electrode. There may be some
3 cases in which the multi-electrode catheter is
4 positioned relatively high in the right
5 atrium, and the physician may not have wanted
6 to ablate the superior vena cava. So in that
7 case, the electrode wasn't used.

8 The endpoints that we had proposed
9 using initially were the three listed here.
10 We eventually agreed with FDA that an
11 amplitude decrease would be sufficient, and I
12 remind everyone that an amplitude decrease is
13 a standard measurement in almost all ablation
14 procedures done with RF catheters.

15 Here's a table from the PMA
16 amendment. It's a little bit difficult to
17 see, but I summarize here. Electrogram
18 amplitudes were measured in 87 percent of
19 procedures. In 78 percent of procedures there
20 were before-after measurements. There was a
21 mean 56 percent reduction in electrogram
22 amplitude, and this was a statistically
23 significant change.

24 This is a little bit difficult to
25 see, but it lists the number of patients by

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 lesion, by electrode, by investigator, and you
2 can see that the number of measurements pretty
3 closely matches the number of patients that
4 the investigator treated. This table is
5 simply to let you know that electrogram
6 amplitude measurement was done.

7 But what did the data actually
8 show? Here's what we're looking at. This is
9 the amplitude reduction by lesion, the lateral
10 septal lesion by electrode, and what we have
11 here is the mean reduction in the log of the
12 amplitude. We use log because log was
13 ultimately more normal distribution.

14 Here are the T values, which you
15 can see are very high, and the P values which
16 you can see are very low. Let's plot this.
17 They are very low in every situation.

18 Here's a graph of amplitude
19 reduction, and I just want to parenthetically
20 say that I think this is probably the largest
21 data set of amplitude reductions available.
22 I've never seen anything like this in other
23 papers of AF ablation. The red dots show the
24 electrogram amplitude before ablation at a
25 particular electrode one through eight, and

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 the black dots show amplitude after reduction.

2 The blue dot is the mean before. The green
3 dot is the mean after. You can see it in
4 every single case we observed a large decrease
5 that was statistically significant.

6 FDA has seen these data before.
7 This is Figure 7 from the PMA amendment. What
8 I've plotted here is the electrogram amplitude
9 after versus the electrogram amplitude before.

10 If you think about it, if there were no
11 changes whatsoever, all of the dots would fall
12 on the identity line, the dark line here. If
13 there were a 50 percent or more reduction,
14 they'd all fall below this dotted line here.
15 It's really difficult to see, but it's there.

16 As you can see, the vast majority
17 of points show that we observed a decrease in
18 electrogram amplitude.

19 With respect to amplitude
20 measurements, they were performed. They were
21 not performed in everyone, granted, but they
22 were highly statistically significant, and
23 they certainly are consistent with
24 electrophysiologist experience and represent a
25 significant, clinically important change.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 Most importantly, they are proof to us that
2 cardiac muscle ablation occurred in the study.

3 In summary, the Cardima study meets
4 the regulatory standard of providing
5 reasonable assurance for safety and
6 effectiveness, and as I told you, a randomized
7 trial is not required for this study to be
8 interpreted. This study is internally
9 consistent, and it's also consistent with the
10 ablation literature as I reviewed for you in
11 quite a bit of detail. The bases that FDA
12 have proposed are both unproven and
13 overemphasized, but most importantly they do
14 not impair our ability to interpret the study
15 and find the study approvable.

16 Thank you.

17 CHAIRPERSON RAMSEY: You are at
18 just about ten minutes now.

19 DR. SAKSENA: Thank you, ladies and
20 gentlemen. I will just add to the discussion
21 in certain aspects that relate to endpoint
22 issues and some clinical issues for AF trials
23 in the subsequent set of slides, and I will
24 probably skim over some material for you.
25 There are a variety of standards for endpoints

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 for AF trials, for drug trials devices and
2 ablation, and they vary from time to first
3 detected recurrence, a symptomatic recurrence
4 to actual freedom from recurrence, percentage
5 freedom, permanent AF, and in ablation we've
6 added acute procedural success. Let me
7 summarize it in this table by saying that in
8 drug trials, device trials, and in ablation
9 and for some reason the headers are not
10 showing up here, acute success is only freedom
11 from recurrent AF and quality of life have
12 been a common feature in all of these trials,
13 and these are all present in today's trial.

14 We've had discussions of definition
15 of acute procedural success, and I'll make
16 some comments on that. I'll make some
17 comments on detecting recurrent AF and on
18 outcomes.

19 We need to do a reality check of
20 what are acute procedural outcomes and what we
21 can really expect. In fact, decreased
22 electrograms have been convincingly
23 demonstrated. Things like increased facing
24 pressure have been largely abandoned because
25 they are unreliable at the line of block.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 The line of block demonstration has
2 been confirmed to you. There's no definition
3 of fragmentation. This doesn't exist in right
4 atrial ablation. I've run several guideline
5 panels in catheter ablation for the Heart
6 Rhythm Society. We have no definition for
7 fragmentation in the right atrium. So this is
8 an unrealistic expectation.

9 Arrhythmia induction has been
10 abandoned because it's a nonspecific
11 observation in the atrium and reflects local
12 reentry. Isthmus log is simply not an
13 endpoint for AF trials. So many of these
14 issues are really peripheral to our
15 discussion. We've shown substrate
16 modification and the targeting of atrial
17 electrograms.

18 What we want to illustrate is how
19 we have to do it today. Look at the number of
20 lesions I had to do in this patient to produce
21 compartmentalization. We're talking close to
22 100 lesions, each a minute long. That's how
23 long that procedure takes with current
24 technology, which is also not approved.

25 This procedure can be seriously

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 shortened for patient benefit by the use of
2 the Revelation catheter whether it's placed at
3 this site and on the other septal wall. You
4 can achieve a complete line with one
5 placement.

6 What about the endpoints? Are they
7 still current? The amplitude electrogram
8 measurements are still current. This is taken
9 from a Johns Hopkins trial that was just
10 published, showing that reduction in
11 electrogram amplitude is a relevant endpoint
12 even in 2006 and was used by them.

13 Finally, the important issue of
14 detecting AF recurrences. Well, think about
15 how we are doing this in landmark trials, such
16 as Affirm and Race published in the New
17 England Journal. We're doing this at routine
18 follow-up at three to six month ECG intervals
19 and some symptoms can prompt a visit, and none
20 of them are on a mandated tri-celephonic
21 monitoring or electrogram monitoring.

22 I sit today on a steering committee
23 of a heart failure trial for the NIH where two
24 ECGs are done in a four-year period to detect
25 atrial fibrillation. The current study far

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 exceeds the standards that are used there.

2 The JHU trial looked at six months
3 success rates, and that is a valid point at
4 which to look at the results of catheter
5 ablation procedure.

6 They also included in their long
7 term improvement patients taking anti-
8 arrhythmic drugs. We know that this is the
9 real world, and we look at anti-arrhythmic
10 drugs in conjunction with ablation.

11 In this trial, you can look to the
12 follow-up. Was it eight to 12 weeks? And the
13 subsequent follow-up was at the discretion of
14 the M.D. So the patient often going to the
15 doctor is part of that follow-up, and ECGs
16 occurred at these follow-up visits.

17 There were three month telephone
18 interviews making that a normal process. But
19 what we see now in these studies is a fall-off
20 in left atrial ablation success rates. We're
21 talking 60 percent. We're no longer talking
22 80 and 90 percent.

23 In fact, in some of these studies,
24 we censor the initial follow-up period of one
25 month. Even one cardioversion was allowed in

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 this particular randomized trial, a much more
2 softer measurement of recurrences. These
3 recurrences were simply excluded from the
4 analysis.

5 So let's put this study in the
6 landscape that we have of AF ablation
7 literature and with that censoring, we still
8 have only 60 percent success rate.

9 In fact, if you look at a single
10 procedure of left atrial ablation in the study
11 that was recently published from Hopkins, it
12 falls into the 20 to 40 percent range,
13 depending on the procedure you read, and we
14 have fallen below the halfway mark, and this
15 is a realistic assessment of what is happening
16 in the real world.

17 In the worldwide survey, we add
18 patients who get drugs into the successes, and
19 we can plot them over time. The use of an
20 anti-arrhythmic drug is conventional practice
21 today in judging the results of ablation.

22 The only way to know true ablation
23 results or true recurrence rates is to
24 increase surveillance. So here is a study
25 that shows seven-day Holter monitoring in the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 patient post ablation. Look at the median.
2 The median didn't really change. Increased
3 surveillance shows more recurrences. So the
4 more surveillance you do, you see more
5 recurrences.

6 But does AF ever go away? This is
7 data we published a few years ago with
8 implanted pacemakers and looked at the natural
9 history of AF, and you can see that the total
10 AF burden never goes away. It never goes down
11 to zero. So it was there.

12 And, in fact, whether you do a six
13 month or a 12 month study, the median remains
14 fairly constant.

15 Finally, look at compliance rates.
16 Here's a study published in the New England
17 Journal. Patients don't report and comply
18 with event monitoring. In this case 30-day
19 Vinn monitors are only worn by 30 percent of
20 patients. That's the real world of clinical
21 trialing in this field.

22 Finally, you heard a discussion of
23 anti-arrhythmic drugs here and prior use of
24 two or more drugs. There's little more
25 evidence of any further benefit of the third

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 or fourth drug. The use of amiodarone has
2 been shown to increase efficacy in the Affirm
3 trial and standard DDDR pacing has no impact
4 on results.

5 But the use of increased drug was
6 minuscule and has no real likely benefit on
7 the outcome. Only one pacemaker was put in
8 that was an adverse event, and there's no
9 evidence that pacing in a single site improves
10 outcomes, and the use of flutter ablation with
11 a non-protocol catheter, flutter ablation, has
12 no efficacy in preventing AF.

13 And if you look at this, you can
14 see even in surgical series where you do left-
15 sided atrial ablation with an epicardioprobe,
16 never touch the right side, post op. pacemaker
17 implantation is routine because bradycardia
18 coexists in these patients.

19 So let me conclude by saying that
20 we need to give our patients more opportunity
21 for improvement, and we can do that by making
22 tools available that allow us to do these
23 hybrid forms of treatment, that give us the
24 kind of results that we have shown here over a
25 five-year and beyond period, and this is one

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 of the tools we need, and you can see that
2 this is valuable in both paroxysmal and
3 persistent AF.

4 We can document these efficacy with
5 implanted device data logs. Here's a right
6 atrial Maze of patient with an implanted
7 device data log showing resolution of the
8 atrial fibrillation after the procedure.

9 And here's a review of literature
10 that shows that our realistic assessment of
11 recurrence rates are in the 33 percent range.

12 So let me now conclude by saying to
13 you that we have to weigh our comparative
14 therapies. The right atrial ablation efficacy
15 has to be weighed versus left atrial ablation.

16 The risks of left atrial ablation are well
17 defined, and they include stroke, perforation
18 of the heart, atrioesophageal perforation, and
19 pulmonary vein stenosis and death.

20 There's major damage done to the
21 left atrium in these procedures. Just look at
22 these pictures of voltage maps. Multiple
23 procedures, major complications, six percent
24 and beyond, and most importantly, there are
25 risks that we have not even assessed.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701