

1 For example, this study of
2 transcranial dopplers shows microbubbles and
3 the possibility of microembolic signals in all
4 of these patients with a stroke risk.

5 Even more disturbing, this report
6 from Bonn, Germany. Ten percent of patients
7 who had MRIs after left atrial ablation had
8 silent CVAs. So the editorial that went with
9 it had this line. The potential long term
10 effects of silent emboli in terms of memory
11 deficits, early dementia and subtle cognitive
12 defects are essential for ablationists to
13 consider and patients to consider.

14 We need to give our patients
15 information, and that's validated by this
16 study from St. Luke's-Roosevelt where they
17 show that during --

18 CHAIRPERSON RAMSEY: One minute.

19 DR. SAKSENA: -- a left atrial
20 ablation procedure we are seeing strokes.

21 So what is the contrast? The right
22 atrial Maze procedure as an average of one
23 procedure per patient, occasional
24 cardioversion, no deaths and strokes.

25 So let me conclude by saying that

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1 we have a place, and we can discuss this in
2 the rebuttal section, of the kinds of places
3 where we would use this procedure.

4 So thank you very much for your
5 attention.

6 DR. CHER: I know that we're
7 limited in terms of times, but we have one
8 more presenter. Could I ask the Chairman for
9 five minutes for him?

10 CHAIRPERSON RAMSEY: Unfortunately
11 I can't do that because I have to give FDA the
12 same amount of time. You are free to use the
13 rebuttal period to present your five minute
14 presentation.

15 DR. CHER: Okay. Thank you.

16 CHAIRPERSON RAMSEY: We now have a
17 brief session where the panel may ask the
18 sponsor clarifying questions, and I want to
19 emphasize these are clarifying questions about
20 the presentation. We'd only like to do this
21 for about five minutes. There will be time
22 for a more involved discussion, of course, as
23 we get in later.

24 So let me turn it to the panel and
25 ask if they have any clarifying questions for

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1 the sponsor.

2 DR. SACKNER-BERNSTEIN: In the
3 presentation, you refer to the compliance of
4 the transmissions, and you broke it down by
5 those who transmitted at least three, those
6 who transmitted at least four. Can you tell
7 me how many subjects who transmitted at least
8 four times, which would mean weekly in the
9 month six period, transmitted those four times
10 that were all asymptomatic?

11 Four weekly asymptomatic whether
12 they had additional or not, how many of those
13 were there?

14 DR. CHER: I don't have that number
15 exactly right now. However, in the slide we
16 did present the number of patients who had
17 four transmissions during the six month
18 period. I can tell you that the vast majority
19 of those asymptomatic transmissions were
20 normal sinus rhythm. They were not atrial
21 fibrillation.

22 DR. SACKNER-BERNSTEIN: So you
23 don't know how many of those more than four,
24 four or more, included 100 percent compliance
25 for the individual patients with four weekly

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1 transmissions as per schedule?

2 DR. CHER: The data that I showed
3 in that table -- and I'm sorry I can't recall
4 the numbers exactly -- did show the number of
5 patients with four transmissions during the
6 sixth month. I believe that was roughly half
7 of the patients, but I can't recall the exact
8 number.

9 CHAIRPERSON RAMSEY: Yes.

10 DR. BROWNER: I believe that Dr.
11 Cher stated that -- and I think I'm quoting
12 you -- that regression to the mean is
13 irrelevant, but to me even your own data
14 suggests that regression to the mean would
15 explain 16 percent of successes. So you
16 consider the 16 percent irrelevant or did I
17 misunderstand that 16 percent would be
18 explained solely by a regression to the mean?

19 DR. CHER: I acknowledge that
20 "irrelevant" may have been a strong word. I
21 think what our analysis shows is that due to
22 random variation alone, there's a very small
23 proportion of patients who might have episode
24 reductions consistent with our definition of
25 success compared to what we actually observed,

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1 58 percent of successes. I would argue that
2 that 16 to 20 percent that might be due to
3 regression to the mean is not relevant.

4 CHAIRPERSON RAMSEY: Thank you.

5 Any further questions? Yes.

6 DR. BROWNER: I had a question
7 along the same line as Dr. Sackner-Bernstein.

8 I find it a little difficult to understand
9 how many patients transmitted at six months,
10 whether they were symptomatic or not, and how
11 many transmitted at each week within the six
12 months. Is that data available?

13 DR. CHER: I did not do an analysis
14 by week, but rather than the total number of
15 transmissions and the total number of weekly
16 transmissions by month.

17 If the Chair permits, I can go back
18 to that slide. I could probably discuss it in
19 more detail.

20 CHAIRPERSON RAMSEY: We have a
21 couple of minutes. If you'd like to do that,
22 you can.

23 DR. CHER: Okay. Could I ask for
24 the presentation to be put back up? Perhaps
25 while that's happening we can go on to the --

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1 oh, here we go.

2 I think this will be helpful for
3 the panel. There were a total of 43 patients,
4 roughly half of the 84, who had three or more
5 weekly strips. Then there were a total of 35
6 patients, about -- I can't do the calculation
7 -- perhaps 40 percent that were entirely
8 compliant with four weekly rhythm strips
9 during the sixth month of transmission. So
10 here are the numbers.

11 And as you can see, amongst these
12 35, the success rate was actually very high.
13 So, again, I'd like to point out the
14 importance of this in that in those patients
15 who were highly compliant, we did not observe
16 a lower success rate. We actually observed a
17 higher success rate.

18 It makes us wonder. Obviously we
19 don't have the data, but it makes us wonder if
20 these patients were more compliant might we
21 also have a higher success rate, but at the
22 same time I told you that these patients were
23 also ones that included several people who
24 were already study failures and may have
25 already undergone, for example, an AV node

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1 ablation and a pacemaker treatment. Those
2 patients would not be that motivated to send
3 in those weekly transmissions, which is
4 reasonable. They've already undergone a
5 definitive salvage treatment.

6 DR. BROWNER: Thank you.

7 CHAIRPERSON RAMSEY: We might have
8 time for one more quick question. Go ahead.

9 DR. SACKNER-BERNSTEIN: The success
10 rate that you showed on your slide for the
11 primary endpoint at six months was 49 out of
12 84, which comes out to 58 percent. I noticed
13 that the slide did not have confidence
14 intervals for that estimate. Can you provide
15 those?

16 DR. CHER: They're roughly plus or
17 minus ten percent. The study power was based
18 on the binomial distribution requiring 80
19 percent -- I'm sorry -- 80 patients with a
20 power of 80 percent and an alpha of .05 to
21 give a confidence limit of plus or minus ten
22 percent. That's what the power calculation
23 was based on, and it was deemed sufficient to
24 have enough information to get a sense of the
25 precision of the success rate estimate.

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1 CHAIRPERSON RAMSEY: Real quick.

2 DR. SLOTWINER: During the ablation
3 procedures did the electrophysiologist use a
4 certain amplitude reduction to decide whether
5 more ablation was required at that site or was
6 it a set duration ablation for each electrode?

7 DR. CHER: The instructions to the
8 physician were to ablate for 60 seconds at 50
9 degrees, 35 watts, with a maximum impedance of
10 200 ohms, and the physician could use his
11 discretion as to whether or not another
12 ablation could occur. So some physicians may
13 have ablated twice, but it was at their
14 discretion and was dependent on what they
15 observed in terms of electrogram amplitude
16 decrease.

17 You know, we had to let the
18 physicians do what they know how to do, which
19 is apply an ablation catheter to the atrial
20 wall.

21 DR. KOCHERIL: If I could add to
22 that quickly, basically we were looking at 50
23 percent reduction, but often by a visual
24 estimate. The usual crux of the procedure is
25 to make sure that if a single lay of the

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1 catheter doesn't encompass the line from SBC
2 to IVC, was to make sure we overlapped so that
3 there would be adequate lesion placement.

4 And you know, there is all kinds of
5 variation, as you would know, from catheter
6 movement and patient breathing and all of
7 that, but, yes, we were looking for at least a
8 50 percent decrease, and the major issue was
9 making sure that we covered the entire region
10 of the line.

11 DR. CHER: One more thing I'd like
12 to clarify is that the before or after
13 amplitude measurements rely on extreme patient
14 participation, that is, the catheter has to be
15 in exactly the same place, and if the patient
16 takes a deep breath or coughs or sneezes, the
17 catheter position might move a tiny bit,
18 somewhat limiting the amount of reduction that
19 we would see.

20 So I think that the numbers we are
21 seeing are actually an underestimate of the
22 actual ablation and the improvement in
23 electrogram amplitudes that's really existing.

24 CHAIRPERSON RAMSEY: Okay. Well,
25 thank you to the sponsor for your

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1 presentation, and thanks for your questions,
2 everyone.

3 We're going to take a 15 minute,
4 slightly less than 15 minute break. I'd like
5 everyone back at 11, please, to resume.

6 (Whereupon, the foregoing matter went off the
7 record at 10:50 a.m. and went back
8 on the record at 11:03 a.m.)

9 CHAIRPERSON RAMSEY: Okay. We are
10 all here now.

11 So it's now time for ODE to give
12 their presentation on the issue, and they will
13 introduce the speakers, and as with the
14 sponsor, it's 90 minutes.

15 Go ahead.

16 DR. TILLMAN: Thank you.

17 Good morning. My name is Dr. Donna
18 B. Tillman, and I am the Director of the
19 Office of Device Evaluation, or ODE, in the
20 Center for Devices and Radiological Health.

21 On behalf of ODE, as well as the
22 Division of Biostatistics and the Office of
23 Surveillance and Biometrics, I'd like to
24 welcome the panelists and thank you in advance
25 for the time and effort you have put into and

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1 will put into the review of this challenging
2 topic.

3 This morning I will introduce the
4 FDA review team and provide a summary of their
5 presentation. I'd like to point out that
6 throughout the presentation, different
7 presenters may refer to the PMA review team as
8 the FDA review team, FDA, or ODE, and it's
9 really one and the same thing.

10 This morning the FDA review team
11 will summarize for you their reasons for
12 issuing the two not approvable letters for the
13 Cardima Revelation Tx with NavAblator system.

14 Dr. Bram Zuckerman, the Director of the
15 Division of Cardiovascular Devices, or DCD,
16 will provide an overview of the device design
17 and file history, as well as some background
18 information relating to atrial fibrillation.

19 He will also provide a brief
20 overview of the FDA review and the reasons for
21 the not approvable decision.

22 Next Dr. William Maisel will then
23 provide a short presentation of the current
24 approaches to treatment of atrial
25 fibrillation, as well as discuss the

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1 importance of acute procedural endpoints for
2 trial design.

3 Dr. Maisel is Assistant Professor
4 of Medicine in the Cardiovascular Division of
5 Beth Israel Deaconess Medical Center in the
6 Harvard Medical School. He also served as the
7 co-primary reviewer for the May 29th, 2003
8 Cardima panel meeting, and he completed a
9 homework assignment of the Amendment 6 data
10 for the FDA review team.

11 Dr. Leslie Ewing, the clinical
12 reviewer for the PMA, will then present FDA's
13 clinical review of the Cardima clinical trial,
14 followed by Dr. Hang Li, the statistical
15 reviewer of the PMA, who will provide the
16 statistical review.

17 Dr. Maisel will then come back to
18 the podium to give a brief discussion of his
19 views on the highlights from the May 29th,
20 2003 Cardima panel meeting.

21 And lastly I will close with a
22 brief conclusion and recommendations.

23 So with all of that being said, I'd
24 like to turn the podium over to Dr. Bram
25 Zuckerman, who will provide an introduction to

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1 FDA's review of the Revelation Tx system.

2 DR. ZUCKERMAN: Thank you, Dr.
3 Tillman, and thank you, panel members, for
4 your time here today.

5 Atrial fibrillation is an important
6 public health problem. It is the most common
7 arrhythmia seen in clinical practice and is
8 estimated that more than two million Americans
9 have this disorder. AF manifests in multiple
10 ways and is a highly heterogeneous condition.

11 The hemodynamic impairment and thromboembolic
12 events associated with this rhythm disorder
13 can result in significant morbidity and
14 mortality in affected patients.

15 Treatment options for rate and
16 rhythm control include medical therapy, the
17 surgical Maze procedure, and percutaneous
18 catheter ablation therapy. While percutaneous
19 catheter ablation therapy is currently being
20 actively investigated for the treatment of
21 atrial fibrillation, it should be understood
22 that there are currently no FDA approved
23 catheter systems for treatment of atrial
24 fibrillation.

25 The FDA Division of Cardiovascular

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1 Devices, otherwise known as DCD, has been
2 actively involved in promoting device
3 development in this area. In addition to
4 publishing a guidance document in 2004 on
5 trial design for atrial fibrillation, DCD has
6 also been working with multiple sponsors and
7 professional societies in this dynamic and
8 challenging area.

9 While there may be significant
10 debate in the electrophysiological community
11 about the best type of percutaneous ablation
12 procedure that should be performed, the
13 division of cardiovascular devices does not
14 have an established preference. Instead, the
15 ablation study, whether right or left sided,
16 should be designed and executed to support the
17 claims sought by the device manufacturer.

18 The sponsor has already shown you
19 the Cardima ablation system and reviewed
20 principles of operation. Please remember that
21 the NavAblator catheter, as well as the
22 Revelation Tx catheter is an integral part of
23 the Cardima ablation system. Therefore, the
24 safety and effectiveness of both catheters
25 used as a system is what this dispute is

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1 about.

2 While the sponsor believes that
3 this system has demonstrated a reasonable
4 assurance of safety and effectiveness, FDA
5 does not agree.

6 FDA has issued two not approvable
7 letters, the first for the original PMA and
8 the second one after reviewing Amendment 6.
9 The proposed indications for use from both of
10 these submissions is shown on this slide.

11 We recognize that the sponsor has
12 proposed a new indication statement in this
13 dispute resolution panel pack. However, the
14 newly proposed indication was not the
15 statement that was used when FDA issued the
16 two not approvable decisions.

17 The primary difference between the
18 original indications for use and the revised
19 indication statement is the removal of the
20 mentioning of the NavAblator catheter.

21 As will be discussed in greater
22 detail by subsequent presenters, the Cardima
23 trial was a single arm, unblinded trial. The
24 chronic clinical effectiveness endpoint relied
25 on patients to self-report symptomatic

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1 episodes they believed were atrial
2 fibrillation. The frequency of self-reported
3 symptomatic episodes reported during the 30
4 day baseline period prior to ablation were
5 compared to the 30 day baseline period six
6 months post ablation.

7 Although individual patient success
8 was defined, there was no predetermined goal
9 for the number of patient successes that were
10 necessary for the trial to be considered
11 successful. It was determined that the panel
12 would decide if the number of patients with
13 sufficient episode decrease was clinically
14 meaning.

15 Although the trial design may not
16 be ideal, it was agreed by FDA at the time of
17 the IDE submission that this design was
18 feasible and could produce if executed
19 appropriately valid scientific evidence to
20 support a marketing approval. Unfortunately,
21 as you will hear, the trial has not been
22 conducted well and, thus, the FDA review team
23 believes that the trial data are insufficient
24 to support approval.

25 The sponsor submitted the original

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1 PMA in September 2002. At this time the
2 pivotal trial was still ongoing. On May 29th,
3 2003, the Cardima trial data were reviewed by
4 the FDA Circulatory Systems Devices Advisory
5 Panel. The panel voted against approval of
6 the device.

7 The reasons for the not approvable
8 vote included concerns regarding, one, the
9 lack of appropriately measured acute
10 procedural data; two, noncompliance with
11 patient reporting; three, confounding factors,
12 such as a change in medications and treatment
13 with pacemakers; and four, the excessive
14 number of protocol deviations.

15 You will hear more regarding the
16 panel deliberations from Dr. Maisel shortly.

17 FDA agreed with the panel
18 recommendation and issued the first not
19 approvable letter on June 26th, 2003. In
20 response to this not approvable letter,
21 Cardima submitted Amendment 6 to the PMA on
22 January 21st, 2004. Amendment 6 of the PMA
23 focused only on the Phase 3 study patients and
24 included data for some of the patients that
25 had not yet finished follow-up at the time of

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1 the original PMA submission.

2 The FDA review team carefully
3 reviewed these data. It was felt that the
4 additional data and analyses provided in this
5 amendment did not adequately address the
6 critical study problems raised in the first
7 not approvable letter. FDA, therefore, issued
8 a second not approvable letter on May 21st,
9 2004.

10 Following the issuance of the
11 second not approval letter, Cardima met with
12 the FDA review team to discuss appropriate
13 next steps in June 2004, June 2005, and
14 February 2007. Cardima also met with senior
15 FDA management in mid-2004 and late 2005
16 regarding appeals of FDA review team
17 decisions.

18 In addition to these meetings,
19 there have been multiple telephone and E-mail
20 communications with Cardima representatives in
21 attempts to work towards resolution.
22 Throughout this correspondence FDA has
23 consistently expressed to Cardima that new
24 clinical data are necessary to support
25 approval of the device.

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1 In conclusion, the key reasons that
2 led us to the not approval decisions for the
3 Cardima Revelation Tx Microcatheter with
4 NavAblator system are threefold.

5 First, the acute procedural
6 effectiveness was not demonstrated with either
7 ablation catheter of the Cardima ablation
8 system.

9 Second, the study did not show
10 chronic clinical effectiveness of the system.

11 And, third, the risk-benefit
12 profile cannot be assessed.

13 The acute procedural effectiveness
14 was not demonstrated with either ablation
15 catheter of the Cardima ablation system. For
16 the Revelation TX the data needed to determine
17 acute procedure success is missing in all of
18 the study patients. For the NavAblator
19 catheter, although the acute procedure data
20 was collected and recorded, the results
21 demonstrate that the catheter was not
22 successful in a sufficient number of patients
23 in producing the required lesion line.

24 Several factors contribute to the
25 inability to adequately assess chronic

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1 clinical effectiveness of the system. Because
2 acute successful use of the Cardima ablation
3 system was not shown in any individual
4 patient, chronic clinical effectiveness cannot
5 be attributed to the use of the system.

6 Additionally, if we do accept that
7 chronic effectiveness can be accurately
8 evaluated, only 25 percent of the patients
9 reach the per protocol chronic effectiveness
10 endpoint.

11 Finally, the extent of the bias
12 associated with over reporting of baseline and
13 under reporting at follow-up of the subjective
14 endpoints of symptomatic atrial fibrillation
15 is also unknown.

16 The risk-benefit profile of the
17 Cardima ablation system cannot be assessed
18 since neither the effectiveness nor the safety
19 of the system can be accurately determined.

20 In conclusion, without this
21 information approval of the system cannot be
22 supported.

23 I'd now like to introduce Dr.
24 William Maisel from the Beth Israel Hospital,
25 who will talk briefly about RF ablation.

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1 DR. MAISEL: Good morning. I'm Dr.
2 William Maisel. I am a practicing cardiac
3 electrophysiologist at Beth Israel Deaconess
4 Center, Assistant Professor of Medicine at
5 Harvard Medical School. I'm also the current
6 chair of the FDA Circulatory System Panel and
7 was a panel member at the initial Cardima
8 panel meeting in 2003.

9 What I'd like to do is just provide
10 a little bit of background regarding ablation
11 catheters in general and specifically talk
12 about the factors that affect lesion size;
13 talk about the importance of acute procedural
14 endpoints, and then touch briefly on the role
15 of the right atrium in ablation of atrial
16 fibrillation.

17 Well, the first message is that all
18 lesions are not made the same, and one thing
19 that affects lesion size is the power, the
20 amount of power delivered through the catheter
21 to the electrode.

22 This shows an epicardial ablation
23 in a dog using a four millimeter electrode.
24 So the electrode is the same. All of the
25 slides and data I'm showing you are not

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1 Cardima catheters. This is just general
2 ablation, and you can see that a 40 watt
3 lesion is larger than a 30 watt lesion. So
4 same catheter, different amount of energy
5 creates a different size lesion.

6 Well, the other things that can
7 affect the size of the lesion are both the
8 electrode size and the catheter orientation.
9 On the top is a catheter positioned on a dog
10 thigh muscle that is perpendicular to the
11 muscle and on the bottom is a catheter that's
12 parallel to the muscle. On the right-hand
13 panel there are two different types of
14 electrodes. There's a two millimeter
15 electrode and a five millimeter electrode.
16 For the parallel orientation what you can see
17 is that the two millimeter electrode actually
18 creates a bigger lesion than the five
19 millimeter electrode, all other factors being
20 the same, the same amount of power delivered,
21 and that's because with a smaller electrode
22 there's a higher current density, and the
23 current density results in a larger lesion.

24 So it's not as simple as big
25 electrode, big lesion, small electrode, small

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1 lesion. There are other factors. You can
2 also see on the bottom that just changing the
3 catheter orientation, particularly for that
4 five millimeter electrode, greatly changed the
5 size of the lesion. So there are many factors
6 that affect lesion size.

7 This is an example of a single
8 catheter used on a thigh muscle in a dog, and
9 different parameters were varied, constant
10 voltage on the left, constant temperature in
11 the middle. This is an irrigated catheter.
12 So if you add irrigation, you get a larger
13 lesion.

14 And what you can see is that
15 despite it being the same catheter, depending
16 on the settings, you can get a greatly
17 disparate lesion volume. In fact, the lesion
18 on the right is more than five times greater
19 than the lesion on the left, the same
20 catheter, different settings.

21 So what we've seen is that lesion
22 size can be affected by power, temperature,
23 electrode size, catheter orientation,
24 certainly the catheter type or the type of
25 energy delivered, and atrial anatomy is the

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1 other big factor that can affect lesion size.

2 Here's a picture of a human
3 pathologic specimen of a right atrium. It's
4 sliced open. At the back wall, the smooth
5 back wall is shown. SVC refers to the
6 superior vena cava and the ICV, the inferior
7 vena cava. FO is the fossa ovalis, and the CS
8 OS is where the coronary sinus is.

9 You can see that right atrium is
10 very complex. It's not a smooth structure all
11 the way around. Part of the right atrium has
12 these invaginations that make it challenging
13 and more difficult to get adequate ablation
14 lesions. In fact, there are smooth and rough
15 lesions.

16 And if you imagine a catheter
17 sitting in a parallel orientation on the
18 smooth surface, you can imagine that the
19 lesion will be very different than if it's
20 sitting in an area where there are
21 invaginations in crevices.

22 And, in fact, this does greatly
23 affect the lesion size, temperature of the
24 burn, and potentially the effectiveness of a
25 catheter.

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1 So because of these varying lesion
2 sizes and the factors that can affect ablation
3 with a given catheter and a given patient,
4 acute procedural endpoints are critical to
5 safe and effective ablation. All
6 electrophysiologists use them. We use them in
7 every procedure for every arrhythmia.

8 There are a variety of examples of
9 acute procedural endpoints, and it is not
10 widely accepted that there is only one right
11 answer for the type of acute procedural
12 endpoint that should be used, and these are
13 examples of some, but not necessarily all of
14 the acute procedural endpoints that have been
15 used: decrease in electrogram size, increased
16 pacing threshold before and after ablation,
17 creation of a line of electrical block,
18 fragmentation or widening of the local
19 electrogram, or sometimes induction of
20 arrhythmia at baseline with inability to
21 induce the arrhythmia following ablation. All
22 of these are acute procedural endpoints.

23 Well, here's an example of an acute
24 procedural endpoint, the reduction in
25 electrogram size, and this is from a human

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1 right atrium. On the left-hand side of the
2 screen is pre-ablation. On the right-hand
3 side of the screen is post ablation, and if
4 you just focus on the very top panel where it
5 says A and there's an arrow, that shows the
6 size of the electrogram pre-ablation, and on
7 the right you can see that the electrogram
8 size got smaller.

9 These are extremely simple to
10 measure. They are measured essentially
11 instantaneously. All EP recording systems can
12 be set to record continuously so that you
13 don't have to actually even do anything to
14 record these electrograms other than have the
15 catheter in the heart. They can be
16 automatically recorded continuously. They're
17 very simple to do.

18 So this shows increased pacing
19 threshold as an acute procedural endpoint. On
20 the left is the change in threshold pre and
21 post ablation. On the right is lesion volume,
22 and what you can see is that the changing
23 pacing threshold goes up as the lesion volume
24 increases, and in fact, this is a widely used
25 and easily measured acute procedural endpoint

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1 during ablation procedures as well.

2 We also frequently measure evidence
3 of a creation of a line of blocks. So rather
4 than just assessing individual lesions we
5 measure a series of lesions. On the left-hand
6 panel in the red circle is an example of an
7 electrogram that's measured. On the right-
8 hand side of a line of block there's pacing
9 occurring on the left-hand side of that line
10 of block.

11 When you look at the right-hand
12 panel in the same patient after ablation,
13 there's nothing in that red circle, and that's
14 because a complete line of block has been
15 created, and there's no electrogram; there's
16 no conduction across that line and, therefore,
17 no electrogram on the other side of the line
18 of block.

19 Creation of a line of block is much
20 harder to measure, but it can be measured.
21 It's not adequate to measure it in a single
22 patient and assume it's happening in every
23 patient because of the variables that I have
24 discussed earlier.

25 So the challenge is that what we

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1 know is that the more ablation we apply, the
2 more radio frequency energy we apply, the
3 larger the lesion will get, and the more
4 likely we are to be effective in ablating what
5 we're trying to ablate. Bigger lesions are
6 more likely to help eliminate arrhythmia, but
7 the problem, the ying-yang, if you will, is
8 that less ablation is likely to be safer
9 because bigger lesions are more likely to
10 cause problems.

11 And so these are a variety of
12 examples of potential injuries that can occur
13 when we ablate, particularly in the right
14 atrium. You can get phrenic nerve injury.
15 The nerve runs right near the right atrium and
16 you can end up with diaphragmatic paralysis.
17 You can get thrombus formation, tamponade or
18 perforation, char on the tip of the catheter
19 which can potentially embolize, and superior
20 vena cava stenosis if you apply cautery near
21 the superior vena cava.

22 So, again, these are all things
23 that have been observed during ablation in the
24 right atrium, not necessarily with the
25 catheter that you're considering today.

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1 Well, just finally to touch on
2 where right atrial ablation stands currently
3 in the scheme of ablation for atrial
4 fibrillation. This is data from the Cappato
5 worldwide survey. They sent surveys to close
6 to 800 centers worldwide who perform ablations
7 and got answers back from about a quarter of
8 them. This involves close to 8,000 ablations
9 over several years, and what you can see is
10 that right atrial ablation alone for atrial
11 fibrillation was very popular in the mid-1990s
12 most likely because it's a little easier to
13 perform, but it has fallen out of favor
14 because right atrial ablation alone, the
15 consensus generally is that it's less likely
16 to be successful.

17 Now, I would caution you when
18 interpreting data in general about the role of
19 right atrial ablation. There's a very
20 important distinction between right atrial
21 ablation alone and bi-atrial ablation where
22 lesions are also made in the left atrium or
23 right atrial ablation that occurs after
24 someone has had a left atrial ablation in the
25 past. Those are very different circumstances,

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1 and this chart shows you right atrial ablation
2 alone.

3 So to summarize, I hope you get the
4 message that many factors affect lesion size,
5 and because of that, it's critically important
6 to measure acute procedural endpoints, and
7 it's critically important to measure them at
8 the time you do the ablation on the lesion
9 that you've just created. Because of the
10 different topography and the different amounts
11 of energy that can be supplied, one lesion can
12 be effective and a lesion right next to it can
13 be ineffective.

14 So in general, we don't just
15 measure acute procedural endpoints on some of
16 the lesions we do. We like to have a measure
17 that each of the burns as we go is effective
18 in some way.

19 I hope you can appreciate the role
20 of the right atrium in the ablation of atrial
21 fibrillation. It certainly doesn't
22 necessarily have no role, but it has fallen
23 out of favor with regard to stand alone
24 procedures.

25 At this point I'd like to introduce

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1 Dr. Leslie Ewing who will provide the FDA's
2 clinical review.

3 DR. EWING: Thank you, Dr. Maisel.

4 I will be presenting the FDA
5 clinical review of the Cardima study. The
6 Cardima clinical trial was a single arm,
7 unblinded investigation conducted in three
8 phases. Phase 2(a) and 2(b) were feasibility
9 and Phase 3 was a pivotal trial. Each patient
10 was given a transtelephonic event recorder
11 with which to record and transmit episodes of
12 symptoms. A 30-day period at baseline was
13 compared to another 30-day period six months
14 after ablation to determine the chronic
15 clinical effectiveness of the catheter system.

16 There were two main submissions of
17 data from this trial to the FDA. The first
18 submission we'll call the original PMA, had
19 data from Phases 2(b) and 3. This data was
20 presented to the Circulatory Systems Advisory
21 Panel in May of 2003. Dr. Maisel will later
22 present a summary of that panel meeting.

23 The second large submission was
24 Amendment 6 to the PMA, submitted in January
25 2004 after the first not approvable letter.

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1 This amendment contained data on patients from
2 Phase 3 or the pivotal trial only.

3 The procedures in Phase 3 were
4 performed from September 2000 to August 2003.

5 The pivotal trial was ongoing when the
6 original PMA was submitted. The original PMA
7 contained six month follow-up data on 88
8 patients, all of the patients in the
9 feasibility trial Phase 2(b), and the initial
10 52 patients with six month follow-up data from
11 the pivotal trial.

12 This was the data presented at the
13 May 2003 panel meeting. Amendment 6 contains
14 six month follow-up data on 84 patients, all
15 from Phase 3. This amendment also included
16 multiple additional analyses which included a
17 re-analysis of compliance with event recording
18 at the sixth month, a sensitivity analysis of
19 event recordings, and an analysis of anti-
20 arrhythmic medications.

21 The most important protocol
22 difference between Phase 2(b) and 3 was the
23 addition of the NavAblator catheter. Ablation
24 lesions, acute procedural effectiveness
25 endpoint, and chronic clinical effectiveness

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1 endpoints were the same. Each patient was to
2 have three lines of ablation lesions performed
3 in the right atrium, one between the inferior
4 vena cava and superior vena cava or a
5 posterior lateral line; another on the
6 posterior atrial septum; and a third at the
7 cavotricuspid isthmus.

8 An anterior line was optional
9 during Phases 2(a) and 2(b) and was removed
10 from the protocol early in Phase 3 due to
11 risk of sinus node damage. The protocol
12 specified these lines in both Phases 2(b) and
13 3. All of these lesions were first to be
14 attempted with the Revelation Tx catheter, and
15 if the isthmus lesion was not created
16 successfully, then the NavAblator catheter was
17 to be used.

18 The protocol states that the acute
19 procedural success endpoint for the Revelation
20 Tx was a demonstration of reduction in
21 amplitude, fragmentation, or widening of local
22 electrograms, split potentials, or increase in
23 pacing threshold at the line of ablation.
24 Measurement of acute procedural success is a
25 per patient assessment.

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1 During the development of the
2 investigational protocol, FDA and Cardima
3 agreed that decreasing the size of atrial
4 electrogram will be recorded as a proxy
5 endpoint for documenting a line of block at
6 the site of the ablation lesions.

7 The preclinical animal data showed
8 that the best indication of a transmural or a
9 full thickness ablation lesion as increase in
10 pacing threshold. The next best was at least
11 50 percent decrease and atrial electrogram
12 amplitude.

13 Cardima set up in the protocol an
14 objective method for assessing the atrial
15 electrogram measurements. The atrial
16 electrogram measurements were to be recorded
17 and sent to a core lab for blinded review.

18 Core lab review of the atrial
19 electrograms would help decrease the impact of
20 investigator bias. The NavAblator, a
21 procedural success endpoint was a
22 demonstration of bi-directional conduction
23 block at the cavotricuspid isthmus. The FDA
24 performance goal for this lesion set is at 90
25 percent of patients treated will have bi-

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1 directional conduction block with lower bound
2 of 80 percent.

3 Use of nonprotocol catheters is
4 considered a failure of the investigational
5 device. This was communicated to Cardima
6 throughout the history of the investigational
7 study, and this is standard for all ablation
8 catheter investigations. If the
9 investigational catheter is unable to produce
10 the desired result and the investigator
11 chooses to use another catheter to adequately
12 treat the patient, then that patient is
13 considered an acute and chronic study failure.

14 The chronic effectiveness endpoint
15 was decrease in number of self-reported
16 symptomatic AF episodes at the sixth month
17 compared to the baseline 30-day period. If
18 the patient had three or four symptomatic AF
19 episode recorded during the baseline period,
20 they're required to have 75 percent reduction
21 in numbers of AF episodes at the six months to
22 be considered as success of the ablation
23 procedure while on this same medications or
24 reduced dose.

25 If a patient had five or greater AF

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1 episodes, they were required to have 50
2 percent reduction.

3 To insure compliance with the
4 recording procedure, the patients were
5 required to record once a week plus
6 symptomatic episodes during both the third and
7 sixth month post ablation. Therefore, the
8 minimum number of transmissions required to
9 assure good compliance would have been the
10 four routine transmissions each during the
11 third and sixth month post ablation.

12 After enrolling in the trial,
13 patients were required to have three episodes
14 of symptomatic AF to be eligible for the
15 ablation procedure. There was no mechanism in
16 place to insure that all reported episodes
17 were discrete. In other words, there's no
18 requirement to document normal rhythm between
19 episodes. Therefore, patients could have
20 reported multiple times during a single
21 episode of AF.

22 There is a secondary effectiveness
23 endpoint described in the protocol which is a
24 clinically meaningful improvement in the
25 quality of life measured by the short Form 36

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1 and the atrial fibrillation severity scaled
2 questionnaires compared to baseline. Patients
3 completed the questionnaires at baseline and
4 at three and six months.

5 The safety endpoint of the trial
6 was the incidence of complications both during
7 the first seven days after ablation and in the
8 24 months' follow-up.

9 CHAIRPERSON RAMSEY: Sixty minutes.

10 DR. EWING: This slide shows the
11 total numbers of patients per study phase. As
12 stated previously, the ablation procedure did
13 not change during Phases 2(b) and 3.
14 Amendment 6 reported the pivotal study data
15 only, and that portion of the trial, the
16 safety cohort was described to be the 93
17 patients with procedural data and the
18 effectiveness cohort for the pivotal trial
19 included only 84 patients with six month
20 follow-up data.

21 We've included safety information
22 on patients in Phase 2(b) also. This patient
23 accountability slide is similar to what you've
24 seen from Dr. Kocheril and shows that there
25 are 178 patients screened, 98 received the

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1 ablation procedure. There are 93 that had
2 verified data at the time of the submission of
3 Amendment 76 and those of the Phase 3 safety
4 patients, there were 84 that had six month
5 follow-up data, and those are the
6 effectiveness cohort. There were 64 patients
7 with 12 month follow-up and 30 with 24 month
8 follow-up.

9 The safety group was 131 patients
10 from both Phases 2(b) and 3.

11 A number of catheters and catheter
12 combinations were used in this study. There
13 are a total of 95 procedures performed in 93
14 patients. Two patients had a repeat ablation
15 procedure to treat atrial flutter. Fifteen
16 percent have the revelation procedure to
17 treat A-12 flutter. Fifteen percent have the
18 Revelation Tx used only. Fifty-seven had both
19 the Revelation Tx and the NavAblator used, and
20 in 28 percent of the procedures a nonprotocol
21 catheter was needed to be used because the
22 Cardima ablation catheter failed to produce
23 the desired ablation lesion or required
24 electrophysiologic effect.

25 There are five different

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1 nonprotocol catheters used in this study.

2 The first of the FDA main concerns
3 with the study is assessment of procedural
4 effectiveness. The acute procedural
5 effectiveness was not demonstrated with either
6 ablation catheter of the Cardima ablation
7 system. I will go into some detail on the
8 measurement of the acute procedural success
9 for the Revelation Tx in the next several
10 slides.

11 For the Revelation Tx, the complete
12 data needed to determine acute procedural
13 success are missing in all of the study
14 patients. For the NavAblator catheter,
15 although acute procedural data was collected
16 and recorded, the results demonstrate that the
17 catheter was not successful in a sufficient
18 number of patients in producing the required
19 ablation line.

20 Cardima has stated in the original
21 PMA, the presentation of the 2003 panel and in
22 Amendment 6 to the PMA that the data was not
23 collected on acute procedural endpoint of the
24 Revelation Tx catheter. Cardima states that
25 they cannot determine which, if any, of the

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1 individual patients met the acute procedural
2 endpoint for the Revelation Tx catheter.

3 This slide shows an excerpt from
4 the protocol on the use of the Revelation Tx
5 during the ablation procedure. The Revelation
6 Tx catheter has eight electrodes that can be
7 used for making ablation lesions. The
8 investigator determines which electrodes that
9 he or she will use depending on tissue
10 contact. Each electrode is used individually.

11 After the first ablation application, the
12 protocol directs the investigator to continue
13 RF ablation with the next electrodes in line
14 and complete the entire sequence of the burn
15 line, then move the catheter to overlap the
16 gap.

17 The investigator is instructed to
18 look at the catheter after the end of each
19 burn line to look for thrombus or coagulum on
20 the catheter.

21 This slide show a picture of the
22 Revelation Tx ablation catheter with its eight
23 ablation electrodes. Each electrode is six
24 millimeters long and separated from the next
25 electrode by a thermocouple. Thermocouple

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1 measures temperature does not ablate.

2 After the catheter is determined to
3 be in good place by the investigator, each
4 electrode is activated one by one. The atrial
5 electrogram is to be recorded prior to energy
6 delivery and then after energy delivery for
7 each electrode. So if eight electrodes are
8 used, then there would be eight paired
9 measurements or 16 total measurements.

10 After the initial lesions are
11 placed, the catheter is moved and lesions
12 performed to overlap the gap. If each
13 electrode has a decreased amplitude after
14 ablation, then that line of ablation could be
15 considered successful for that patient.

16 After the clinical memo for the
17 panel pack was written and sent to you, we
18 pulled numbers of missing atrial electrogram
19 measurements from the Cardima raw data. This
20 data was submitted after Amendment 6.

21 This slide shows the average number
22 of lesions or burns per lateral and septal
23 line performed by the Revelation Tx. All of
24 the patients have missing electrogram
25 measurements.

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1 Cardima has reported in Amendment 6
2 504 measurements for the posterior lateral
3 line and 424 for the septal line. They've
4 averaged the measurements across the entire
5 patient group instead of providing per patient
6 acute effectiveness. They report that the
7 complete data, the pre and post ablation
8 electrogram measurements were electrode were
9 not collected. One hundred percent of
10 patients had missing atrial electrogram data.
11 Therefore, the per patient acute procedure
12 success cannot be determined.

13 As you've heard already, acute
14 procedural endpoints are necessary for
15 assessment of clinical ablation procedures and
16 the FDA assessment of safety and effectiveness
17 of ablation devices. Procedural endpoints are
18 necessary to identify the goal of the ablation
19 procedure and, therefore, the point at which
20 applications of ablation lesions can be
21 stopped by the investigator. They are
22 necessary to assess whether or not the patient
23 truly received the therapy.

24 We do not have any objective
25 evidence that the patient actually received an

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1 effective line of ablation lesions with the
2 Revelation Tx. You cannot attribute the
3 ultimate outcome of the patient to the device
4 treatment unless you know the patient had a
5 successful use of the investigational device.

6 They are also necessary to assure
7 the device is used in the same way in all
8 patients in the trial, provide data upon which
9 the base instructions to new users of the
10 device system, and to identify potential
11 safety issues.

12 There were several patients that
13 required a catheter other than the Revelation
14 Tx to create the septal and posterior lateral
15 lines of lesions. There are at least four
16 patients that have the NavAblator used to
17 create the septal line and three for the
18 lateral line, and there are at least three
19 patients that had nonprotocol catheters used
20 to create the lines.

21 Acute procedural effectiveness data
22 was collected for the NavAblator catheter.
23 The catheter was used in 77 of the 93
24 patients. Forty-eight of the 77, or 62.3
25 percent, had successful demonstration of bi-

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1 directional conduction block without the use
2 of a nonprotocol catheter.

3 Several factors contribute to the
4 inability to assess chronic clinical
5 effectiveness of the system. Because acute
6 procedural success of the Cardima ablation
7 system was not shown in any individual
8 patient, chronic clinical effectiveness cannot
9 be attributed to the use of the system.

10 Additionally, if we did accept that
11 chronic effectiveness could be accurately
12 evaluated, only 25 percent of the patients
13 reach the per protocol success endpoint.

14 Cardima classified 49 patients as
15 having chronic clinical success in Amendment
16 6. The FDA review team disputes that
17 classification in 28 patients. Therefore, the
18 FDA believes in number of patients that reach
19 the chronic clinical success endpoint in the
20 evaluation of the Cardima catheter system is
21 21 of 84, or 25 percent.

22 Because there is no placebo group
23 or comparator group with an ineffective
24 therapy, it is unknown if the 25 percent would
25 be higher than the placebo rate. The placebo

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1 rate seen in several anti-arrhythmic drug
2 trials ranges from 25 to 40 percent.

3 The protocol specifies that success
4 occurs in the patient on the same medication
5 regimen or decreased dose. The protocol also
6 specifies that patients that are implanted
7 with a pacemaker prior to the sixth month are
8 to be considered a failure.

9 Also, if the investigational
10 catheter system fails to produce the desired
11 electrophysiologic result and a
12 noninvestigational catheter is needed to treat
13 that patient, that patient is considered a
14 study failure.

15 As you can see, the 28 patients not
16 considered by the FDA to be a success of the
17 clinical trial have a combination of reasons.

18 Most commonly, an intervening treatment that
19 could change the perception of symptoms in the
20 patient and, therefore, was prespecified in
21 the protocol to make the patient a failure of
22 the study.

23 The FDA review team and Cardima had
24 multiple conversations about the use of
25 nonprotocol catheters in this investigation.

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1 As documented here, Cardima agreed that the
2 FDA would consider these patients to be study
3 failures.

4 Now, how do the Amendment 6 chronic
5 clinical success numbers compare to what was
6 presented at the 2003 circulatory systems
7 device panel? This is a slide taken from the
8 clinical review presentation at that meeting.

9 As you can see, 24 patients out of 88 were
10 found to have chronic clinical success of the
11 Cardima ablation system, or 27 percent.

12 This is comparable to the 25
13 percent in Amendment 6 from only the pivotal
14 trial. The method of assessing which patients
15 met the chronic clinical success criteria from
16 the investigational protocol were the same for
17 both reviews.

18 An additional problem with the
19 assessment of chronic clinical effectiveness
20 of the system is that we do not know the
21 extent of bias associated with over and under
22 reporting of the subjective endpoint of
23 symptomatic atrial fibrillation episodes.

24 The per patient percent of
25 symptomatic transmissions that were diagnosed

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1 to be AF range from 13 to 100 percent in the
2 baseline transmissions. Patients varied a
3 great deal in their ability to distinguish
4 atrial fibrillation from other causes of
5 symptoms or patients had different thresholds
6 for recording and transmitting rhythm strips.

7 Also, there was no mechanism in
8 place to determine if each transmission
9 represented a discrete AF episode. There were
10 several patients that transmitted frequently
11 during the same day at baseline.

12 Patient compliance with event
13 recording at six months is critical to the
14 determination if there really was a decrease
15 in symptomatic AF episodes. If only one
16 symptomatic episode was not recorded by the
17 patient, it might make a difference if that
18 patient was considered a success or failure in
19 the target level of decrease in episodes.

20 Remember that we do not have any
21 objective measurements to show that the
22 patients actually received an effective line
23 of lesions with the Cardima ablation system.

24 In the original PMA there were 22
25 of 83 patients that had no transmissions in

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1 the sixth month, and 31 additional patients
2 that had between one and three transmissions,
3 which is a total of 63.8 percent with poor
4 compliance. For Amendment 6, Cardima
5 reevaluated the transmission data for the
6 sixth month after ablation. They found that
7 in the original PMA, the sixth month was
8 considered to be 151 to 180 days after the
9 date of the ablation procedure.

10 They also found that the date was
11 not recorded, that the site study coordinator
12 called the patients to tell them to start
13 using their event recorder again.

14 So for Amendment 6, Cardima
15 reanalyzed the transmission data that
16 classified a new sixth month period to be this
17 time at which there were the most event
18 recordings. The analysis of the new six
19 months showed a different success profile and
20 different compliance rates.

21 This new analysis showed that 24 of
22 84 patients had less than four transmissions
23 in the new sixth month time period, or 28.5
24 with poor compliance.

25 The FDA feels that the quality of

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1 life data from this trial can only be
2 supportive. It cannot be used as a primary
3 endpoint. The placebo rate cannot be measured
4 to to an absence of a concurrent control group
5 because of the lack of acute procedural
6 endpoint data. We cannot correlate
7 improvement in QOL with the use of the
8 investigational device system. And this same
9 problem with intervening treatment affects the
10 interpretation of QOL data just as it does the
11 effectiveness of the ablation procedure on AF
12 systems.

13 The third main concern with the PMA
14 is the ability to assess risk versus benefit.

15 As the effectiveness cannot be determined and
16 the details of the use of the ablation
17 catheters, specifically the Revelation Tx, are
18 unknown.

19 In the FDA review five patients had
20 major complications in the first week after
21 ablation. Four other patients required a
22 pacemaker within two weeks of the procedure.
23 If these four patients were included in the
24 adverse event rate, there was a 6.9 percent of
25 the patients that had a major complication.

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1 It is unknown how the investigators used the
2 Revelation Tx catheter during the ablation
3 procedure. It is possible if the procedure
4 had been performed in a standard way with all
5 investigators striving to achieve a large
6 decrease in atrial electrogram amplitude, then
7 the adverse event rate may have changed.

8 The other possible safety concern
9 raised by the study was that 27 patients in
10 Phases 2(b) and 3 had a pacemaker implanted.
11 Fourteen also had AV node ablation. This is a
12 rate of 20.6 percent.

13 It's very difficult to put this in
14 perspective without a concurrent control
15 group. FDA does recognize that these patients
16 are at increased risk of sinus node
17 dysfunction and a need for pacing.

18 So in conclusion, the three key
19 reasons that FDA found the device system not
20 approvable twice is that acute procedure
21 effectiveness was not demonstrated with either
22 ablation catheter of the Cardima ablation
23 system. The study did not show chronic
24 clinical effectiveness of the system, and a
25 risk-benefit profile cannot be assessed.

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1 Dr. Hang Li will now discuss the
2 statistical evaluation of the system.

3 DR. LI: Thanks, Dr. Ewing.

4 As has been indicated in the
5 previous presentations, there are three major
6 concerns that FDA has with regard to the
7 Cardima ablation system in this presentation.

8 In this presentation I will focus on
9 explaining from a statistical perspective
10 FDA's position that the study did not show
11 chronic clinical effectiveness of the system.

12 Let us briefly revisit the primary
13 clinical effectiveness endpoint and the
14 associated definition of chronic success that
15 has been described in Dr. Ewing's
16 presentation.

17 In the next slide, we provide a
18 visualization of it using a graph. This is a
19 graphical representation of the definition of
20 the target level reduction in frequency of AF
21 episodes necessary for a patient to be called
22 a chronic success. The horizontal axis
23 represents the frequency at baseline. The
24 vertical axis represents the frequency at six
25 months.

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1 A patient falling in the blue
2 region meets the target level of reduction in
3 frequency. A patient falling in the white
4 region fails to meet the target level of
5 reduction in frequency. A patient in the
6 purple region is a screening failure and,
7 therefore, is excluded from the pivotal study.

8 A major obstacle to the evaluation
9 of chronic effectiveness of the
10 investigational device system is that we do
11 not have any information on the proportion of
12 chronic success under a completely ineffective
13 therapy investigated in a study similar to the
14 Cardima pivotal study.

15 To elaborate on this observation,
16 let us take a constructive approach. For a
17 patient any difference between the frequency
18 of AF episodes at sixth month follow-up and
19 the baseline frequency under a completely
20 ineffective investigational therapy may be
21 conceptualized as a result of the
22 superimposition of at least three components
23 which we call intra-patient variability,
24 confounding factors, and reporting bias for
25 the purpose of this presentation.

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1 Before going into more detail, let
2 us briefly describe the above three components
3 by looking at the study participant.

4 First of all, to be selected into
5 the study at least three AF episodes per month
6 is needed, which is the starting point.
7 Suppose over the next six months the patient
8 is in a reference state defined as follows.
9 The frequency of AF episodes goes up and down
10 randomly without any systematic change.

11 In such a reference state, the six
12 month frequency differs from the baseline by a
13 random amount. This random difference
14 generates a probability for this patient to
15 reach the target level reduction in AF episode
16 frequency.

17 Now, let us superimpose on the
18 above difference any beneficial effect of
19 confounding factors on this patient. The
20 probability of reaching the target level
21 reduction is increased.

22 Finally, let us add any reporting
23 bias on top of intra-patient variability in
24 the confounding factors. The probability of
25 reaching the target level reduction is further

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1 increased.

2 In the next few slides, we consider
3 our patient population undergoing a study in
4 which the investigational therapy is known to
5 be completely ineffective and every patient is
6 in a reference state.

7 In such a population every
8 patient's frequency of AF episodes goes up and
9 down randomly over a period of time of six
10 months without any systematic change. Let us
11 call the population so constituted the
12 reference population.

13 By definition, in the reference
14 population the frequency of AF episodes at the
15 baseline and at six months must follow a
16 bivariate or joint distribution that has the
17 feature that the marginal distribution of the
18 baseline frequency is the same as the marginal
19 distribution of the frequency at six months.

20 With this in mind, let us picture
21 the joint or bivariate distribution of the
22 baseline in the sixth month AF frequency in
23 the reference population. It should be clear
24 that if this joint distribution has enough
25 scatter or spread, a non-negligible proportion

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1 of patients in the reference population will
2 reach the target level reduction in AF
3 episodes associated with chronic success, and
4 with baseline selection, this proportion is
5 even larger.

6 In a moment I will show an
7 illustrative graph. This slide provides
8 specifications in order to set up the
9 illustrative graph. The common marginal
10 distribution of base line and six month
11 frequencies is specified as Poisson with a
12 mean of four episodes per month.

13 The joint distribution is that of
14 two independent Poissons with a mean of four
15 episodes per month. The selection threshold
16 is three or more episodes per month at the
17 baseline, resulting in a 24 percent screening
18 failure which is in line with what happened in
19 the Cardima pivotal study.

20 This is an illustrative graph of
21 the joint distribution specified in the
22 previous slide. On the top is a histogram of
23 the baseline frequency. On the right is a
24 histogram of the frequency at six months. The
25 purple part of the graph contains screening

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1 failures because the baseline frequency of AF
2 episodes falls below three. The part of the
3 graph to the right of the purple area contains
4 the patients selected into the study. The
5 blue area contains patients who meet the
6 target level of reduction. The proportion of
7 patients who meet the target level of
8 reduction is the total in the blue area
9 divided by the total to the right of the
10 purple area.

11 We can see that even in a reference
12 population in which confounding factors and
13 the reporting bias are both assumed to be
14 absent, there may be a sizable proportion of
15 patients meeting target level of reduction in
16 frequency of AF episodes just due to intra-
17 patient variability and baseline selection.

18 The next slide contains some
19 numerical values. For the joint distribution
20 in the picture in the previous slide, without
21 selection the mean frequency of AF episodes is
22 four, both at baseline and at six months.

23 After selecting patients with three
24 or more episodes per month at the baseline
25 into the study, resulting in the exclusion of

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1 about 24 percent of the patients, the baseline
2 mean becomes 4.77, while the mean at six
3 months is still four due to the specification
4 of independence.

5 So there is a difference between
6 baseline and the six month mean just because
7 of selection.

8 The expected proportion of patients
9 reaching the target level reduction in
10 frequency of AF episodes would be 21.5 percent
11 with baseline selection. It would have been
12 16.3 percent as a proportion of the entire
13 population.

14 For other marginal or joint
15 distributions, for example, a marginal
16 distribution closer to the baseline
17 distribution observed in the Cardima pivotal
18 trial, the above proportions may be
19 considerably higher.

20 Now, let us proceed to the second
21 component of the three component
22 conceptualization, namely, confounding
23 factors. This slide displays some of the
24 instances of confounding factors. They
25 include medication or changing medication,

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1 pacemaker use, and the use of
2 noninvestigational catheters and other
3 experimental artifacts, such as placebo effect
4 which can all service to make the probability
5 of a patient's reaching the target level
6 reduction higher than if the patient is in the
7 reference state.

8 Likewise, those confounding factors
9 result in higher proportion of patients
10 reaching the target level reduction relative
11 to the reference population. In order to
12 address some of the confounding factors, it is
13 specified in the protocol that patients with
14 medication change or dose increase are to be
15 classified as chronic failures, and it is
16 standard practice that patients in whom
17 noninvestigational catheters are used are also
18 to be classified as chronic failures. But
19 those measures can only address some, but not
20 all confounding factors.

21 Let us now turn to the final
22 component of the three component
23 conceptualization, namely, reporting bias.
24 This slide displays some of the underlying
25 causes of reporting bias. Over reporting at

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1 the baseline may be a result of inadvertent
2 multiple transmissions of a single episode due
3 to inexperience or due to overenthusiastic
4 desire to be enrolled in the study.

5 On the other hand, under reporting
6 at follow-up may be a result of lack of
7 motivation or enthusiasm, lack of compliance,
8 or placebo effect.

9 Reporting bias when superimposed on
10 confounding factors further increases the
11 probability of a patient's meeting the target
12 level reduction in AF episode frequency.
13 Likewise, reporting bias results in a higher
14 proportion of patients reaching the target
15 level reduction relative to that resulting
16 from the superimposition of confounding
17 factors on the reference population.

18 Reporting compliance is one
19 indication of the dependability of the
20 measurement of the number of AF episodes. In
21 the original PMA, it was found that 63.8
22 percent of patients had poor compliance in the
23 reporting of AF episodes at sixth month
24 follow-up.

25 In Amendment 6, the sponsor

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1 reported that 28.5 percent of patients had
2 poor compliance. It should be noted that in
3 reporting the 28.5 percent, the sponsor used a
4 definition of poor compliance that is
5 different from the one used to obtain the 63.8
6 percent.

7 The definition underlying the
8 reported 28.5 percent for compliance in the
9 previous slide is based on the sliding 30-day
10 window that contains maximum number of
11 transmissions for each patient. This
12 definition is guaranteed to lead to a better
13 compliance number than a definition in terms
14 of a fixed time window. But it is unclear how
15 much reporting bias this approach can address.

16 It should be noted that the sponsor
17 conducted a post hoc analysis which the
18 sponsor refers to as a sensitivity analysis.
19 In this analysis, reported AF episodes both at
20 baseline and at six month follow-up less than
21 a certain amount of time apart are counted as
22 one episode. Hence, the reported number of AF
23 episodes at six month follow-up is replaced by
24 a smaller number for some patients and left
25 unchanged for the others.

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1 Such an analysis cannot serve to
2 alleviate concerns about reporting bias, nor
3 can it alleviate any other concerns regarding
4 the effectiveness of the investigational
5 device.

6 A useful sensitivity analysis
7 addressing the issue of reporting bias is not
8 available because there is no information
9 regarding the extent to which under reporting
10 has occurred at six month follow-up.

11 This slide goes back to the three
12 component conceptualization. It illustrates
13 our lack of information on the rate of chronic
14 success under a completely ineffective therapy
15 investigated in a study similar to the pivotal
16 study. We don't know the proportion of
17 patients reaching the target level of
18 reduction in frequency of AF episodes in the
19 reference population, and we don't know how
20 much confounding factors in the reporting bias
21 adds to that proportion.

22 Now, let us look at the chronic
23 success rate based on the reported frequency
24 of AF episodes in the Cardima pivotal study.
25 There is a disagreement between the sponsor's

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1 calculation and FDA's assessment. FDA would
2 like to clarify that. Out of 84 patients
3 specified by the sponsor to constitute the
4 effectiveness cohort, which incidentally may
5 not be considered as an intention to treat
6 analysis set, only 21 can be classified as
7 chronic success as defined in the protocol,
8 resulting in an observed rate of 25 percent.

9 Again, we do not have any
10 information on the proportion of chronic
11 success under completely ineffective therapy
12 investigated in the study similar to the
13 Cardima pivotal study and, therefore, cannot
14 evaluate the chronic effectiveness of the
15 investigational device system.

16 CHAIRPERSON RAMSEY: Thirty
17 minutes.

18 DR. LI: A caveat about the
19 calculation in the previous slide. Since
20 there is evidence that in 75 patients the
21 cavotricuspid isthmus lesion was not made per
22 protocol and that there is no evidence that
23 the acute treatment of protocol for the
24 Revelation Tx catheter was followed in the
25 same way in all sites, it remains a question

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1 how analyses that pool data across
2 investigational site can be meaningful or
3 interpretable.

4 The secondary quality of life
5 endpoints share a common set of concerns with
6 the primary clinical effectiveness endpoint
7 regarding interpretability. We do not have
8 any information on what the expected results
9 of the QOL endpoints are under a completely
10 ineffective therapy investigated in a study
11 similar to the Cardima pivotal study.

12 The conceptualization that has
13 served as a framework in understanding chronic
14 success associated with a primary clinical
15 effectiveness endpoint is also applicable to
16 understand the QOL endpoints.

17 Selection of patients based on AF
18 frequency at baseline translates to selection
19 on baseline QOL due to lack of independence
20 between those two variables. The QOL would be
21 better on the average at six months than at
22 baseline in the reference population just
23 because of selection and intra-patient
24 variability.

25 The confounding factors for the

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1 primary clinical effectiveness endpoints are
2 also confounding factors for the second QOL
3 endpoints.

4 The same factors causing reporting
5 bias for AF events may also cause bias in QOL
6 measurement. Reporting bias for AF events
7 itself may lead to bias in QOL measurement.

8 Given the above considerations, P
9 values corresponding to secondary QOL
10 endpoints presented by the sponsor are of
11 questionable interpretability. Not only are
12 the appropriate hypothesis testing not
13 prespecified in the protocol. The appropriate
14 null hypotheses for QOL endpoints are unknown.

15 In summary, baseline selection and
16 intra-patient variability will produce some
17 proportion of chronic successes even with an
18 ineffective therapy. We don't know what that
19 proportion is. Confounding factors in the
20 reporting bases make results even more
21 uninterpretable. Since we don't have any way
22 to satisfactorily address all of these in this
23 study, chronic clinical effectiveness of the
24 Cardima ablation system cannot be determined.

25 This concludes my presentation.

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1 Dr. William Maisel is the next speaker.

2 DR. MAISEL: Good morning, again,
3 or it might be afternoon by now.

4 What I'd like to do over the next
5 few minutes is provide a brief summary of the
6 panel meeting that occurred on May 29th, 2003.

7 I was a panel member and primary reviewer at
8 that meeting. My comments will be
9 specifically only about the data that was
10 presented and available at the time of that
11 meeting. My comments will not pertain to any
12 amendments that may have been submitted after
13 the meeting.

14 The panel was comprised of ten
15 participants with diverse expertise and
16 ultimately the panel voted that the
17 application was not approvable for a variety
18 of reasons, but primarily because of lack of
19 consistently measured acute procedural
20 endpoints, a failure to demonstrate device
21 effectiveness, some safety concerns, and there
22 are some other issues. And I'll try to cover
23 each of these points briefly.

24 As we've heard, the protocol
25 required at least one of the following:

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1 reduction in electrogram amplitude,
2 fragmentation or widening of the local
3 electrogram, appearance of slip potentials or
4 an increase in the pacing threshold. This
5 latter acute procedural endpoint was
6 subsequently removed from the protocol.

7 The panel felt that these acute
8 procedural endpoints were not consistently
9 measured or recorded on the data forms; that
10 there were significant amounts of missing data
11 which could not be retrieved because they were
12 not collected; that the procedural endpoints
13 were not particularly well defined, and by
14 that I mean there were not very specific
15 instructions regarding RF duration.

16 The temperature goals and the
17 amplitude reduction specifics, and in general,
18 it was felt by the panel that acute procedural
19 endpoints were critically important for
20 assessing adequacy of RF delivery, for making
21 a determination about whether additional RF
22 was needed in that patient at that time, and
23 perhaps most importantly, for developing
24 instructions for use.

25 Specifically, while there were a

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1 broad description of the amount in duration of
2 RF that was required, as indicated by the
3 sponsor, when specifically asked how many
4 patients received the recommended amount of
5 RF, if you will, there's no data to support or
6 refute whether or not patients actually
7 receive the indicated amount of RF.

8 Device effectiveness was to be
9 assessed during the sixth month post
10 procedure. Patients were supposed to transmit
11 a recording when they were symptomatic and
12 weekly whether or not they were symptomatic.
13 This would result in a minimum of four
14 transmissions per patient.

15 So based on that minimum four
16 transmissions per patient at the time of the
17 panel meeting, of the 83 patients available
18 for analysis 22 patients had absolutely no
19 transmissions during the sixth month. Thirty-
20 one had fewer than the four minimum
21 transmissions per patient, and so
22 approximately two-thirds did not make the
23 minimum number of transmissions. It was
24 difficult to get at the precise number who
25 made the four weekly transmissions versus

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1 symptomatic transmissions.

2 It was the feeling of the panel
3 that you cannot assume that the patients who
4 did not make transmissions were symptom free
5 and they simply didn't make their
6 transmissions because they didn't feel like it
7 and that they were otherwise feeling well.

8 There was also a sense that this
9 called into question the accuracy of the
10 outcome assessment even for patients who made
11 the minimum number of transmissions, and so it
12 just questions the whole data collection
13 issue, and as has been well discussed, there
14 was an overall poor compliance with the
15 protocol.

16 In addition, the results were
17 somewhat confounded by anti-arrhythmia drug
18 use. The primary endpoint in the protocol was
19 defined as reduction in frequency of
20 symptomatic episodes of atrial fibrillation
21 during the sixth month of follow-up compared
22 to baseline frequency while on the same
23 medications or reduced dosages, and close to a
24 quarter of the patients had an increase in the
25 medication dose or a new medication added.

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1 And then there were a variety of
2 other issues which you may or may not choose
3 to discuss today with the new data set, but I
4 don't have time to go into great detail, but
5 there were multiple catheters including the
6 investigational catheters used in individual
7 patients. There was an overall low rate of
8 isthmus block with the investigational
9 catheters alone.

10 As mentioned, there were variable
11 procedures performed, and we don't have a good
12 sense of exactly what those variable
13 procedures were. Some patients go certain
14 lines. We're not clear on exactly how much RF
15 and where it was applied, and multiple
16 patients ended up receiving AV junction
17 ablation which can confound a symptom
18 assessment and affect quality of life
19 interpretation.

20 And finally, from a safety
21 standpoint, there was a high pacemaker rate.
22 The study protocol states that subjects
23 electing to receive implantable pacemakers
24 prior to six months follow-up will be
25 considered failures. Overall 20 patients

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1 received pacemakers, two within ten days of
2 the procedure, 13 within six months of the
3 procedure.

4 And so as way of a summary, the
5 panel felt that effectiveness was not
6 demonstrated. There was a lack of
7 consistently measured acute procedural
8 endpoints. Significant amounts of missing
9 data, poor compliance with the protocol, use
10 of multiple catheters in individual patients,
11 a low rate of isthmus block within
12 investigational catheter alone, AV junction
13 ablation, confounding symptom assessment, and
14 concerns regarding the high pacemaker implant
15 rate, and this resulted in a vote of not
16 approvable due to these concerns about
17 effectiveness and safety.

18 Thank you.

19 And at this time I will invite Dr.
20 Tillman to provide the FDA summary.

21 DR. TILLMAN: Thank you.

22 Okay. In summary, as you've heard,
23 there's been extensive interaction between the
24 sponsor and FDA throughout the IDE and the PMA
25 process. ODE and the Division of

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1 Biostatistics have reviewed all the data
2 presented by the sponsor fairly and
3 objectively.

4 During the course of our review
5 we've applied substantial internal and
6 external resources and expertise to this
7 project and in an effort to fully evaluate the
8 data submitted.

9 FDA agrees with Cardima that AFIB
10 is an important clinical problem for which
11 additional treatment options are needed. The
12 question of the role of right-sided ablation
13 and treatment of AFIB is a complex one, but
14 it's not the question you have to address
15 today.

16 Today you have to evaluate the
17 safety and effectiveness data of a specific
18 device, the Cardima Revelation system.
19 Unfortunately, as you have heard, the FDA
20 review team continues to have several
21 significant concerns regarding the clinical
22 data and its interpretation.

23 In conclusion and one last time I'd
24 like to revisit and summarize these main
25 concerns. The acute procedural effectiveness

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1 was not demonstrated with either ablation
2 catheter of the Cardima ablation system. For
3 the Revelation Tx, the data needed to
4 determine acute procedural success is missing
5 in all the study patients.

6 For the NavAblator catheter,
7 although the acute procedural data was
8 collected and recorded, the results
9 demonstrate that the catheter was not
10 successful in a sufficient number of patients
11 in producing the required ablation lesion
12 line. This makes it very difficult to write
13 labeling for the device.

14 Several factors contribute to the
15 inability to adequately assess chronic
16 clinical effectiveness of the system. Because
17 acute successful use of the Cardima system was
18 not shown in any individual patient, chronic
19 clinical effectiveness cannot be attributed to
20 the use of the system.

21 Additionally, if we do accept that
22 chronic effectiveness can be accurately
23 evaluated, only 25 percent of the patients
24 reach the per protocol chronic effectiveness
25 endpoint.

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1 Finally, the extent of biases
2 associated with over reporting of baseline and
3 under reporting at follow-up of the subjective
4 endpoint of symptomatic atrial fibrillation
5 is also unknown.

6 The risk-benefit profile of the
7 Cardima ablation system cannot be assessed
8 since neither the effectiveness nor the safety
9 of the system can be accurately determined.

10 In considering whether or not to
11 approve a new device, FDA must determine that
12 there is sufficient valid scientific evidence
13 to support a reasonable assurance of safety
14 and effectiveness. Although a manufacturer
15 may submit any form of evidence to the FDA,
16 the agency relies upon only valid scientific
17 evidence to determine whether there is
18 reasonable assurance that the device is safe
19 and effective.

20 Although randomized control trials
21 are the gold standard for medical devices, we
22 do have a fair amount of discretion in
23 deciding what the appropriate quality and
24 quantity of evidence is needed for a
25 particular device.

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1 It's important to note that valid
2 scientific evidence requires that not only
3 must a trial be well designed; it must also be
4 well executed. So a study such as Cardima's
5 which lacked matched controls could on its
6 face potentially constitute valid scientific
7 evidence.

8 Failure to adequately control
9 concomitant patient medications or insure
10 patient compliance with transtelephonic
11 reporting requirements can turn a valid study
12 into an invalid one.

13 Furthermore, in determining whether
14 or not there is a reasonable assurance that a
15 device is safe, FDA must consider do the study
16 data constitute valid scientific evidence.
17 This requires that we consider study design
18 and conduct.

19 Can the device be labeled with
20 adequate warnings against unsafe use? In
21 Cardima's case, the lack of data on acute
22 endpoints makes it difficult to see how much
23 labeling could be written.

24 Do the probable benefits outweigh
25 the probable risks? In Cardima's case, we

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1 must consider the uncertain decrease and the
2 frequency of patient self-reporting of AFIB
3 versus the very real risks associated with
4 performing of percutaneous ablation procedure
5 inside the heart.

6 In determining whether or not
7 there's reasonable assurance that a device is
8 effective, FDA must consider once again do the
9 studies constitute valid scientific evidence.

10 They must also consider is the result seen in
11 a significant portion of the target
12 population.

13 FDA's analysis suggests that only
14 25 percent of the patients studied met the per
15 protocol primary endpoint.

16 Does the device produce a
17 clinically significant result? The FDA review
18 team believes that the data provided by
19 Cardima do not provide valid scientific
20 evidence of a reasonable assurance of safety
21 and effectiveness.

22 For these reasons, the FDA review
23 team does not believe that the sponsor has
24 provided sufficient valid scientific evidence
25 that demonstrates a reasonable assurance of

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1 safety and effectiveness for the Revelation Tx
2 system in its intended use. Therefore, we
3 continue to recommend that the Cardima
4 Revelation Tx Microcatheter and NavAblator
5 System be determined not approvable at this
6 time.

7 We will welcome the opportunity to
8 work interactively with the sponsor to design
9 an additional premarket study.

10 That concludes FDA's presentation
11 for the Cardima Revelation Tx system. Our
12 reviewers and expert consultants will be
13 available throughout the day to answer any
14 additional questions you may have for us.

15 Thank you for your attention.

16 CHAIRPERSON RAMSEY: Thank you for
17 that presentation.

18 We now have about five minutes for
19 our panel to ask clarifying questions of the
20 FDA regarding their presentation. Yes.

21 DR. HIRSHFELD: I think the FDA
22 presentation has indicated that the Achilles
23 heel of this situation has been the weakness
24 of the original study design, the fact that
25 it's not controlled and the difficulty with a

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1 valid assessment of endpoints.

2 And I'd like to know whether these
3 issues were discussed at the time that the
4 trial was launched and to what degree there
5 was unanimity between FDA and the sponsor in
6 terms of the acceptance of the study design.

7 DR. ZUCKERMAN: Thank you for that
8 question, Dr. Hirschfeld.

9 In order to understand the study
10 design, I think we have to put it in the right
11 contextual format, and as both the sponsor and
12 FDA indicated, atrial fibrillation is an
13 important problem, and it's very challenging
14 to design these studies.

15 As a result, in 1998, there was a
16 special meeting of the Circulatory Systems
17 Advisory Panel, the panel upon which you and
18 others now sit, in which trial design was
19 discussed extensively for this type of device.

20 At the time, the advisory panel
21 indicated that the type of trial design that
22 you've heard about today, patients using
23 themselves as, quote, unquote, their own
24 control was acceptable with the following
25 caveats, the caveats that you've pointed out,

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1 meaning that trial execution needs to be
2 superb or otherwise there are potentially
3 multiple other factors that hinder the ability
4 to clearly understand what you have at the end
5 of the day.

6 So that, you know, FDA and the
7 sponsor did move down this path. Our main
8 comment is that this can be an acceptable
9 trial design for the type patients enrolled,
10 but it needs to be executed extremely well,
11 and there, I think, is the problem currently.

12 CHAIRPERSON RAMSEY: Any others?

13 DR. SACKNER-BERNSTEIN: I have a
14 question for Dr. Tillman just to clarify
15 something. On your Slide No. 44 where you
16 list the patient accountability for Phase 3,
17 I'm wondering if you can explain. I think it
18 was yours. No? Have I got the wrong -- well,
19 Slide 44 on my handout here. Okay. Sorry.

20 There's a comment. There's one box
21 that says out of the 98 ablated, there were
22 five without verified data. Could you explain
23 what that means?

24 DR. EWING: Sure, and thank you for
25 promoting me to Dr. Tillman's position.

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1 (Laughter.)

2 DR. TILLMAN: You can have it.

3 DR. EWING: What that just means,
4 my interpretation of this is that the sponsor
5 didn't have the study monitors fully check the
6 data and put it into their database.

7 DR. CHER: May I add some
8 clarification there?

9 CHAIRPERSON RAMSEY: Sorry. You
10 can't. You can clarify at the rebuttal
11 session.

12 DR. EWING: That's my understanding
13 of verified data.

14 DR. SACKNER-BERNSTEIN: As a
15 follow-up, and congratulations on the
16 promotion, was this study one that went
17 through standard audit process as part of the
18 submission where sites were audited?

19 DR. EWING: Yes, I believe so.

20 CHAIRPERSON RAMSEY: Yes.

21 DR. SCHMID: I have a question for
22 Dr. Li. In the simulation that you
23 did, you showed that 16 percent of the
24 patients might be expected to be treatment
25 successes by chance, and you noted that that

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1 number might be an overestimate because of
2 other factors, like confounding and bias.

3 The study as reported by Cardima
4 had a 58 percent success rate, which FDA
5 decided was more like 25 percent because of
6 some of those situations, such as the need for
7 other drugs or pacemakers.

8 It would seem to me as if the
9 appropriate comparison to your 16 percent
10 would be the 58 percent rate before the
11 adjustment for these other factors, in which
12 case it would seem to me that there would be a
13 larger than -- if 16 percent is your estimate
14 of the chance rate, then the 58 percent is
15 much higher.

16 I was wondering if you could
17 comment on that.

18 DR. LI: Okay. In my simulation,
19 the expected proportion is about 21 percent,
20 if I remember correctly. So this proportion
21 is in the reference population. This refers
22 to in the reference population where other
23 confounding factors and reporting bias are
24 assumed to be absent.

25 So we would interpret this number

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1 in that perspective. So if we add confounding
2 and if we add reporting bias, the percent
3 could be much higher than 21 percent, and this
4 21 percent was simulated under a marginal
5 distribution of Poisson with a mean of four
6 episodes per month, which is very different
7 from the marginal distribution actually
8 observed in the pivotal trial.

9 If we redo the simulation using a
10 marginal distribution, that's closer to what's
11 observed in the trial. Again, this percentage
12 may change, and actually we have done such
13 simulations.

14 CHAIRPERSON RAMSEY: Go ahead.

15 DR. SACKNER-BERNSTEIN: In terms of
16 that model, I'm just wondering if perhaps you
17 could address one question for this
18 nonstatistician. It would seem to me that to
19 create a model such as that, not only would
20 you need to assume a distribution of episode
21 frequencies, but you also would need to
22 assume, which you don't as a Poisson
23 distribution, but you'd also need to assume a
24 certain magnitude of variability.

25 I'm wondering what your assumption

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1 was. If that's correct in my interpretation
2 that you need to assume a certain amount of
3 variability in order to say how much of the
4 subject variability could potentially explain
5 differences over that six month period, what
6 was the variability you assumed and what was
7 the source for that assumption?

8 DR. LI: Okay. You are absolutely
9 right that what drives the expected percent of
10 patients reaching target level of reduction is
11 driven by the two dimensional variability in
12 the bivariate or joint distribution. In the
13 simulated example I used in my presentation,
14 this bivariate variability corresponds to two
15 independent Poisson distributions with a mean
16 of four episodes per month.

17 And, again, we don't know what the
18 correct reference, correct joint distribution
19 is to use for the reference population. So we
20 used this as an illustrative example to
21 concretize our concerns. So it's an
22 illustration. There's no claim that this
23 distribution that was used in my presentation
24 is in any way close to the distribution that
25 should be used for the reference population.

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1 However, we have conducted
2 additional simulations in which the marginal
3 distributions match the ones observed in the
4 Cardima pivotal trial.

5 CHAIRPERSON RAMSEY: We have
6 perhaps time for one more quick question.

7 (No response.)

8 CHAIRPERSON RAMSEY: Well, then
9 seeing none, we will break for lunch. We will
10 reconvene in this room at 1:15, and the room
11 after you leave will be secured by FDA staff,
12 and so please take anything that you want to
13 keep with you because you won't be allowed
14 back in the room until we reconvene.

15 So we'll see everyone back at 1:15.

16 Thank you.

17 (Whereupon, at 12:32 p.m., the
18 meeting was recessed for lunch, to reconvene
19 at 1:25 p.m., the same day.)

20 CHAIRPERSON RAMSEY: If everyone is
21 ready, I would like to call the meeting back
22 to order. This is the rebuttal period and we
23 will start with the sponsor, with Cardima.

24 Cardima has 15 minutes to rebut the
25 FDA's presentation. You may use a portion of

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1 that 15 minutes if you wish to present the
2 slides that you weren't able to get to, but it
3 would still be a 15-minute total presentation.

4 And I will give you a warning at five
5 minutes. So when you are ready, go ahead.

6 CARDIMA FOLLOW-UP/REBUTTAL

7 DR. CHER: Good afternoon. Daniel
8 Cher again representing Cardima. We have
9 prepared a series of slides. Can those slides
10 be put up?

11 While he is putting those slides
12 up, I would like to let everyone know that the
13 first slide that we're putting up shows -- I'm
14 sorry. I would like to first say that the
15 panel today has heard about data that were
16 presented earlier in an earlier panel meeting
17 in May 2003. Those data were based on a
18 combined analysis of phase 2 and phase 3 data.

19 I think that those data are not
20 relevant for this panel to be concerned with.

21 Rather, we ask that the panel consider only
22 the data that are presented in phase 3 with
23 the 84 patients. And, just to let you know,
24 we have put an official objection through
25 counsel in the record.

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1 I put this slide up to express my
2 confusion and perplexity with some of the
3 information that was presented by FDA. With
4 respect to the acute procedural endpoint, we
5 used one that was entirely acceptable, one
6 that was designed in concert with the 1998
7 panel as well as with electric key opinion
8 leaders in electrophysiology. And, in fact,
9 it's one that continues to be used.

10 In the next few minutes, I will
11 have some of our study investigators talk
12 about the directions that physicians were
13 given in the trial as well as reasons why
14 measurement in every single electrode is not
15 only not feasible. It's actually impossible
16 and highly unlikely to have been done in the
17 study.

18 More importantly, we believe that
19 the acute procedural data that we have are
20 substantially sufficient to provide reasonable
21 evidence that we, in fact, did ablate cardiac
22 tissue during the ablation procedures and
23 that, in fact, the ablation procedures were
24 done similarly across studies.

25 With respect to chronic endpoints,

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1 I would like to say that I am again puzzled by
2 the comments that the FDA has given us. We
3 are told that the study was poorly conducted.

4 However, this study was designed according to
5 a 1998 panel that's one of the widest, largest
6 multi-center studies of atrial fibrillation
7 conducted to date.

8 This is known to be a difficult
9 study topic, but I think our investigators did
10 do a good job. It's a bit disturbing to me
11 that we are told that the study was poorly
12 conducted. And, yet, several investigators
13 had BIMO audits by FDA.

14 Finally, we are going to talk
15 briefly about risk-benefit. First let me ask
16 Dr. Saksena to address acute procedural
17 outcomes with respect to endpoint
18 measurements.

19 DR. SAKSENA: Thank you, Dr. Cher.

20 I would like to speak to the panel
21 on the issue that has been repeatedly said
22 that the acute procedural endpoint was not
23 collected in 100 percent of patients.

24 One of the hats I wear is I am one
25 editor-in- chief of one of the major cardiac

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1 EP journals. I see about 500 manuscripts that
2 come across my desk. To me this is the
3 largest body of electrogram data that I have
4 seen in a report in cardiac ablation
5 literature.

6 What is absolutely correct is that
7 every one of those 16 or 17 points where an
8 electrogram is to be collected before an
9 ablation is done and after ablation is done
10 was not done. And the reason is quite simple.

11 Those who do cardiac ablation know that the
12 heart moves during the process of ablation or
13 moves back and forth. Electrograms are
14 obtained from a substantial proportion of the
15 electrodes of any catheter but they are never
16 obtained from every electrode in every
17 catheter.

18 So in a reality check, there is
19 more than enough electrogram information here
20 to show a decrease in electrogram amplitude
21 across each and every electrode.

22 So the issue of pacing threshold,
23 well, this has kind of fallen out of favor.
24 This was in the '90s, we used to think about
25 that to show how we would do a look at

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1 ablative tissue. We rarely look today at a
2 pacing from a site of ablation to show that
3 it's ablated. It is largely not done.

4 You have seen examples of the line
5 of block. I have written about three or four
6 co-authored statements on standards for
7 ablation for the Heart Rhythm Society. We
8 have no definition of fragmentation because we
9 cannot define it. So it was nice that people
10 wanted to look at that, but that is a very
11 qualitative phenomenon, even in the ventricle
12 where it is talked about.

13 Arrhythmia induction. The only
14 study that has looked at the specificity of AF
15 induction in patients with AF was done in my
16 lab. We published the only prospective study.
17 And we can tell you that after ablation,
18 arrhythmia induction is a non-specific
19 endpoint.

20 Finally, isthmus block, as we have
21 discussed repeatedly, is not an endpoint in
22 the trial.

23 DR. CHER: Thank you.

24 By way of reminder, I would like to
25 share with the panel -- this is a slide that

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1 you have seen already -- the amount of data
2 that was collected in the clinical trial. As
3 you can see, this amount is substantial. And
4 although, as Dr. Saksena said, not every
5 electrogram amplitude was collected from every
6 electrode, we believe that these data are
7 substantial.

8 As I showed you this before, there
9 is substantial information to make us feel
10 comfortable that cardiac ablation tissue was
11 ablated in patients who underwent this
12 procedure.

13 Let me turn next to chronic
14 effectiveness. Actually, let me turn next to
15 information with respect to whether the
16 procedure was done the same across study
17 sites.

18 This is a screen shot of
19 information from our clinical trial protocol
20 that describes how the system would be set up.

21 We also have a number of pictures from our
22 clinical protocol. And I would like to ask
23 Dr. Kocheril to describe briefly the
24 instructions to the investigators.

25 DR. KOCHERIL: Thanks, Danny.

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1 There were explicit instructions
2 for use. And we found that new investigators
3 coming online to do the trial had very little
4 difficulty following these instructions and
5 putting down the lines.

6 As I mentioned previously, the
7 major issue was to make sure that the line was
8 complete so if the electrodes on one pass of
9 the catheter doesn't hit the SPC to IVC, then
10 you need to overlap electrodes to make that
11 happen.

12 And on the point of missing
13 electrode data, the other thing to realize is
14 that some people have small atria. So you
15 can't even put the eight electrodes down
16 contiguously. So they're going to be missing
17 data from the electrodes that don't make
18 contact with the atrium.

19 In this study, there were explicit
20 instructions. I think the next slide shows
21 the power and temperature, temperature 50
22 degrees, 35 watts, 60 seconds. So there were
23 specific instructions for what to do at each
24 electrode in terms of ablating tissue.

25 You have already seen the Netter

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1 diagram of where the lines go. And these, Dr.
2 Maisel showed a nice picture of the cutout, a
3 cutaway of the right atrium.

4 So we know where the septum is. We
5 know where that posterior lateral line should
6 go, near the Christa terminalis. This is
7 anatomy that all EPs learn because we have to.

8 That's where we are ablating a lot of the
9 time.

10 So I think it is unreasonable to
11 say that there weren't explicit instructions
12 for use, and it's unreasonable to say that the
13 same procedures weren't done at different
14 study sites because this is our anatomy. This
15 is where we are doing ablation.

16 DR. CHER: Thank you.

17 I would like to talk a little bit
18 about study conduct. A BIMO audit was done at
19 several sites and in no case did the FDA
20 auditors find that the study was being poorly
21 conducted. As I mentioned, it is one of the
22 widest multi-center trials.

23 I am concerned and puzzled about
24 the under-reporting and over-reporting
25 hypothesis that FDA has put forward. It is a

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1 strong word, but it is a type of conspiracy,
2 it seems to me.

3 This would occur if all the
4 patients got together and said, "Hey, at
5 baseline, let's over-report our episodes" and
6 then they all got together in follow-up and
7 said, "Hey, let's under-report our episodes.
8 Let's also consider episodes that may occur
9 close together in time." We all know that
10 this absolutely can occur.

11 We looked at patients who had
12 episodes that occurred close together. And we
13 actually assumed that those patients were
14 incorrect. We assumed that they reported two
15 episodes during one underlying run if they
16 occurred close together. When we eliminated
17 those, there was no difference whatsoever.

18 I would also like to point out that
19 the trial as designed was designed
20 consistently with recommendations from a
21 single arm. Recommendations from the 1998
22 panel, no trial execution qualifications were
23 stated in that panel meeting in distinction to
24 what Dr. Zuckerman told us this morning.

25 I would like to turn next to

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1 NavAblator. As you are aware, there was use
2 of non-investigational catheters in this
3 study. I remind the panel that these
4 catheters were used for ablation of the
5 cavo-tricuspid isthmus, which was a preventive
6 maneuver to preventive isthmus, to prevent
7 atrial flutter, an illness that the patient
8 did not have.

9 The data that I showed you this
10 morning can help us to interpret these
11 findings. They show that which catheter was
12 used was not important. And they showed that
13 the achievement of bidirectional conduction
14 block, the acute endpoint that one would look
15 for in isthmus ablation did not make any
16 difference whatsoever. And I remind the panel
17 that three approved catheters are now
18 available for cavo-tricuspid isthmus ablation.

19 I want to make a brief comment on
20 zero TTMs. This question came up this
21 morning. There were a total of seven patients
22 in the phase 3 trial and eight patients in the
23 phase 2 trial who had no TTMs at six months.
24 In general, patients who had no TTMs were
25 treated as failures.

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1 And I would like to explain the
2 difference between the analysis we did in
3 phase 3 and phase 2. As was reviewed this
4 morning, in the earlier analysis, we made the
5 assumption that all patients transmitted in
6 the 6-month period from day 150 to day 180 -#
7 that was an unrealistic assumption that we
8 subsequently found out was not happening. The
9 trial protocol allowed flexibility in the
10 six-month visit date. And it also allowed
11 flexibility in the 30-day reporting period.

12 We took a very conservative
13 approach, which was to identify windows in
14 which there was maximum 30-day reporting of
15 episodes. And we used that, instead, to
16 calculate success rates and overall numbers of
17 transmissions.

18 CHAIRPERSON RAMSEY: Just over four
19 minutes.

20 DR. CHER: Thank you.

21 In summary, let me talk about
22 risk-benefit. FDA has expressed a concern
23 that the data are simply insufficient for us
24 to evaluate risk-benefit. I'm perplexed. I'm
25 confused by this. Right atrial ablation of

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1 the type that we have done, the risk is very
2 well-defined in our study.

3 We had only one device-related
4 serious adverse event. The ablation
5 literature as a whole is growing and it's
6 growing rapidly. I feel that our data
7 combined with what is known about atrial
8 ablation allows us to have a very precise
9 estimate, a very precise knowledge of what the
10 risks are in right atrial ablation.

11 Finally, with respect to benefit,
12 we think that the benefit is clearly
13 demonstrated. We are aware that some patients
14 underwent pacemaker placement during the
15 study. But, as I reviewed for you this
16 morning, many patients underwent pacemaker
17 placement because they are already counted as
18 failures and sought additional treatment.

19 Second, we have a small number of
20 patients who underwent pacemaker placement for
21 bradycardia. This is not a treatment for
22 atrial fibrillation. It's a treatment for
23 bradycardia.

24 And, finally, let me turn to the
25 anti-arrhythmic drug issue. We presented you

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1 data this morning that showed that a small
2 number of patients had new anti-arrhythmic
3 drugs used. Based on our analysis of previous
4 data, we expect that after having failed three
5 anti-arrhythmics, the likelihood of responding
6 to yet another anti-arrhythmic is very low.

7 For that reason, we believe that
8 what we know about the natural history of
9 paroxysmal atrial fibrillation combined with
10 what we observed in our trial allows us to
11 have a really good handle on what would happen
12 to these patients had they not undergone the
13 treatment. None of them would have gotten
14 better. Many of them would have progressed to
15 chronic atrial fibrillation.

16 For this reason, we believe that
17 the trial itself does demonstrate sufficient
18 evidence in both the safety and effectiveness
19 profiles for us to be able to make a
20 conclusion.

21 Finally, I want to make one comment
22 on Dr. Li's modeling. There was a question
23 about it this morning. Dr. Li and I actually
24 did very similar modeling. He made an
25 assumption which I believe was unrealistic.

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1 He assumed that patients actually had a
2 relatively low occurrence rate of underlying
3 atrial fibrillation.

4 He noted for us this morning that
5 in alternative models, where we model AF
6 distribution more along the lines of what we
7 observed, the likelihood that a patient would
8 be a success due to chance alone would go
9 down. And that's modeling that I showed you
10 this morning.

11 So, in summary, we're perplexed by
12 the issues that were presented to us. We
13 believe there is sufficient information to
14 evaluate the acute procedural endpoint. We do
15 believe that there is sufficient information
16 to evaluate chronic effectiveness. And we
17 believe that we showed an effectiveness rate
18 that far exceeds what we would observe from a
19 placebo effect or any other biases. And,
20 finally, we believe there is sufficient
21 information to make a risk-benefit judgment.

22 Thank you.

23 CHAIRPERSON RAMSEY: Thank you very
24 much.

25 We will now turn to the FDA, who

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1 also will have 15 minutes to rebut Cardima's
2 presentation, if you choose. Yes. You will
3 see a yellow light up there. And I will give
4 you a warning at five minutes and one minute.

5 ODE FOLLOW-UP/REBUTTAL

6 DR. MALLIS: Good afternoon. My
7 name is Elias Mallis, Branch Chief of the
8 Cardiac, Electrophysiology, and Monitoring
9 Branch, the FDA group that has reviewed the
10 Cardima submission to date.

11 Before we move into the open panel
12 discussion that will follow on in a few
13 minutes, I would like to offer a few remarks
14 on behalf of the FDA review team.

15 Earlier this morning you have been
16 presented with much information about
17 Cardima's study, both from Cardima's
18 representatives and FDA.

19 As you consistently heard
20 throughout FDA's presentation, Cardima has not
21 provided sufficient clinical data which
22 demonstrate the safety and effectiveness of
23 its device system. As a result, it is its
24 lack of evidence that led to FDA's not
25 approvable decisions. I would like to take a

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1 few minutes now to recap FDA's concerns for
2 you.

3 First, a key procedural
4 effectiveness was not demonstrated with either
5 the Revelation Tx or the NavAblator, the two
6 catheters that compose the Cardima ablation
7 system.

8 The sponsor did not document that
9 the Revelation Tx was consistently used for
10 each patient within the ablation procedure.
11 In particular, it is unknown whether the lines
12 of lesions, as required in the study protocol,
13 were successfully created. Accordingly, the
14 data needed to demonstrate acute procedural
15 success is missing in all patients.

16 While acute procedural data on the
17 NavAblator catheter was collected and
18 recorded, the NavAblator was not successful in
19 a sufficient number of patients in producing
20 the required ablation lesion line.

21 Second, the study did not show
22 chronic clinical effectiveness of the ablation
23 system. Several factors contribute to this
24 conclusion. Because acute successful use of
25 the Cardima ablation system was not shown in

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1 any individual patient, chronic clinical
2 effectiveness cannot be attributed to the use
3 of the system.

4 Additionally, as you have heard
5 from Dr. Ewing earlier, if we do accept that
6 chronic effectiveness can be accurately
7 evaluated, the protocol chronic clinical
8 success rate was only 25 percent.

9 Finally, the scent of bias
10 associated with over-reporting at baseline and
11 under-reporting at follow-up or the subjective
12 endpoint of symptomatic paroxysmal atrial
13 fibrillation is also unknown.

14 Third, because neither the safety
15 nor effectiveness of the device system can be
16 accurately determined, FDA cannot assess the
17 system's risk-benefit profile.

18 This risk-benefit assessment is
19 fundamental to FDA's evaluation of this novel
20 technology in our decision to approve or
21 disapprove a device. This problem is
22 compounded by the fact that we cannot confirm
23 how the device system was used in any single
24 patient, coupled with the fact that we don't
25 know whether the system was used in the same

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