

1 the preclinical data prior to initiation of
2 the clinical trial. Some areas of FDA's
3 review were catheter and console mechanical
4 evaluation, electrical performance, electro-
5 magnetic compatibility, software,
6 biocompatibility, sterilization and device and
7 packaging shelf life. At this time FDA has no
8 outstanding engineering concerns with the
9 device.

10 The sponsor conducted two studies,
11 a feasibility and a pivotal study. I won't go
12 into detail at this time and these will be
13 discussed further by Dr. Brockman. In July of
14 1998, the Circulatory System Devices Panel met
15 to discuss radio frequency ablation studies
16 for atrial flutter and to develop
17 recommendations for FDA regarding appropriate
18 end points for these studies. This table
19 lists the end points that were developed for
20 RF ablation based on the panel's comments.
21 Note that these are the same end points that
22 were also used for supraventricular

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1 tachycardia studies and these goals were used
2 in the sponsor's study.

3 I'd like to briefly describe the
4 history of this PMA review. The PMA was first
5 submitted in July of 2005. In October of 2005,
6 FDA issued a letter which identified several
7 outstanding issues with the submission and the
8 sponsor responded later that month. In
9 January of 2006, FDA issued a second letter
10 which identified issues with the chronic
11 effectiveness results. In November the
12 sponsor responded to FDA's letter, providing a
13 readjudication of chronic effectiveness
14 results. I'll discuss the reasons for the
15 readjudication in the next slide. In March of
16 this year, the sponsor provided updated
17 statistical information and additional
18 analysis. The panel discussion today is
19 focused on the November and March submissions.

20 As previously discussed by the
21 sponsor, the submission that is the subject of
22 today's discussion is based upon a re-analysis

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1 of the event recorder tracings by Dr.
2 Schienman's core lab. The original analysis
3 relied solely upon the event monitor company
4 interpretation and did not include
5 investigator over-read or export core lab.

6 Upon a more detailed review, the
7 sponsor concluded that the original
8 adjudication may have misinterpreted some
9 complex electrograms, specifically those with
10 atrial fibrillation as a recurrence of atrial
11 flutter. For the re-analysis, Dr. Schienman's
12 core lab reviewed all tracings that were not
13 from patients with clearly documented
14 recurrence of atrial flutter as demonstrated
15 by EP study or other treatments for atrial
16 flutter.

17 This readjudication is the primary
18 basis for the amended submission currently
19 under review, the results of which are
20 presented later. FDA's review included
21 examination of all tracings from patients for
22 whom the chronic effectiveness classification

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1 was changed by the readjudication. Although
2 the readjudication was not explicitly pre-
3 specified in the clinical investigational
4 plan, the readjudication mechanism is
5 conceptually consistent with the study plan.

6 FDA considers the core lab revised
7 chronic effectiveness patient classifications
8 to be scientifically valid. These are the
9 members of FDA's review team that will be
10 presenting today. Dr. Randy Brockman will
11 present the clinical results. Dr. Shanti
12 Gomatam will present the statistical analyses
13 and Dr. Dale Tavris will present the
14 epidemiology. I'd now like to introduce Dr.
15 Randy Brockman.

16 DR. BROCKMAN: Good morning. I'm
17 Randy Brockman. I'm an electro-physiologist
18 with FDA and I'll be presenting the Agency's
19 clinical review. I'd like to briefly discuss
20 atrial flutter and atrial flutter ablation,
21 spend just a moment on the feasibility study
22 and then spend most of my time discussing the

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1 pivotal study. Well, I can't talk about
2 atrial flutter ablation without showing at
3 least one electrogram. This is a single EDCG
4 and I think you can see the fairly classic
5 sawtooth waves -- P waves here.

6 The most common type of atrial
7 flutter is the consequence of macro reentry
8 within a large circuit confined to the right
9 atrium. This is a pathologic specimen with
10 the right atrium opened. Just to orient you,
11 this is the superior vena cava. This is the
12 lateral wall. You can see a little bit of the
13 tricuspid valve here and this is the cava
14 tricuspid isthmus. This is an example of
15 counterclockwise flutter in which the wave
16 passes counterclockwise around this circuit.

17 Pre-ablation, there's generally
18 bidirectional conduction across the cava
19 tricuspid isthmus. This picture demonstrates
20 clockwise conduction across the isthmus when a
21 pacing impulse is provided from the low septum
22 such as pacing from the coronary sinus. You

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1 can see clockwise conduction across the
2 isthmus and up the lateral wall. At the same
3 time, a wave front travels us the septum,
4 across and then down the lateral wall with the
5 wave fronts colliding somewhere here on the
6 lateral wall.

7 After ablation, you see
8 bidirectional conduction block at the isthmus
9 here. The counterclockwise wave front travels
10 up the septum, across, down the lateral wall
11 and then to the isthmus where it's blocked.
12 The clockwise wave front is blocked at the
13 isthmus. This is a fluoroscopic image of a
14 fairly common catheter setup for atrial
15 flutter ablation. There's a catheter here in
16 the coronary sinus coming from above. There's
17 a catheter sitting at the hisbundle region.

18 There's an ablation catheter
19 adjacent to the isthmus and there's a multi-
20 pole catheter sitting within the right atrium.

21 Please note the most proximal pair, 19, 20
22 here at the roof, the lateral wall and then at

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1 the isthmus most distal pair, you can see is
2 1, 2. This slide is a little bit busy but it
3 represents intracardiac electrograms obtained
4 before, during and then after tricuspid --
5 cavo-tricuspid isthmus ablation. On top you
6 can see cartoons with a multiple catheter
7 sitting around the right atrium. The
8 numbering is similar to what I showed you on
9 the last fluoroscopic image. The first panel
10 demonstrates pre-ablation clockwise conduction
11 across the isthmus. A pacing stimulus from
12 the coronary sinus travels clockwise across
13 the isthmus and up the lateral wall, and you
14 can see that here with the distal pair being
15 activated early and traveling upwards.

16 At the same time, that stimulus
17 travels counterclockwise around the septum,
18 across and then down the lateral wall, and
19 again, you can see the proximal pair, 19, 20,
20 being activated early and then the wave front
21 traveling in this direction. The meet
22 somewhere on the lateral wall.

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1 The second panel demonstrates
2 delayed but persistent conduction and then the
3 third panel demonstrates clockwise conduction
4 block. So a pacing stimulus from the coronary
5 sinus travels up the septum, across, down the
6 lateral wall and then to the isthmus where
7 it's blocked but the most distal pair on that
8 multiple catheter is activated last. And you
9 can see that here; 1, 2 is activated last. So
10 this shows clockwise conduction block. It's
11 part of bi-directional conduction block. This
12 is the acute procedural or acute effectiveness
13 end point. So now I'd like to discuss the
14 clinical studies.

15 The sponsor performed a feasibility
16 clinical trial in which 58 patients with
17 atrial flutter were enrolled; 48 patients
18 actually underwent cryoablation. Acute
19 effectiveness, bi-directional block was
20 present in 94 percent. Chronic effectiveness
21 which was freedom from recurrent atrial
22 flutter at six months was present in 84

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1 percent. A serious adverse event rate
2 throughout the course, this is not limited to
3 the first seven days, was 12.5 percent.

4 The pivotal trial was a
5 perspective, multi-center, single arm trial.
6 The patients meeting all enrollment criteria
7 received cavo-tricuspid isthmus ablation using
8 the Cryocore system and end points were tested
9 against performance goals. Patients had to
10 have symptomatic atrial flutter with at least
11 one episode atrial flutter documented within
12 six months prior to the procedure and they had
13 to have documentation of isthmus dependent
14 right atrial flutter as evident from pacing or
15 mapping in the pre-ablation AP study.

16 Key exclusion criteria included
17 clinically significant structural heart
18 disease that was well-defined in the protocol,
19 any prior ablation for atrial flutter or
20 concomitant atrial fibrillation requiring
21 anti-arrhythmic with drugs other than Class 1
22 or Class 1C or Class 3 for conversion to

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1 atrial flutter. The safety end point was the
2 occurrence of serious adverse events within
3 seven days of the procedure. Acute
4 effectiveness was the presence of bi-
5 directional conduction block in the cavo-
6 tricuspid valve isthmus.

7 Chronic effectiveness was sixth
8 month freedom from recurrence of atrial
9 flutter for those patients who achieve acute
10 success. While chronic effectiveness was
11 described as a secondary end point in the
12 protocol, FDA made it clear to the sponsor
13 before the pivotal trial that we would
14 consider chronic effectiveness to be critical
15 in the assessment of device performance. These
16 are the performance goals that you have seen
17 multiple times already.

18 This is a patient accountability
19 chart. A hundred and eighty-nine patients
20 were enrolled; 160 had the catheter inserted.

21 The difference is due to 28 screening
22 failures, almost all of which were due to the

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1 inability to induce isthmus-dependent right
2 atrial flutter on the pre-ablation EP study
3 and then one patient who withdrew consent
4 prior to the investigational ablation.

5 Of the 160 that had the catheter
6 inserted, there were 140 acute successes. Of
7 the 140 acute successes, eight were censored
8 here from the chronic effectiveness analysis
9 due to several deaths and several patients who
10 were not compliant with event recordings. Of
11 note, none of these eight censored patients
12 had even monitor recordings that demonstrated
13 atrial flutter.

14 This shows the baseline
15 demographics. Of the 160 patients that had
16 the investigational catheter inserted, I'll
17 just note that probably in part due to the
18 exclusion criteria, was a relatively low
19 incidents of certain other heart disease, low
20 incidents of congestive heart failure, low
21 incidence of ischemic heart disease and a
22 relatively low incidence of left ventricular

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1 systolic dysfunction.

2 Subjects who had acute procedural
3 success were monitored for evidence of
4 recurrence of atrial flutter for six months
5 following the procedure. These subjects were
6 provided with an event recorder and instructed
7 to make a weekly, once -- random once-per-week
8 recording until the end of the six-month
9 follow-up visit or to make recordings for any
10 symptoms. Recurrent atrial flutter on an
11 event monitor recording resulted in that
12 patient being classified as chronic
13 effectiveness failure. Other assessments could
14 also result in a classification as a chronic
15 effectiveness failure such as a repeat EP
16 study with or without ablation, that
17 documented isthmus dependent atrial flutter,
18 the need to undergo a cardioversion or
19 evidence of recurrent flutter on pacemaker
20 logs.

21 There were 104 protocol deviations,
22 75 of which were classified as minor, 29 is

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1 major, and I've just summarized the major
2 protocol deviations here. I have more detail
3 if you're interested. But FDA's review
4 indicated the recorded deviations did not
5 substantially alter the study results. Now,
6 I'd like to move onto a discussion of the
7 results.

8 The goal of the safety end point
9 was to show that the occurrence of serious
10 adverse events within seven days of the
11 procedure was less than or equal to seven
12 percent. The numbers I presented are slightly
13 different than those presented in the panel
14 pack due to a single event that was removed
15 that I'll describe in a moment. The study
16 showed that nine patients experienced 10
17 serious adverse events within seven days of
18 the procedure, so the seven-day serious
19 adverse event rate, 95 percent one-sided upper
20 confidence bound was 9.6 percent the safety
21 end point was not met.

22 This table shows the serious

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1 adverse events that occurred within the first
2 seven days. And as I said, this table differs
3 slightly from the one presented in the panel
4 pack in that this table reports only a single
5 episode of atrial flutter. The table in the
6 panel pack shows two. The episode shown here
7 was actually left atrial flutter that was
8 diagnosed on EP testing which occurred on the
9 day after the investigational procedure and
10 prolonged the hospitalization. According to
11 the protocol, this was correctly classified as
12 a serious adverse event within the first seven
13 days. We removed a second episode of atrial
14 flutter that was recurrent right atrial
15 flutter. It resulted in hospitalization 13
16 days after the procedure. So according to the
17 protocol, this event should be included in the
18 analysis of serious adverse events that
19 occurred after the first seven days.

20 This gets small. This is a list of
21 the serious adverse events that occurred after
22 the first seven days. After the first seven

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1 days, the most common adverse events were
2 recurrent atrial arrhythmias, atrial
3 fibrillation, there were eight, atrial
4 flutter, four events in three patients but
5 otherwise the events were largely isolated and
6 many of them appeared to have nothing to do
7 with the investigational device.

8 There were three deaths in the
9 study. I reviewed each of them. They
10 included a suicide two and a half weeks after
11 the procedure, a patient with a pulmonary
12 embolism and subsequent death several months
13 after the procedure, another patient with a
14 drug overdose six months after the procedure.

15 The patient that committed suicide had a
16 history of depression and was taking multiple
17 psycho-active drugs. The patient that had a
18 pulmonary embolism had a history of morbid
19 obesity and deep venous thrombosis. Warfarin
20 was documented as a prescription medication
21 but the INR at the time of the pulmonary
22 embolism was sub-therapeutic. The DSMB

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1 reviewed all deaths and felt that none of the
2 three were related to the investigational
3 device or the procedure.

4 The goal of the acute effectiveness
5 end point was to show that the proportion of
6 patients achieving bidirectional block across
7 the cavo-tricuspid isthmus was greater than or
8 equal to 80 percent. The study showed 140
9 patients out of 160 had bidirectional block at
10 the end of the procedure, the 95 percent one-
11 sided lower confidence bound was 82 percent
12 and the acute effectiveness end point was met.

13 The goal of the chronic
14 effectiveness end point was to show that
15 freedom from recurrence of atrial flutter at
16 six months for those patients who achieved
17 acute success was greater than or equal to 80
18 percent. According to the protocol, chronic
19 efficacy is defined as those patients who had
20 acute efficacy after the procedure and did not
21 document atrial flutter on event recordings
22 through six months.

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1 For chronic effectiveness, the
2 proportion of patients free from recurrence of
3 atrial flutter was 81.6 percent with a 95
4 percent lower confidence bound of 74.7
5 percent. This analysis is based on 140 acute
6 successes, however, the analysis is a Kaplan-
7 Meier survival analysis and I'll defer other
8 discussion of how this is calculated to our
9 statistician. The sponsor presented the
10 results of a post hoc chronic effectiveness
11 analysis. It's based on investigator
12 assessment rather than relying on event
13 monitor recordings. The final determination
14 was made by CryoCor in an unblinded manner and
15 therefore, it was subject to bias. It
16 resulted in the reclassification of 13 chronic
17 failures as adjudicated by the core lab based
18 on event recordings as chronic successes.

19 So the post hoc analysis allowed
20 patients classified by the core lab as chronic
21 failures, in other words, those with a
22 documented event monitor recording, that

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1 showed recurrent atrial flutter, to be
2 classified as a chronic success. This is an
3 example of an event monitor tracing from one
4 such patient. This recording was adjudicated
5 by the core lab to be a true flutter, yet in
6 the post hoc analysis, this patient was
7 classified as a chronic effectiveness success.

8 As an electro-physiologist, it isn't clear to
9 me how a patient with documented recurrent
10 atrial flutter can be considered to have had a
11 successful atrial flutter ablation but this
12 reclassification of patients with documented
13 recurrent atrial flutter as chronic successes
14 occurred 13 times in the post hoc analysis.

15 The sponsor presented additional
16 data from 111 sequential patients with atrial
17 flutter, who were treated with the CryoCor
18 ablation system at a single center outside of
19 the United States. Acute effectiveness was
20 defined as the presence of bidirectional
21 block. Chronic effectiveness was defined as
22 the absence of atrial flutter as documented by

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1 electrocardiograms collected during regular
2 clinical follow-up. The sponsor has already
3 presented the results. These are our
4 observations.

5 The clinical experience reported is
6 based on a single site. It was retrospective.

7 There was no clinical protocol and there were
8 no case report forms. The sponsor could not
9 make the ECG recordings available to FDA.
10 Patients were not systematically provided
11 event monitors for rhythm monitoring and only
12 device related complications that occurred on
13 the day of the procedure were evaluated.

14 The sponsor also provided a report
15 on the pain perception associated with
16 cryoablation versus radio frequency ablation.

17 It consisted of 14 patients randomized to
18 radio frequency energy or to the CryoCor
19 cryoablation system for ablation of atrial
20 flutter. There were seven patients in each
21 arm. The end point was subjective and at
22 least the cited paper makes no reference to

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1 the pain assessment being performed in a
2 blinded fashion.

3 So in summary, the safety end point
4 was not met. However, FDA believes the safety
5 events that occurred are consistent with what
6 we would expect for a atrial flutter ablation
7 population. The acute effectiveness end point
8 was met but the chronic effectiveness end
9 point was not met. FDA is asking for the
10 panel's clinical interpretation of these
11 aggregate results.

12 Thank you for your attention. Now,
13 I'd like to introduce Dr. Shanti Gomatam, who
14 will provide FDA's statistical review.

15 DR. GOMATAM: Good morning. I am
16 the statistical reviewer for this PMA. The
17 study for the CryoCor Cryoablation System was
18 a perspective single-arm multi-center study at
19 24 US sites. One hundred and eighty-nine
20 patients were enrolled, 28 subjects failed
21 secondary screening, one withdrew consent
22 before the procedure, so 160 patients had a

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1 CryoCor catheter inserted. As Dr. Brockman
2 mentioned earlier, the following were the
3 major end points of the trial.

4 The safety and acute effectiveness
5 end points were specified as primary end
6 points in the sponsor's protocol; however, the
7 FDA informed the sponsor during the ID review
8 that the chronic effectiveness end point would
9 be considered to be critical for device
10 approval.

11 Here is a reminder of the
12 performance goals used in this protocol. Note
13 that the performance goals for safety were for
14 all seven-day -- sorry, serious adverse
15 events, not just device and procedure related
16 ones. The safety end point is the occurrence
17 of serious adverse events within seven days of
18 the procedure. The alternative hypothesis to
19 be established was that the proportion of
20 patients with serious adverse events within
21 seven days post-procedure was less than seven
22 percent.

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1 This is a bound on the 95 percent
2 upper confidence limit. The hypothesis were
3 tested using all patients with CryoCor
4 catheter inserted. Ten serious adverse events
5 were noted in nine patients. The estimated
6 proportion of patients with seven days serious
7 adverse events was 5.63 percent and the one-
8 sided upper 95 percent confidence bound was
9 9.61 percent. Hence, this end point did not
10 meet it's performance goal. The acute
11 effectiveness end point was documentation of
12 bi-directional block in the cavo-tricuspid
13 valve isthmus. The alternative hypothesis was
14 that the proportion of patients with
15 successful creation of bi-directional block
16 was greater than 80 percent. The hypotheses
17 were tested on all patients with CryoCor
18 catheter inserted. One hundred and forty
19 patients achieved acute effectiveness
20 indicating that an estimated proportion of
21 87.5 percent of patients would have documented
22 bi-directional block in the cavo-tricuspid

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1 valve isthmus. The lower confidence bound of
2 82.36 percent met the performance goal.

3 Note that chronic effectiveness is
4 conditional on acute effectiveness here.
5 Patients who had achieved acute effectiveness
6 were chronically effective if they had no
7 documented atrial flutter on event recordings
8 through six months. So only 140 patients were
9 used for the chronic effectiveness assessment.

10 A 60-day window was used for the six-month
11 end point. The Kaplan-Meier estimate of time
12 to occurrence was used to estimate the
13 proportion of patients free from atrial
14 flutter recurrence at six months and the
15 estimate of the lower bound was used.

16 For the chronic effective analysis
17 based on core lab readjudication, results from
18 a blinded adjudication by Dr. Scheinman's core
19 lab were used. Eight patients did not have
20 complete six-month follow-up and there were 26
21 recurrences. Recall that 140 patients were
22 acutely effective, so only these 140 patients

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1 were a part of this analysis. Results from
2 two analyses are provided in the table; one
3 from a Kaplan-Meiers' survival analysis and
4 the other for a simple proportions worst case
5 analysis.

6 The Kaplan-Meier analysis was the
7 protocol specified analysis for chronic
8 effectiveness. Eight patients were censored.

9 It seems unlikely that the censoring was
10 linked to the chronic effectiveness outcome;
11 however, since this cannot be established
12 definitively, a simple proportions worst case
13 estimate is provided. For this worst case
14 analysis, all 140 acutely effective patients
15 are considered in the denominator. In
16 addition to the 26 recurrences, the eight
17 patients with incomplete follow-up are also
18 considered as failures. Ninety-five percent
19 lower confidence bounds of both estimates
20 indicate that the performance goal for the
21 lower confidence bound has not been met.

22 This plot shows the Kaplan-Meier

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1 estimate. Along the vertical axis we have the
2 survival probability. That is the probability
3 of being free of atrial flutter recurrences at
4 six -- sorry, free of atrial flutter
5 recurrences. Along the lower horizontal axis
6 we have the number of follow-up days. Along
7 the upper horizontal axis, we have the number
8 of patients at risk at any particular follow-
9 up time. So for example, at the start of the
10 study that's at times zero, we have 140
11 patients and at 150 days of follow-up we have
12 108 patients at risk.

13 The dashed vertical lines are at
14 150 and 210 days mark the boundaries of the
15 six-month window. The Kaplan-Meier estimate
16 provided on the previous slide is that for Day
17 180. Note that at Day 189, which is within
18 the six-month window, the point estimate drops
19 to 78.5 percent and the low confidence bound
20 to 65.9 percent. However, at this time, there
21 are only 27 patients in the risk set.

22 The sponsor also presents a post

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1 hoc chronic effectiveness analysis based on
2 clinical determination. For this analysis,
3 chronic effectiveness status for patients has
4 been retrospectively imputed in an unblinded
5 fashion by the sponsor's medical officer,
6 using the treating physician's notes in the
7 patient files. Recall that core lab
8 adjudication indicated 26 atrial flutter
9 recurrences in six months. For the clinical
10 determination analysis, 13 of the atrial
11 flutter recurrences were deemed to be non-
12 recurrences. One hundred and fourteen
13 patients were not adjudicated as recurrences
14 by the core lab. None of these patients were
15 readjudicated as recurrences for the clinical
16 determination analysis.

17 In summary, this post hoc analysis
18 was a retrospective unblinded analysis by
19 CryoCor. It is a potentially biased estimate
20 of the clinical assessment of the treating
21 physician. This analysis only changes the
22 status of some patients documented to have

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1 recurrent atrial flutter as being chronically
2 free of atrial flutter based upon a clinical
3 assessment.

4 The sponsor presents a publication
5 as supportive evidence of the CryoCor
6 Cryoablation System results and less painful
7 procedures. The FDA has the following
8 statistical concerns regarding this
9 publication. This paper discusses a small
10 study of 14 patients, seven of whom were
11 randomized to the CryoCor Cryoablation device.

12 Official exact test was used to compare
13 proportions with visual analogue scale greater
14 than zero used to dichotomize patients' pain.

15 It's not clear if this cut-off was pre-
16 specified, nor is it clear that it is
17 clinically appropriate.

18 It is not clear if any of the study
19 analysis were pre-specified; hence the P-
20 values from the publication are
21 uninterruptible. Pain perception was not
22 assessed as an end point in the sponsor's IDE

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1 study. We summarize on the table on this
2 slide, the end point results discussed
3 previously. Those for safety, acute
4 effectiveness, the Kaplan-Meier estimate of
5 chronic effectiveness and the simple
6 proportions worst case estimate of chronic
7 effectiveness.

8 In conclusion, the statistical
9 analysis of the data from the study for this
10 PMA indicate that the performance goal for the
11 viewed effectiveness end point was met. The
12 performance goals for the safety and chronic
13 effectiveness end points were not met.

14 Our next speaker is Dale Tavis,
15 who is an epidemiologist for the FDA. He will
16 discuss post-approval issues.

17 DR. TAVRIS: Good morning. Today I
18 will talk about some general principles that
19 we utilize when thinking about the need for
20 and designing post-approval studies. And then
21 I have some questions for the panel about your
22 thoughts on the design of a post-approval

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1 study for the CryoCor Cryoablation System if
2 the PMA is approved. Before I talk about
3 post-approval studies, I need to clarify a few
4 things.

5 The discussion of a post-approval
6 study prior to a formal recommendation on the
7 approvability of this PMA should not be
8 interpreted to mean that FDA is suggesting the
9 panel find the device approvable. The plan to
10 conduct a post-approval study does not
11 decrease the threshold of evidence required to
12 find the device approvable.

13 The pre-market data submitted to
14 the Agency and discussed today, must stand on
15 its own in demonstrating a reasonable
16 assurance of safety and effectiveness in order
17 for the device to be found approvable. As we
18 all know, pre-market clinical data are
19 collected from patients who are highly
20 selected and treated by the best trained
21 physicians. In contrast, when a device is
22 permitted to be on the market, patients who

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1 receive the device are more representative of
2 the general population of device recipients
3 and physicians who treat these patients are
4 not limited to the best trained physicians.

5 Additionally, some rare adverse
6 events that were not observed in the pre-
7 market studies might occur in the post-market
8 phase as the observation period extends and
9 the patient population broadens. Therefore,
10 the main objective of conducting post-approval
11 studies is to evaluate device performance and
12 potential device related problems in a broader
13 population over an extended period of time
14 after pre-market establishment of reasonable
15 evidence of device safety and effectiveness.

16 Post-approval studies should not be
17 used to evaluate unresolved issues from the
18 pre-market phase that are important to the
19 initial establishment of device safety and
20 effectiveness. The reasons for conducting
21 post-approval studies are, to gather post-
22 market information, including longer term

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1 performance of the device, data on how the
2 device performs in the real world in a broader
3 patient population that is treated by average
4 physicians as opposed to highly selected
5 patients treated by leading physicians in the
6 clinical trials.

7 Evaluation of the effectiveness of
8 training programs, for use of devices,
9 evaluation of device performance in subgroups
10 of patients since clinical trials tend to have
11 limited numbers of patients or no patients at
12 all in certain vulnerable subgroups of the
13 general patient population and in addition,
14 post-approval studies are needed to monitor
15 adverse events, especially rare adverse
16 events, that were not observed in the clinical
17 trials.

18 And finally, we conduct post-
19 approval studies to address issues and
20 concerns that panel members may raise based on
21 their experiences and observations. The FDA
22 and the sponsor have not discussed the need

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1 for a post-approval study during this PMA
2 review. Therefore, this PMA submission did
3 not include a post-approval study protocol.
4 If the panel recommends that a post-approval
5 study be conducted for this PMA, FDA requests
6 that the panel comment on the following
7 important post-approval study components.

8 First, fundamental study questions
9 or hypothesis; as discussed earlier, the post-
10 approval study should not be used to address
11 questions that are essential for the initial
12 establishment of reasonable assurance of
13 device safety and effectiveness. If the panel
14 recommends the approval of this PMA and a
15 post-approval study, FDA requests that the
16 panel comment on what important questions or
17 hypotheses should be examined in the post-
18 approval study.

19 Secondly, safety end points and
20 methods of assessing those end points. If the
21 panel recommends a post-approval study for
22 this device, and given that the pre-market

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1 study failed to meet the success criteria for
2 safety, FDA requests that the panel comment on
3 what appropriate safety success criteria
4 should be used in the post-approval study
5 where both the patient population and the
6 physician users are likely to be more
7 representative of the general population of
8 patients and users.

9 Thirdly, both acute and chronic
10 effectiveness end points and methods of
11 assessing those end points. Total
12 effectiveness is composed of measures for both
13 acute and chronic effectiveness. Acute
14 effectiveness would be useful as a post-
15 approval study end point only to the extent
16 that it predicts total effectiveness in the
17 post-market period since it is effectiveness
18 over the long-term that is clinically
19 meaningful to patients.

20 Chronic effectiveness is currently
21 defined as conditional on acute effectiveness
22 and therefore, conditional on the definition

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1 that is used for acute effectiveness.
2 Consequently, the chronic effectiveness rate
3 would fail to tell the whole story in the
4 post-market period. Please comment on what
5 would be appropriate success criteria for
6 total effectiveness in the post-approval study
7 and what you would recommend as methods for
8 assessing it.

9 Fourthly, the length of follow-up.

10 Chronic effectiveness in the pre-market study
11 was assessed over a six-month follow-up
12 period. Please comment on the optimal length
13 of follow-up in the post-approval setting.
14 Thank you and this concludes FDA's
15 presentation.

16 CHAIRMAN MAISEL: Thank you very
17 much. I'd like to open up the discussion for
18 panel questions for the FDA at this point.
19 Sharon.

20 DR. NORMAND: I have two questions.
21 I think I'll start with the simple one first.
22 On Slide 27, I think you wrote two people had

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1 prior ablations. Presumably that was for
2 something other than A-fib. It just says
3 prior ablation.

4 CHAIRMAN MAISEL: We heard from the
5 sponsor earlier that, I think, one was WPW and
6 one was PDI maybe.

7 DR. NORMAND: Okay, thank you. So
8 here's the question that I'm grappling with
9 for the FDA and also for the sponsor. If I'm
10 a patient, I really don't care about the
11 conditional probability of chronic
12 effectiveness. That should not be an end
13 point and I strongly believe that. What it
14 should -- the end point it should be is the
15 probability of both acute effectiveness and
16 chronic effectiveness. As a patient, we don't
17 really care about -- we care about whether or
18 not we need acute effectiveness. And so I'm
19 asking the FDA the rationale for using an end
20 point that I think is utterly -- this is
21 obviously my very strong opinion, I think
22 misleading the public. We do not want -- I

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1 want to know if I get treated whether or not
2 I'm going to have a successful end point at
3 six months.

4 And that's apparently the joint
5 probability of both the probability of chronic
6 effectiveness, conditional and acute
7 effectiveness multiplied by the probability of
8 acute effectiveness. So I'd like some comment
9 on that and keeping that question in mind,
10 because clearly having a conditional
11 probability of success is not useful to the
12 public. I'm stating that again and again.
13 And keeping that in mind, the OPC that you're
14 using was at a conditional probability as
15 well.

16 DR. BROCKMAN: Your last question
17 first; yes, the chronic effectiveness OPC is
18 based on conditional success. I agree with
19 you, patients want to know if they go in for a
20 procedure, if they're going to be successful
21 long-term. For the purpose of our studies,
22 though, it is important for us to at least

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1 characterize the difference because we
2 wouldn't want patients who may not have a
3 recurrence, say, let's look at this design at
4 six months, who are acutely unsuccessful, you
5 wouldn't want them to be potentially called
6 successes.

7 DR. NORMAND: But you haven't -- so
8 there is some suggestion of surrogacy here.
9 You haven't shown that. So if you wanted to
10 show surrogacy of acute effectiveness, you'd
11 actually have to look at the unsuccessful
12 ones. So it really does raise a dilemma, I
13 think, in my mind. I'm not saying it's not
14 important to look at chronic effectiveness,
15 but you need to look at it -- the patient
16 population wants the whole probability. I'm
17 trying to get a sense of -- I understand
18 looking at the difference, but I think it's
19 really misleading to say -- to give an
20 estimate of a success that is conditional to
21 the layperson.

22 CHAIRMAN MAISEL: Yes, I mean, my

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1 comment would be -- I mean these OPCs were
2 designed to understand both the acute
3 effectiveness of the device and the chronic
4 effectiveness. We have the information you
5 want to a certain degree, that if you're in an
6 acute failure, you don't count and if you're a
7 chronic failure, you don't count as a success.

8 DR. NORMAND: But that's the wrong
9 -- it's an important point not for whether the
10 OBC was based on that or not. What we want to
11 know, if we're going to give a message to the
12 public that says, "Here is the probability
13 that it will go away." It's not the
14 conditional probability. It's the whole
15 probability. So I really want to emphasize, I
16 think it's very misleading.

17 DR. SOMBERG: Can I interject?

18 CHAIRMAN MAISEL: Please.

19 DR. SOMBERG: I think you're
20 generally right but in this situation more so
21 than many, I think the acute effectiveness end
22 point is not really an acute effectiveness end

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1 point. It's a surrogate for whether the
2 system works and my have predicted value later
3 on. If I gave an anti-arrhythmic, an analogy,
4 and terminated an arrhythmia, but everyone
5 dies an hour or 24 hours later, then, you
6 know, you ask the probability of the acute
7 working and also working a little bit later
8 which is important in that situation here.
9 But I don't think a patient cares whether he
10 has a block at the isthmus or not block at the
11 isthmus. He wants to know if he's going to
12 have, you know, six months or a year later,
13 and I think a year is better even, not going
14 to have atrial flutter.

15 Now, my problem, and I just want to
16 go on for a minute, is my problem is -- and
17 this is a question I was going to ask is, when
18 the FDA met with the company, where you were
19 talking about chronic effectiveness and, you
20 know, whether this technique works or not, did
21 you discuss, you know, what you really meant,
22 because it seems everyone is talking at cross

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1 points here.

2 One of the presenters from the
3 company said something which I believe is very
4 meaningful, that when a patient -- what we're
5 talking about is chronic atrial flutter that
6 occurs, you need a cardio version of an anti-
7 arrhythmic drug, or an ablation procedure to
8 terminate it. I'm not so much interested in
9 what happens on a electrogram, what happens in
10 artifact here. You made the statement that,
11 gee whiz, if you have an atrial flutter on an
12 electrogram, how can you be a clinical
13 success?

14 Well, I mean, these things are at
15 cross purposes. Really you can be a clinical
16 success or you can be a clinical failure and
17 not see anything. The question is, do you
18 have sustained atrial flutter that when you
19 get an electro-physiology study came from the
20 isthmus because atrial flutters can come from
21 other places as well as atrial fibrillation.
22 As a patient and as someone who wants to

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1 potentially or in the community will utilize
2 this type of technology, does it prevent the
3 recurrent atrial flutter that was from that
4 area and was that discussed? Because it seems
5 like electrogram syncope doing an EKG,
6 none of these things exactly are the end
7 points.

8 And you know, I'm just going to go
9 on for another second, in the heart failure
10 field, we wouldn't talk about do you hear
11 valves or do you not hear RALs or do you not
12 hear RALs. We would ask, does the person have
13 an admission for heart failure,
14 hospitalization or death? So it seems to me
15 we're sort of feeling this topic out but we
16 haven't really addressed it critically. And
17 since all this has been done now, I mean, it
18 is nice the bio was talking about two to five
19 years ago, but when the FDA was consulted, I'm
20 not even sure you were there at that time, but
21 if the FDA was consulted, was that brought up
22 because I think that's going to be important

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1 in our decision when you just miss an end
2 point and, you know, this whole thing is very
3 artificial, was that discussed with the
4 company that you know, what are we talking
5 about as chronic effectiveness?

6 DR. BROCKMAN: Well, I wasn't there
7 at the time but to the best of my knowledge,
8 all discussions about chronic effectiveness
9 dealt with documented recurrent atrial
10 flutter. It was not about --

11 DR. SOMBERG: Documented, just what
12 does that mean? You know what --

13 DR. BROCKMAN: Documented on event
14 monitor recordings.

15 DR. SOMBERG: Okay, on an event
16 monitor.

17 DR. BROCKMAN: Yes.

18 DR. SOMBERG: So it's not whether
19 you got hospitalized, whether it was
20 sustained. You could have had that three
21 beats of atrial flutter and that was a
22 clinical recurrence.

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1 DR. BROCKMAN: Yes.

2 DR. SOMBERG: That's not --

3 DR. BROCKMAN: It was a recurrence
4 of atrial flutter.

5 DR. SOMBERG: That's not a
6 clinically effectiveness end point in my mind,
7 unfortunately. So you know, neither side
8 seems to be talking about clinical chronic
9 effectiveness.

10 DR. DOMANSKI: You know, I'd like
11 to -- because of the discussion I think is
12 going to follow, I'd like to ask a couple of
13 questions and the form that discussion. It
14 would appear that neither the safety nor the
15 effectiveness end points that you set were
16 met. And so I guess questions with regard to
17 those two things. First of all, with respect
18 to the safety end points, you know, where did
19 you get them? And there was one slide where
20 somebody said, "Gee, we think they did what's
21 reasonable for atrial flutter but they didn't
22 meet your end points". I don't quite

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1 understand how those two statements comport.

2 I mean, do you think today that the
3 safety end points that were set are the
4 appropriate ones and you know, tell us how you
5 got to them and why. And with regard to the
6 effectiveness, again, at least the chronic
7 effectiveness excepting the discussion that's
8 been had by the way, but not trying to go
9 back, let me just take the simple, kind of
10 country doctor approach and use what they've
11 got for now, anyway, I'd like to know how the
12 effectiveness ones were arrived at and did you
13 ever contemplate a post hoc analysis of
14 clinical data by a physician employed by
15 CryoCor to try to meet those bars?

16 DR. BROCKMAN: The end points were
17 derived -- the performance goals were derived
18 from a 1998 panel meeting. They were based
19 largely on a literature review but the
20 performance goals were developed from the
21 panel meeting.

22 DR. DOMANSKI: Do you regard those

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1 as continuing to be appropriate?

2 DR. BROCKMAN: I think the
3 principal reason we're here is to discuss the
4 data but I think that we would certainly be
5 interested in your opinions if you think that
6 those need to be reconsidered. And the
7 clinical effectiveness, did we ever entertain
8 it, I mean, we have certainly entertained it
9 as a post hoc analysis presented by the
10 sponsor, we did not suggest it.

11 DR. DOMANSKI: Yes, and you didn't
12 contemplate it as you set your standards, your
13 performance standards, I guess. Am I putting
14 words in your mouth or --

15 DR. BROCKMAN: Well, I wasn't
16 around when they were developed but I suspect
17 they were not.

18 DR. DOMANSKI: Well, what about the
19 FDA? Okay. And in terms of the -- and go
20 through the same thing for the safety. I
21 mean, is that -- how did you set the safety
22 end points?

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1 DR. BROCKMAN: I believe it was set
2 the same way.

3 DR. DOMANSKI: Great, that answers
4 the question.

5 CHAIRMAN MAISEL: Dr. Slotwiner.

6 DR. SLOTWINER: Thanks. I just
7 want to address Sharon's point about the
8 importance of acute efficacy versus chronic
9 efficacy from the position of a clinical
10 electro-physiologist. Acute efficacy is very
11 important in the laboratory to know that you
12 have an end point and so, in terms of
13 developing instructions for use, it's hard to
14 imagine interpreting it without that.

15 DR. NORMAND: So just to be clear,
16 I'm not saying they're not important. I said
17 you have to put them back together for the
18 patient. The patient wants to know, "Was I
19 acutely successful and chronic, chronically in
20 the long-term." I'm not saying they're not
21 important, both pieces are important but for
22 usability, I would argue being the only non-

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1 physician on this panel is that as a potential
2 user of this new technology, I want the right
3 estimate and the right estimate is not a
4 conditional estimate.

5 It's not that the unconditional
6 estimates aren't important, but the right
7 estimate is the probability of having both
8 acute success and chronic success, not
9 conditional.

10 DR. SLOTWINER: But how can you
11 have chronic success if you don't have acute
12 success?

13 DR. NORMAND: Because there were
14 160 patients enrolled in this study. So the
15 right denominator as was done by the analysis
16 is 160. I come into this study and I want to
17 know -- the way it's going to work in
18 practice, a patient comes into your office and
19 says, "I want this done", and the estimate
20 you're not going to give them is the
21 probability of chronic success giving you --
22 you pass this first bar. It's the probability

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1 path of passing both the first bar and the
2 second bar.

3 So I hope one's not using the
4 conditional probability as the chronic
5 probability because that's completely wrong.

6 CHAIRMAN MAISEL: Sharon, just to
7 understand what you're saying, you want
8 chronic effectiveness of the 160 patients. I
9 suspect that if that had been the number we
10 were given, your first question when you
11 raised your hand when the question session
12 opened up, would have been who do we compare
13 this to, because there are some people who
14 might just be effective because they're on
15 medication, because they got lucky for
16 whatever reason.

17 DR. NORMAND: Bill, it doesn't
18 matter. The right number is the probability
19 of chronic effectiveness given acute
20 effectiveness multiplied by --

21 CHAIRMAN MAISEL: I don't disagree
22 with you. My point simply is that's not the

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1 only number we need and I certainly -- any
2 labeling we can supply the patient with that
3 number and Linda, maybe you want to comment on
4 what you think is what patients might want to
5 know.

6 MS. MOTTLE: Thank you, Bill. I
7 totally agree with you. You're absolutely
8 right. And I'm a little concerned that we're
9 seeing different outcome data between the
10 pivotal and the OUS, and then the secondary
11 issues of decreased pain but then you look at
12 some of the procedure time, which is
13 secondary. These are not primary safety and
14 efficacy but you've got increased patient
15 procedure time and no relationship to any
16 adverse events dealing with that on the table.

17 CHAIRMAN MAISEL: So important
18 points to discuss. Marcia?

19 DR. YAROSS: Yes, I think I'd add a
20 couple of things. You know, one, of course,
21 we can discuss what's the appropriate form for
22 labeling and that's where I think, you know,

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1 it's important for context to think about how
2 these are typically handled. The second thing
3 I would point out is that in terms of the OPC,
4 again, the issue about whether or not chronic
5 effectiveness is based on the acute
6 effectiveness was the way the OPC was
7 developed and so from that standpoint, again,
8 a level playing field and consistency across
9 applications is probably important.

10 DR. GOMATAM: I have a small point
11 to inform the discussion. I think if I were
12 a patient, I would be interested in all three
13 numbers. If I have the choice of a procedure,
14 then I want to know what the total efficacy is
15 and once I'm on the table, I want to know what
16 the acute efficacy is and if I'm a success, I
17 want to know what chronic rate of success I
18 would have.

19 We did do an analysis of what I
20 call unconditional six-month recurrence, so it
21 was a Kaplan-Meier analysis and the estimates
22 we got for the six-month point were 71.4

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1 percent with a lower bound of 64 percent.
2 Unfortunately, we don't have an OPC to compare
3 it to.

4 CHAIRMAN MAISEL: Yes, Norm.

5 DR. KATO: A question to the FDA;
6 the -- in one of your slides you said, again,
7 -- I'm sorry, getting back to this chronic
8 effectiveness question, it just said chronic
9 effectiveness. Is the time that is six months
10 in this case, is that defined by the sponsor,
11 by you or is it really -- can it be anything
12 longer than acute effectiveness or whatever
13 that is?

14 DR. GOMATAM: Well, that was the
15 time defined in the protocol and I believe
16 that's the time for the OPC definition, the
17 six months.

18 DR. KATO: By FDA?

19 DR. GOMATAM: I believe so, that's
20 correct, right?

21 DR. KATO: Okay, but the chronic
22 effectiveness is defined by the FDA as a six-

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1 month interval. Is that correct, not by the
2 sponsor?

3 DR. FARIS: The protocol specifies
4 the chronic effectiveness will be evaluated at
5 six months, so in our slides that say chronic
6 effectiveness, we mean six-month, yes.

7 CHAIRMAN MAISEL: What was the OPC
8 chronic effectiveness time end point?

9 DR. FARIS: I believe it's defined
10 as six months. No?

11 DR. BAROLD: No.

12 DR. KATO: So it is not.

13 CHAIRMAN MAISEL: Dr. Milan?

14 DR. KATO: Yes, I have it here.
15 It's three months. The other point I want to
16 make --

17 CHAIRMAN MAISEL: Can we just --
18 let's just clarify that point. So was that
19 accurate that the chronic effectiveness end
20 point in the OPC is -- what's the time end
21 point?

22 DR. BAROLD: I have a copy -- three

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1 months.

2 CHAIRMAN MAISEL: Okay, does the
3 FDA -- I just want to get their -- everyone is
4 saying three months except the FDA, is that --
5 is it three months?

6 DR. BROCKMAN: There is a guidance
7 document for generic indication for super-
8 ventricular tachi-arrhythmias. The OPCs that
9 we used for flutter are borrowed largely from
10 that document. Atrial flutter is discussed in
11 there. The OPCs in that document I'm pretty
12 sure specify six months.

13 DR. BAROLD: I can provide you with
14 a document.

15 CHAIRMAN MAISEL: We can do that.
16 We'll let you clarify afterwards. So we're
17 hearing different things. So clearly that's
18 going to be something we need to sort out.
19 Norm.

20 DR. KATO: Sorry, one more follow-
21 up. You also mentioned something about post-
22 approval studies and we've gone through post-

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1 approval studies and recommendations about
2 that. We've learned that at least from what I
3 understand, there's not a whole lot of funding
4 for post-approval studies, how is that -- how
5 is that, you know -- unfortunately FDA often
6 time says, "Well, we'll just defer this to a
7 post-approval study". So how were you -- in
8 the light of the fact that there's no funding
9 for that --

10 CHAIRMAN MAISEL: Norm, I'm going
11 to interrupt you. We're not -- funding is not
12 a relevant issue for us.

13 DR. KATO: Okay. How is that --
14 how are you going to get that -- this approval
15 study done and how are we going to enforce it?

16 DR. ZUCKERMAN: Could I answer
17 that?

18 CHAIRMAN MAISEL: Dr. Zuckerman.

19 DR. ZUCKERMAN: Okay, Dr. Brockman,
20 you weren't here in 2000 so you don't have to
21 be on the hot seat.

22 DR. BROCKMAN: Thank you.

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1 DR. ZUCKERMAN: Again, I wanted to
2 remind the panel what this post-FDA discussion
3 session is about. It's to ask some hot
4 questions to help you focus on in the
5 afternoon, where the Advisory Panel needs help
6 and I would refer you to Dr. Brockman's slide
7 42 where I think it gets to the heart of the
8 matter. The bottom line is that since 2000,
9 the Agency has seen a fair number of catheter
10 ablation studies. I think you've commented
11 this morning as well as the sponsor, on some
12 of the methodological problems with picking a
13 fixed point estimate.

14 The FDA doesn't disagree. That's
15 the problem with picking a fixed point
16 estimate. But what it is incumbent upon you
17 to discuss this afternoon is what was in the
18 protocol agreed upon between FDA and the
19 sponsor, what are the protocol results and how
20 do they match up from a clinical aggregate
21 perspective and that's the point of slide 42.

22 And I hope that we can really advance those

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1 sorts of concepts and questions or if that's a
2 bit confusing, please ask me some questions
3 now.

4 CHAIRMAN MAISEL: Sharon?

5 DR. NORMAND: So I guess my
6 question would be the following; it's sort of
7 a bit of dilemma. This is a study that was
8 done in the past. We have information about
9 the OPC that's based on data that's older and
10 so my question to you is, are we to consider
11 currently what we think the right rates are
12 supposed to be? In other words, do we look at
13 this in isolation and say, "Here's a line in
14 the sand that was developed X years ago", and
15 how do we bring in current information today
16 in our discussions about that? Are we allowed
17 to do that?

18 DR. ZUCKERMAN: I would, you know,
19 commend you for that great question, Sharon-
20 Lise, and look at Bullet 3. FDA has assembled
21 a distinguished panel of clinical experts
22 where we really want them to use their

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1 clinical acumen as well as their statistical
2 acumen. On the other hand, we do want to be
3 sensitive to the fact that the agency and the
4 sponsor did agree a number of years ago to a
5 certain specified protocol. So we aren't
6 asking for quantum leaps in our interpretation
7 of what might be an acceptable bar.

8 CHAIRMAN MAISEL: Other comments or
9 questions for FDA at this point? Marcia?

10 DR. YAROSS: The sponsor has
11 commented about the, in their view,
12 comparative rigor of the follow-up. Was the
13 intensive event monitoring strategy at FDA's
14 request?

15 DR. ZUCKERMAN: Again, the protocol
16 that we will be discussing in detail is a
17 fairly standard catheter ablation type
18 protocol and the FDA team will go into more
19 detail. While, you know, some people may
20 question the point estimates used for the
21 final determinations, the protocol is the
22 protocol.

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1 CHAIRMAN MAISEL: Marcia, I would
2 also comment that if the panel feels that the
3 study failed to meet the OPC because of more
4 rigorous monitoring compared to the data on
5 which the OPC was based, it's certainly within
6 our purview to approve the device with that
7 explanation. Adam?

8 DR. LOTTICK: The -- it sounds as
9 though the original OPC end points were
10 determined based on other SVTs; is that
11 correct? I just want to understand. Before
12 we try to deviate in any way from what was
13 originally specified, what was the basis for
14 that specification?

15 DR. BROCKMAN: The OPCs for atrial
16 flutter are the same as the OPCs for other
17 super-ventricular arrhythmias, meaning there
18 would be no re-entry WPW and creation of heart
19 block, intentional heart block. They are the
20 same. The ones -- the OPCs for those came
21 from a literature review for those types of
22 arrhythmias, the ones for atrial flutter while

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1 they are the same, also incorporated a review
2 of literature for atrial flutter ablations.
3 So I wasn't around at the time. I don't know
4 exactly why they're identical. I don't know
5 how much of it is a little coincidence and how
6 much of it is perhaps drawing somewhat on a
7 similar experience. But atrial flutter
8 studies were incorporated into the decision
9 process for coming up with the performance
10 goals for the atrial flutter ablation.

11 CHAIRMAN MAISEL: Dr. -- oh, I'm
12 sorry, go ahead, Adam.

13 DR. LOTTICK: So since flutter is a
14 fundamentally different arrhythmia, it seems
15 that we're legitimate in being critical of the
16 originally suggested OPCs.

17 DR. BROCKMAN: Again, I think our
18 principal reason for being here is to discuss
19 the data that we have in front of us but we
20 are certainly interested in your opinion on
21 other matters that you think are important.

22 CHAIRMAN MAISEL: Dr. Yancy.

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1 DR. YANCY: I would like to revisit
2 the safety issues from the FDA's perspective.

3 One of the things that's important about the
4 context that we've heard expressed is that if
5 the overall effectiveness is in the 70 percent
6 threshold, that means that for the patient,
7 this has to be juxtaposed with other
8 alternative approaches and what ever the
9 inherent risk is, because in general atrial
10 flutter is not life-threatening and there are
11 other ways to treat this process which the
12 patient should be made aware of.

13 So in that context if we look at
14 the revised definition of safety, looking just
15 at device and procedure related complications,
16 the implication is that we're using that
17 number and comparing it to the reference OPC
18 for all serious adverse events. So is there a
19 revised OPC, a revised standard we can use
20 when we're only looking at device and
21 procedural related complications?

22 DR. BROCKMAN: Not that I'm aware

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1 of. We did not compare the device and
2 procedure related rates.

3 DR. YANCY: Because by protocol
4 specification we didn't meet -- the safety bar
5 was not met and it only comes into context
6 when we look at this revised analysis but it's
7 compared to the reference point for all
8 serious adverse events. So I'm just trying to
9 get a sense of whether or not device and
10 procedures are within those confidence limits
11 or if it's a number that we simply don't know.

12 DR. BROCKMAN: I don't have a
13 performance goal for the device and procedure
14 related adverse events but, you're right, that
15 was put up on the screen.

16 CHAIRMAN MAISEL: Dr. Somberg?

17 DR. SOMBERG: That's a very good
18 point and that's the problem with these
19 procedural performance goals, is that we don't
20 have a control, you know, an actual clinical
21 control where we're making some valid
22 comparison. So I would -- and what I was

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1 thinking of when this was going on is, one
2 solution the committee might have is, I wonder
3 what the FDA might comment on, is to say, "You
4 put it out there. You put it out there in the
5 -- you know, in the materials when the device
6 is approved", and then the clinician who's
7 using it will have to say, "Well, this
8 catheter gives me seven, nine, ten percent
9 incidence of" -- and he looks at what the
10 things are in this catheter gives me this,
11 because in actuality, the patient doesn't
12 choose this. It's the physician who chooses
13 this.

14 You know, it's what tool and you
15 know -- I mean I talk to patients. Everyone
16 here talks to patients and you don't get into
17 a detailed discussion of what tools you're
18 going to use. They have to take the person,
19 the institution and the reputations to say,
20 "You're using the right tools in that
21 situation". So maybe the thing is to put it
22 out there.

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1 But it certainly -- and I just -- I
2 don't know when I'll make this comment but I'm
3 going to make it right now is that I believe
4 in randomized control trials and when one does
5 or one doesn't have a control group, when one
6 has very questionable evaluation end points,
7 and it's not the FDA's fault or the sponsor's
8 fault. You get into all these post hoc
9 scratching the head exercises and I would have
10 liked to have seen a control on the control
11 arm which it could be on of the other devices
12 used in this situation and you would say, "Oh,
13 look, this is twice as bad", or, "this is
14 twice as good", and you would have something
15 to say or there would be a non-inferiority or
16 something on that basis.

17 But we don't have that data, so I
18 underscore what Dr. Zuckerman was saying is,
19 you have to give opinions. Where do you think
20 this is a relatively safe and effective drug,
21 given your clinical opinion, which is not a
22 randomized control study, unfortunately.

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1 CHAIRMAN MAISEL: Marcia?

2 DR. YAROSS: And with respect, I
3 would just remind the panel that there is no
4 requirement in the device regulations for
5 randomized control trials. Other designs,
6 such as OPC control trials are considered
7 valid scientific evidence.

8 CHAIRMAN MAISEL: Mike.

9 DR. DOMANSKI: Yes, but there are
10 two comments that I want to make, because I
11 think it sets the debate. I want to first of
12 all, distance myself from the view that a
13 level playing field is what we're here to do.
14 I think it's very important for the FDA to
15 try to achieve that but I think it's
16 meaningless in the deliberation about a
17 particular device, because only safety and
18 efficacy is important, I think, number one.

19 Number two is yes, I think that
20 this points up not so much that it's not
21 legitimate to use in a non-randomized trial
22 but it certainly appears to be pointing out

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1 the fact that these performance criteria, if
2 they are used instead of a randomized trial,
3 need to be done awfully selectively because
4 here this is going to -- this whole thing is
5 now going to hinge on whether or not we think
6 those criteria are reasonable and there the
7 confidence interval is going to have to be
8 pretty wide if we're going to tell people who
9 come in with a device like this that they
10 can't market it.

11 CHAIRMAN MAISEL: Other comments
12 for the FDA, David?

13 DR. SLOTWINER: I just have a
14 question about the -- how the serious adverse
15 events within the first seven days, how those
16 criteria were derived because it's not clear
17 to me that a lot of those are due to the
18 system and so considering that without a
19 control arm, it seems critical.

20 DR. BROCKMAN: It is difficult to
21 make a full assessment of those without a
22 control arm, I agree with you.

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1 DR. SLOTWINER: So is there an
2 allowance that these may not be related to the
3 system and that we should not evaluate that
4 overall. Serious adverse event, we ought to
5 consider that number as a failure?

6 DR. BROCKMAN: Certainly if the
7 events are tabulated and we get statistics and
8 then we look at them individually. So do we
9 simply look at the number and draw a line as
10 that term has been used? No, of course not.
11 I think it's useful to set that up and look at
12 it and then we look at each event individually
13 and make a call on it.

14 CHAIRMAN MAISEL: Dr. Milan?

15 MS. PRATT: I'm sitting here with
16 this -- what I think is the guidance document
17 that I everybody is talking about and for the
18 major complications which they say the target
19 value is less than 2.5 percent. The
20 definition appears to be procedure or device
21 related adverse events as opposed to just all
22 adverse events, for what it's worth.

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1 CHAIRMAN MAISEL: Thank you for
2 that clarification. Any other questions for
3 the FDA at this point? We'll obviously be
4 able to ask and discuss more later. Okay,
5 good.

6 At this point, Dr. Barold, if you
7 are prepared -- you had mentioned you wanted
8 to make a comment earlier about the timing of
9 the chronic effectiveness end point according
10 to the guidance document.

11 DR. BAROLD: It sounds like you
12 have the OPC in front of you. I have it also
13 just to clarify that, that indeed -- and just
14 as a further clarification, that when I worked
15 for the Agency, I actually worked on the
16 guidance documents. I have a little bit of
17 the history of it and will try to be unbiased
18 in this. But it was set up for SVTs. That
19 was the criteria. However, it was applied to
20 other arrhythmias.

21 And the acute success was
22 considered not a disability of the target

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1 arrhythmia, I'm just reading this. The
2 chronic success was three month freedom from
3 recurrence of the target arrhythmia and the
4 major complications were considered procedure
5 or device related adverse events requiring any
6 intervention to prevent permanent medical
7 intervention. That's the way they were set
8 up.

9 It is slightly different than the
10 way our study is set up. In addition to that,
11 the OPC -- the document itself goes on to
12 discuss different arrhythmias, one of which is
13 atrial flutter and we presented the
14 literature, Dr. Calkins presented the
15 literature that that part of the document was
16 based upon. So you can refer to those slides
17 with those numbers for the data that the FDA
18 used.

19 CHAIRMAN MAISEL: Thank you for
20 that clarification. Could I ask the FDA to
21 comment on that guidance document again,
22 because last we heard from you, you said a

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1 six-month end point and we're hearing three-
 2 month and I think it's an important issue for
 3 us. And I understand the protocol stated six
 4 months.

5 MR. MALLIS: Elias Mallis at FDA.
 6 Just a point of clarification, I believe the
 7 guidance document that was just referred to is
 8 the generic indications guidance. That was
 9 published, I believe, in 2002. The panel
 10 meeting for atrial flutter took place in `98
 11 and we had established the performance goals
 12 after that panel meeting. So the guidance
 13 that was prepared in 2002 was specific to
 14 standard 4 millimeter RF catheters, primarily
 15 trying to expand indications from SVT toward a
 16 more generic indication. So it's possible
 17 that there are parallels to atrial flutter.
 18 But the panel meeting in `98 from which we
 19 obtained the feedback of the expert advisory
 20 panel, is where those goals are derived.

21 In terms of the chronic endpoint
 22 which is the question at hand, we have seen

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1 both three and six months as the end point in
2 studies.

3 CHAIRMAN MAISEL: Elias, I'm sorry,
4 just -- I really want to clarify this. What
5 is the FDA's position about the time of the
6 end point for the OPC? We've been given a
7 number but it's still unclear to me about what
8 the Agency's position is regarding at what
9 point, at what time point should we be looking
10 to determine whether the OPC is met, three
11 months, six months or you don't have a
12 position, three or six?

13 MR. MALLIS: At this point, we do
14 not have a specific position of one time point
15 or another. We would meet with the sponsor
16 and if they provide a specification in their
17 protocol, we would consider whatever the
18 appropriate time is.

19 DR. NORMAND: That's a question.
20 That's not a position question. It's a
21 factual question. What is the OPC based on?
22 Is it based on information that you combine

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1 using three-month -- I don't think it's an
2 opinion question, so help me understand why
3 you're answering from a position. I thought
4 the OPC is a number that you combine using
5 data and I just -- I think we'd all like to
6 know is that based on data that used a three-
7 month end point or a six-month end point?
8 It's not a matter of position, I believe.

9 DR. SOMBERG: Maybe you should --

10 CHAIRMAN MAISEL: Dr. Zuckerman,
11 would you like to comment on that?

12 DR. ZUCKERMAN: We'll have a fuller
13 explanation after lunch.

14 CHAIRMAN MAISEL: Okay. David.

15 MS. PRATT: Only that it would be
16 helpful also to have a full explanation of the
17 safety end point, whether it's all adverse
18 events or just advice and procedure related.

19 CHAIRMAN MAISEL: Okay, we'll look
20 forward to those comments. Any other general
21 comments? We have a little bit of time before
22 lunch. I think one thing I'd be interested in

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1 hearing from the panel is regarding your
2 feelings about what is clinical effectiveness
3 for an atrial flutter ablation catheter.
4 We've been presented a couple of different
5 analyses, one based on procedural end points
6 and ECG monitoring, another one based on
7 symptoms and quote, "clinical feelings" about
8 patients. So I'd like to hear what the panel
9 is thinking. John.

10 DR. SOMBERG: Well, my feeling is
11 that you have to have -- the most important
12 thing is chronic effectiveness, I would say
13 six months. I think if you had a panel today,
14 an expert panel, you might even ask to come up
15 with a year's time for benefits here and we're
16 talking -- and I think you have to be
17 arrhythmia specific and with atrial flutter,
18 we're talking about things like
19 rehospitalization, cardio-version, meaningful
20 end points, not three beats on a wobbly event
21 recorder.

22 And I would -- I would be

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1 interested if we have extra time in the
2 committee and the company over this hiatus --
3 to after lunch, could possibly show us
4 comparative data from the literature on --
5 because they have a retrospective analysis
6 that was post hoc that was obviously trying to
7 meet the performance goals after they didn't
8 meet the performance goals, but how does that
9 compare, since we have to make this
10 evaluation, how does that compare to the
11 therapies that are out there and in terms of
12 you have a clinical -- if it may be bias, but
13 clinical effectiveness end point that I
14 certainly might agree with at some point, but
15 what does that compare with the other
16 alternatives out there and I think that would
17 be important for comparative valuation.

18 I don't have that at my fingertips,
19 and maybe they did -- have thought about that
20 a lot and that might be useful for me.

21 CHAIRMAN MAISEL: We certainly will
22 give the sponsor the opportunity to do that

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1 after lunch if they wish. They're certainly
2 not obligated to and the panel pack is
3 supposed to stand on its own merits. Mike.

4 DR. DOMANSKI: Yes, I actually
5 think it would be -- we have a very learned
6 group of people assembled on behalf of the
7 sponsor here really uniformly and it would be
8 very interesting and helpful to have them also
9 take the end point that's really there, not
10 just a new one, but perhaps a new one as well,
11 and say why these numbers are appropriate and
12 why they shouldn't be held to the OPC as it
13 was constituted some -- you know, based on
14 something that was done many years ago really.

15 That would be very helpful.

16 CHAIRMAN MAISEL: I think it's hard
17 to debate the potential utility of a true
18 clinical end point. I think the problem we're
19 faced with here is the study was not designed
20 to measure that. So we don't know anything
21 about the symptoms prior to the -- prior to
22 the intervention and so I think in --

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1 DR. DOMANSKI: Yes, I'm not
2 advocating that at all. What I'm asking for
3 is taking -- what I'm asking for, I think --
4 the other is interesting but the one that I'm
5 actually particularly interested in is hearing
6 why the -- because if they'd met the OPC, this
7 would be a pretty short discussion. They
8 didn't and that's lengthening it, but I think
9 it's very reasonable for the sponsor to
10 present a compelling case that the numbers
11 used in the OPC are historical and that they
12 are not the right ones. And if they do that,
13 it seems to me that would be pretty
14 compelling.

15 CHAIRMAN MAISEL: Other comments?
16 Dr. Milan?

17 DR. MILAN: I think both are
18 important, again. One of the questions is,
19 when a patient comes to you with symptomatic
20 atrial flutter, what are your chances of
21 getting rid of that and making them feel
22 better? But the other question, it largely

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1 has to do with the way you manage them going
2 forward. It's -- if there is any recurrence
3 at atrial flutter, you have to worry about
4 ongoing intra-coagulation and other -- you
5 manage those patients differently. So I
6 think, you know, in some ways both pieces of
7 information are important to us as clinicians.

8 CHAIRMAN MAISEL: Dr. Slotwiner or
9 Lottick, do you have comments regarding the
10 clinical effectiveness versus the OPC, which
11 is more important or relevant?

12 DR. SLOTWINER: I think it's not
13 reasonable to compare atrial flutter to other
14 super-ventricular tachycardias that we have in
15 terms of efficacy because of the path of
16 physiology and the other arrhythmias that are
17 usually associated with it and it is often not
18 a black and white decision whether or not to
19 ablate it or treat it medically and a clinical
20 success can be different from bidirectional
21 blocks, so I think that the objective
22 performance criteria are probably not correct

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1 for atrial flutter.

2 CHAIRMAN MAISEL: Sharon?

3 DR. NORMAND: I just want to ask a
4 point of clarification, Bill, based on the
5 question you just asked. So I think you just
6 asked clinical effectiveness versus the OPC.
7 But it was my understanding and I may be
8 wrong, that the OPCs were based on data that
9 didn't use these detailed event recording. So
10 I'm not sure what the literature used in the
11 OPC -- It could have been clinical end points.

12 We don't know the answer to that. So I think
13 that we should be clear what we're talking
14 about here.

15 CHAIRMAN MAISEL: I'm sorry. I
16 probably would have been more accurate to say
17 clinical effectiveness based on symptom and
18 physician assessment versus event monitoring
19 looking for EKG evidence of recurrence. We'll
20 worry about the OPC a little later. Yes,
21 David.

22 DR. SLOTWINER: One other point;

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1 I'm glad to see that it's not just me who has
2 trouble interpreting monitor strips. And I
3 saw on the interpretation strip that there was
4 a box for uncertain or unclear and I'm
5 wondering how many tracings just weren't
6 interpretable. Sometimes it's just simply not
7 clear if it's flutter or sinus rhythm or fib.

8 CHAIRMAN MAISEL: So, Dr.
9 Scheinman, do you want to just give us an idea
10 of what percentage of strips were
11 uninterpretable? Turn you mike on, please.

12 DR. SCHEINMMAN: We do have the
13 data where it was just complete interpretable
14 and she can give you that. Can I make one
15 other point while we're on this?

16 CHAIRMAN MAISEL: Sure.

17 DR. SCHEINMMAN: I've heard several
18 representatives from the FDA said that how
19 could they call this a success when there was
20 documented flutter on the EKG? And the point
21 that I'd like to make is that it's a matter of
22 probability. For example, if you had a fib

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1 and a few runs as John has pointed out,
2 flutter and a clinician says the patient is
3 asymptomatic and it only happened once, I
4 think the greater probability is that this was
5 artifact, you see? So I don't think you can
6 take my readings. My readings -- my mandate
7 was be very stringent, "If you find anything
8 that looks like, smells like flutter, call it
9 flutter." But, in fact, if you don't take the
10 clinical context, you're putting in a lot of
11 garbage and that's -- you know, that's in the
12 person who actually read it.

13 CHAIRMAN MAISEL: Thank you. So do
14 we have a number regarding the number of
15 missing or uninterpretable ECG strips?

16 DR. BAROLD: There were 79 out of
17 4,465 were determined to be indeterminate and
18 that was a really small number. I don't have
19 the percentage. It's obviously less than one
20 percent. And the reason being that the
21 mandate for Dr. Scheinman was to make a
22 decision. You know, try not to call it

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1 indeterminate.

2 The overwhelming majority of the
3 indeterminates were artifact like that were
4 shown, but there were a few tracings when he
5 just sort of said, "There's just no way I can
6 tell. But they were a very small number, 79
7 out of 4,465 that he read.

8 CHAIRMAN MAISEL: Yes, Clyde.

9 DR. YANCY: Dr. Barold, while
10 you're still there and you have these numbers
11 at the ready, by my count of what's provided
12 in the panel pack, I think it's Table 2, there
13 were 22 cases that were readjudicated after
14 the over-read by Dr. Scheinman's core lab; is
15 that correct?

16 DR. BAROLD: I'm sorry, let me just
17 refer to that table again. What page was it?

18 I don't know. I'm sorry, can you tell me
19 what table it was again? You're referring to
20 Table 2 in Section 3.9.4 on page 10?

21 DR. YANCY: Table 2 that is pages
22 10 and 11 and sponsor's contribution. By my

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1 count there were 22 cases that were
2 readjudicated by the core lab; is that
3 correct?

4 DR. BAROLD: No, no, everything --
5 here's how it happened.

6 DR. YANCY: But when I say
7 readjudicated, I mean, where the designation
8 was changed.

9 DR. BAROLD: Correct.

10 DR. YANCY: So that's 22 cases out
11 of over 4,000 tracings.

12 DR. BAROLD: No, no.

13 DR. YANCY: He obviously looked at
14 3,000. You held back 1,000 because it was
15 clear.

16 DR. BAROLD: No, no, I think that
17 there's a slight discrepancy between the
18 number of event recordings per patient and
19 then who was reversed. He may have reversed
20 20 event recordings on a patient but it
21 counted as one reversal because the decision,
22 the final decision went from success to

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1 failure. But that could have been due to
2 multiple event recordings or a single event
3 recording.

4 DR. YANCY: So that actually helps
5 me. So there were 3,909 event recordings
6 reviewed by the core lab from 122 patients.
7 So Table 2 are the number of subjects who are
8 reclassified as success or failure; is that
9 correct?

10 DR. BAROLD: That is correct. And
11 you can see that the decisions went in both
12 directions.

13 DR. YANCY: Right.

14 DR. BAROLD: Right.

15 DR. YANCY: So I'm just trying to
16 get a sense of what the error rate was with
17 this previous protocol specified approach to
18 adjudicating the arrhythmias.

19 DR. BAROLD: Yes, I'm trying to
20 think off the top of my head how to calculate
21 that number. I'm not sure that I can give you
22 a number off the top of my head for the exact

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1 error rate. I can tell you that I have a
2 slide that will tell us how many -- this might
3 get to it a little bit.

4 DR. YANCY: Well, there's a fairly
5 strong statement in the panel pack that
6 indicates that there was great concern that it
7 was important to do the over-read because of
8 the complexity of the electrograms.

9 DR. BAROLD: Right.

10 DR. YANCY: And I'm just trying to
11 get a sense of what was the penetration of
12 that after the fact.

13 DR. BAROLD: I think I can get to
14 that by showing you the number of cases that
15 were called flutter by the core lab that were
16 read as atrial fibrillation. It would be
17 backup slide 49. This might help a little bit
18 to get to what you're asking, I think. I
19 don't know if you can put it up there. It's
20 not exactly what you're saying but of the --
21 of all of the tracings that -- and Dr.
22 Scheinman actually reviewed more than the

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1 three. He actually reviewed 400 to 475 of
2 these, 4,475. We recalculated the number.

3 And there were 179 of the event
4 recordings, again, this could be, you know,
5 multiple per patient, that the Life Watch
6 initially interpreted as atrial flutter. He
7 reversed 103 of those. So those would have
8 been in the positive direction. I don't have
9 the number in the negative direction, though,
10 of the number of events recordings.

11 All right, but that gets a little
12 bit to your question.

13 DR. YANCY: That does help, thank
14 you.

15 CHAIRMAN MAISEL: Thank you. I'd
16 like to come back to the clinical
17 effectiveness issue, just so we can try to
18 deal with it and move on and not have to keep
19 coming back to it. So is there anyone on the
20 panel who feels that we have adequate data?
21 We saw a post hoc clinical assessment of
22 patients. Does anyone on the panel feel that

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1 that data is the appropriate end point to be
2 looking at rather than the ECG data? Mike?

3 DR. DOMANSKI: Yes, I feel very
4 uncomfortable with that. I think it's -- I
5 think it's post hoc. I think it's done by
6 somebody who actually, I know well and is an
7 extraordinarily competent physician,
8 absolutely, vouch for on the basis of things I
9 know. Still, it's somebody employed by the
10 company doing a clinical adjudication and I
11 frankly would throw it out.

12 CHAIRMAN MAISEL: Anyone want to
13 use it? David.

14 DR. SLOTWINER: I feel very
15 uncomfortable using the post hoc analysis but
16 I do think it's important to recognize the
17 limitation of only the electrograms. They're
18 not a true measure of atrial flutter. They're
19 only a surface recording.

20 CHAIRMAN MAISEL: Adam? John?

21 DR. SOMBERG: Yes, I certainly
22 concur with that, that I have great

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1 trepidation, but with lack of anything else to
2 talk about and comparing it to the
3 electrograms, which I don't think are
4 meaningful to see momentary. And you know,
5 you used to talk about well, maybe someone had
6 -- you know, if they had one hour of sustained
7 atrial flutter, I'd be very concerned about
8 that patient. But what happens if they have
9 three or four beats of what looks like
10 electrical atrial flutter to Dr. Scheinman and
11 looked like it to a technician. I mean, still
12 that's just looks like, it's still guessing.

13 So I think what we have to say is
14 you know, what happened to these patients,
15 what did the clinicians who treat them, and if
16 someone carefully did that and I haven't been
17 able to review that but if people have
18 reviewed that and said they carefully went
19 through it step by step, then that would be
20 more meaningful to me than the electrograms,
21 although this is all retrospective analysis
22 and all of that.

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1 CHAIRMAN MAISEL: Sharon?

2 DR. NORMAND: So I agree with the
3 worries that one has with retrospective
4 analyses. So I definitely worry about that.
5 The other thing I worry about, this is present
6 also in looking at the agreed upon measure,
7 looking at the electrograms, is that I believe
8 the sponsors have treated -- I think there's a
9 problem with treating missing data censored.
10 And that's happened in several cases. And so
11 I don't know how that missing data which is
12 problematic in terms of the analysis that they
13 did do, but I don't even know how that plays
14 into the retrospective analysis with the
15 missing observations with people not coming
16 in. So that's an issue that is going to be
17 more problematic with a retrospective
18 analysis.

19 CHAIRMAN MAISEL: Adam.

20 DR. LOTTICK: One of the problems I
21 have with using the clinical data is that I
22 don't know what the clinical baseline is. I

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1 don't know how frequently people were actually
2 experiencing atrial flutter before they
3 underwent the flutter ablation. If they had
4 one episode of flutter ever, then a six-month
5 follow-up may not be a clear change in the --
6 be providing us with a clear change in the
7 flutter rate, if I'm making any sense.

8 CHAIRMAN MAISEL: Jeff?

9 DR. BRINKER: I believe the
10 representatives from the company said that
11 some of the telemetered monitored strips were
12 based upon patient symptoms, that they could
13 activate it themselves. Do you know how many
14 of those, in fact, were initiated and what the
15 incidents of flutter or other arrhythmia was?

16 CHAIRMAN MAISEL: Would you step up
17 to the mike?

18 DR. BAROLD: No, I don't have that.
19 We did not -- while the patients could send
20 in symptomatic recordings, when we collected
21 the data, we did not categorize them into
22 symptomatic and asymptomatic for this type of

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1 analysis which -- so we don't have that
2 available. We could individually go through
3 each one and look to see if they wrote a
4 symptom on the top but we don't have that
5 currently.

6 DR. BRINKER: Because that might
7 address some of the issues people have here
8 about dividing clinical events from
9 electrocardiographic events.

10 CHAIRMAN MAISEL: That's an
11 excellent point. Probably the only surrogate
12 we could use is if patients had five
13 transmissions in a month would be the only way
14 we'd know for sure, but there may be many
15 others who had symptoms. Clyde.

16 DR. YANCY: I would agree that it
17 seems as if our best metric right now with all
18 its limitations is going to be the core lab
19 and it would be great to have the information
20 that Dr. Brinker just requested.
21 Theoretically, it probably is ideal to use the
22 clinical construct because that's the basis

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1 upon which the OPC was derived. But I'm
2 uncomfortable with the way it's come about in
3 this study. So I think that we have to
4 qualify that very carefully.

5 CHAIRMAN MAISEL: So it seems, I
6 won't say to a person because we haven't heard
7 from everyone but the general consensus is
8 that a post hoc clinical assessment that
9 wasn't prespecified in a trial that wasn't
10 designed to assess that just isn't going to be
11 quality enough data for us to make a
12 determination on which brings us back to the
13 ECG monitoring. So I'd like to move on to
14 discussing the OPC, both -- first
15 conceptually. I mean, we know that the OPC
16 was based on data from the 1990s, a relatively
17 small number of trials. We've already heard
18 about some of the shortcomings.

19 Is there anyone who feels
20 comfortable that this is the perfect OPC, they
21 totally agree with it and you know, it is a
22 line in the sand. And I make that statement

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1 for a reason, obviously, because the next
2 question is going to be if we don't feel that
3 way, then certainly my sense is that we feel
4 there might be a little wiggle room. We
5 haven't discussed which way that wiggle should
6 go but is there anyone who feels that it's a
7 good OPC where -- not that it's bad but is
8 there anyone who feels that the numbers are
9 perfect and that there should be no wiggle
10 room? Jeff?

11 DR. BRINKER: I don't feel that way
12 but I'll -- just to be a little bit
13 provocative, I'll throw this out. Let's say
14 that the OPCs, what they were, and the company
15 made those, but the data now would suggest
16 that those OPCs weren't really the state of
17 the art. They were not something that people
18 would feel comfortable with now. Would we be
19 having this discussion on the opposite side of
20 the OPCs, in other words, discourage approval
21 of the device that met the OPCs that weren't
22 relevant now?

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1 CHAIRMAN MAISEL: I think the
2 answer -- I mean, we can hear from other panel
3 members. Let me ask it a little differently.

4 Let's say they made their OPC and their --
5 for both their effectiveness and their safety
6 but there was a particular safety issue we
7 were very concerned about, even though the
8 rate might have been low. I think it's
9 certainly within our purview to not approve
10 the device and I would say if we feel the
11 clinical bar has raised so much that this
12 device just doesn't cut it, then it doesn't
13 cut it. Mike.

14 DR. DOMANSKI: You know, this is
15 where I'd really like to hear also from the
16 panel of experts that has come with the
17 sponsor because this is really, really a high
18 power group, and I'd like to hear them talk
19 about the reasonableness of the OPCs in
20 addition to the panel. I know it's -- you
21 know, they come with the sponsor, but they're
22 really good people and I'd like to hear a full

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1 discussion of that because I think that the
2 whole approval of this thing hinges on whether
3 or not this is the right metric or not. So
4 what's the right metric and why?

5 CHAIRMAN MAISEL: So we'll hear
6 from the sponsor. Hugh, maybe you want to
7 start. You presented the OPC data. What are
8 your thoughts and we'd be happy to hear from
9 any other members of the sponsor on that
10 topic.

11 DR. CALKINS: Well, I think as I
12 presented earlier, the OPC data was based on
13 these four studies with clinical follow-up
14 only without event monitoring. And just like
15 now, you know, in the field of A-fibrillation,
16 the more you look, the more you see with event
17 monitors. That's guaranteed. And the fact
18 that this study was doing weekly event
19 monitoring as opposed to the OPC trials which
20 did not event monitoring, clearly will impact
21 what kind of efficacy bar you set. In the
22 field of A-fib usually it's a 20 percent lower

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1 success rate when you start monitoring
2 aggressively.

3 But the study that I think is the
4 most -- and the question came up earlier in
5 terms of RF cryo -- whatever, the study which
6 I think is -- just because I was -- not just
7 because I was involved with, but it was a
8 prospective multi-center study published in
9 2004, which is three years ago, which is 100
10 watt generator, not four millimeter catheters.

11 And the numbers in that study even -- were 88
12 percent acute efficacy, 87 percent, quote,
13 unquote, "chronic efficacy", and 2.7 percent
14 device or procedure related complication rate.

15 So the device and procedure related
16 complication rate is almost identical to what
17 was in this study and then you can argue about
18 is 87 percent significantly different than 82
19 percent when you're doing four times as much
20 event monitoring looking for these three beats
21 of atrial flutter and I would say that, you
22 know, there is no difference, that this is an

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1 equivalent device. That's just my thoughts
2 but certainly Mel and Al have far more
3 experience than I do.

4 DR. NORMAND: Can I ask a follow-up
5 since you looked at the four studies? Was it
6 a three-month end point or a six-month end
7 point for those, since you apparently know
8 these studies?

9 DR. CALKINS: Yes, those studies,
10 the follow-up was variable in each of those
11 studies. It varied from short to long. Some
12 of them were a year follow-up and so I think
13 they just looked at what was published but
14 again, these were, you know, clinical trials,
15 usually single center, clinical trials, you
16 know, not carefully or rigorously performed.
17 I think the data I referred to was the closest
18 we have, multi-center, 17 centers, you know,
19 150 patients with event monitoring but those
20 OPC studies were sort of the history of A-
21 Flutter ablation. And it's amazing to me, a
22 lot of the SVT ablation data, even though it

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1 ranged WPW, we all know were current traits
2 for that in reality are closer to three to
3 five percent.

4 So how the OPC comes up with a 20
5 percent recurrence rate and then for atrial
6 flutter, they say, well, that's the same
7 recurrence rate we should apply for WPW
8 ablation, it seems to make no sense. It's
9 apples and oranges, you know, flutter versus
10 an anatomical AV ablation or WPW ablation or -
11 -

12 DR. NORMAND: So I hear what you're
13 saying but I guess I'm wondering then why did
14 you agree to do an OPC rather than a
15 concurrent controlled --

16 DR. CALKINS: Well, I wasn't there
17 when the study was designed and I think that
18 was discussed with the FDA but I don't know.

19 DR. NORMAND: But that's the
20 relevant point, because you pointed out lots
21 of problems with the OPC, yet that was the
22 decision that apparently the sponsors made was

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1 to use the OPC. So I guess I'm having a
2 little bit of trouble recognizing
3 retrospectively looking at this didn't work,
4 now the OPC --

5 DR. CALKINS: Well, I think -- I
6 think the strength you can think about this
7 study was the intensity of event monitoring.
8 You know, a weekly event monitor tracings is a
9 very intensive monitoring and very different
10 than any other prior study of atrial flutter
11 ablation I'm aware of and even the events that
12 I referred to was just once monthly and as Mel
13 talked about, it's a probability issue in
14 terms of how often you're monitoring and you
15 know, the issue became this over-play between
16 atrial fibrillation and atrial flutter. And
17 I think we now very much realize that these
18 arrhythmias are -- sometimes you get some
19 focal firing, a brief episode of HL that
20 triggers a flutter.

21 Atrial flutter is a clinical
22 problem because it's very hard to slow it down

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1 to rate control atrial flutter where atrial
2 fibrillation you can rate control it very
3 easily. So there's lots of reasons to get rid
4 of atrial flutter, you know, in terms of rate
5 related cardiomyopathy and other things, you
6 know, that make it relevant.

7 The anti-coagulation issue, I
8 think, just depends on what the risk factors
9 for stroke are because we know the longer we
10 follow these flutter patients, you'll get
11 little bursts of A-Fib, like, you know, Dr.
12 Somberg, you know, mentioned over time and
13 anti-coagulation should just be based on the
14 risk factors for stroke and not whether you
15 deem something, you know, successful or not.

16 But we have the inventors of atrial
17 flutter here on the panel so they can make
18 some comments.

19 DR. WALDO: That's a little much
20 but, I am from the George M. Cohen days of
21 atrial flutter. Well, I couldn't say it any
22 better than Hugh did. I think so many of

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1 these questions, you can't separate atrial
2 fibrillation from atrial flutter. I mean,
3 it's rare that you get atrial flutter without
4 preceding atrial fibrillation of some duration
5 and we understand why -- the physiology,
6 because it's during atrial fibrillation that
7 critical parts of atrial flutter reactions are
8 formed, principally a line of block between
9 the vena cava. So once you get rid of flutter
10 it's very common to have atrial fib.

11 Most studies show that you look
12 long enough, at least 70 percent of patients
13 manifest critical atrial fibrillation, not
14 asymptomatic, afterwards, long term. So it's
15 a real issue and you saw so many of the
16 patients in this trial came in already having
17 recognized clinical atrial fib. So it makes
18 all the symptom problems difficult to try and
19 measure before and after and it makes the
20 anti-coagulation problem difficult because as
21 Hugh said, it's the atrial fibrillation that
22 really governs when you use anti-coagulation.

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1 So there's no question that in
2 managing atrial flutter -- and Hugh was
3 exactly right about in the presence of fib and
4 flutter, why we ablate atrial flutter is
5 because of rate control, it's very hard. So I
6 think going -- you've heard us say it many
7 times. We've tried to do it as objectively as
8 we could, but I think it's pretty obvious to
9 any clinician who's seriously involved in
10 this, we never -- we're glad to have -- we're
11 always glad to have the monitor but we rarely
12 make a total commitment about patient care on
13 the basis of one rhythm strip.

14 It's just very unusual and you
15 heard it said very well. I mean, I don't
16 think I could say it any better. And I'm not
17 -- so maybe that's enough for now. I mean, so
18 I think really that you understand it well. I
19 think the OPC was based on a clinical
20 assessment and not on a rigorous follow-up
21 with event monitoring. And so I think that's
22 a different standard, and I think the company

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