

SUMMARY MINUTES

**MEETING OF THE MEDICAL DEVICES DISPUTE RESOLUTION ADVISORY
PANEL**

April 19, 2007

**Ballroom, Holiday Inn
Gaithersburg, MD**

MEDICAL DEVICES DISPUTE RESOLUTION PANEL
April 19, 2007

Chair:

Scott D. Ramsey, MD, PhD
Fred Hutchinson Cancer Research Center and
University of Washington

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California Pacific Medical Center Research Institute
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John W. Hirshfeld, MD
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David J. Slotwiner, MD
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Industry Representative:

Melissa Walker, MS, RAC
Stereotaxis, Inc.

Consumer Representative:

Connie F. Whittington, NSN, RN
Piedmont Hospital

Executive Secretary:

Nancy Collazo-Braier, PhD

CDRH Ombudsman:

Les S. Weinstein, Esq.

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CALL TO ORDER

Chairman Scott D. Ramsey called the meeting to order at 8:54 a.m. and noted the presence of a quorum. He had the Panel participants introduce themselves and noted that they had received training in FDA device law and regulations.

He read the Ombudsman's Summary of the Scientific Issues in Dispute into the record. Cardima Inc.'s Revelation Tx Microcatheter Ablation System was proposed for use in the treatment of atrial fibrillation (AF) in patients with drug refractory AF. The Office of Device Evaluation (ODE) had determined that the PMA was not approvable, due to study design and results inadequate to demonstrate reasonable assurance of safety and effectiveness. ODE believed the data showed some support, but only limited conclusions can be drawn. The PMA trials lacked a control arm, accurate measurement of effectiveness endpoints, and effectiveness in creation of bi-directional conduction block (BDB) at cavotricuspid isthmus. Cardima appealed these findings, and the matter was sent to the Dispute Resolution Panel.

Executive Secretary Nancy Collazo-Braier read the deputization of temporary voting members and conflict of interest statements into the record. Drs. Schmid, Hirshfeld, and Slotwiner were appointed as voting members. The Panel members were screened for conflicts of interest. A waiver was issued for Dr. Ramsey, due to a consulting interest with a competing firm. Ms. Walker, Industry Representative, was employed by Stereotaxis. The Executive Secretary urged all participants to disclose financial relationships with any firms at issue.

Chairman Ramsey opened the floor for public comment. Seeing none, he called for the Sponsor's presentation.

SPONSOR PRESENTATION

Richard F. Gaston, MD, described the device as a 3.7 French, multi-electrode, flexible radio frequency catheter and noted that it was different from currently-used, stiff catheters. The device has multiple electrodes with thermocouples to measure temperature. The thermal injuries from the electrodes overlap to create a linear lesion. The device construction allows for high current density with little heat sink effect, resulting in less power being needed to produce the same depth of lesion, compared to standard catheters. This effect was demonstrated in canine thigh muscle. Standard catheters are not ideal for creating long, linear lesions to treat AF.

The Sponsor initiated its pivotal trial using the half Cox maze procedure, addressing only the right atrium, the thought being that it was safer than entering the left atrium and

would be a shorter procedure. Right atrial ablation had fallen out of favor when the pivotal trial was completed, in 2003, but right atrial ablation is regaining favor.

The device's proposed indication is for the symptomatic treatment of drug-refractory paroxysmal atrial fibrillation by creating continuous RF ablation lesions in the right atrium. The basis for approvability was the 84-patient, prospective, pivotal study, which showed reduction in total AF frequency and improvement in AF symptoms and was published in the Journal of Interventional Cardiac Electrophysiology. In the May 2004 nonapprovable letter, the FDA disputed that safety and effectiveness had been established and identified three issues it said impaired the analysis of the data: 1) Single arm trials may be subject to placebo effects, 2) Clinical study effectiveness endpoints were possibly confounded, 3) Data provided demonstrates that the NavAblator catheter may not be sufficiently effective in creation of bi-directional conduction block at the cavo-tricuspid isthmus. The Sponsor stressed that the standard of care for AF, a large and growing problem, included ablation for all patients after one drug failure and in all patients unable to tolerate medications. However, there are no approved devices for AF and no universally accepted lesion set. The Sponsor said that a prior non-approval letter was not relevant to the discussion.

Sanjeev Saksena, MD, FHRS, FESC, FACC, FAHA, presented on the Cardima application and on AF ablation in general. He said there had been an exponential increase in ablation procedures, despite the unavailability of an approved device in the US, and right atrial ablation remains an important procedure. AF genesis varies by presentation and disease state, and increased surveillance has shown a decline in left atrial ablation success rates. To understand AF, biatrial and regional mapping is necessary. Surface ECGs do not reflect intracardiac arrhythmias. Multi-focal and bi-atrial triggers are present in both atria, and there is organized atrial activation in AF. Using a biatrial catheter array and three-dimensional mapping, the sponsor discovered that both atria are always involved in AF. There is a biatrial and multi-focal origin to triggers and organized tachycardias in AF. There is biatrial involvement in paroxysmal and persistent AF. Structural heart disease magnifies the biatrial origins of AF, and right atrial tachycardias often surpass left atrial tachycardias in structural heart disease and persistent AF. Persistent AF is the only condition in which simultaneous right and left atrial tachycardias can occur.

For these reasons and due to multiple triggers, trigger ablation is not likely to be effective. Organized tachycardias have multiple unilateral, biatrial locations in AF, and patients with heart disease and persistent AF have more extensive distribution. Trigger ablation is unlikely to be effective, though it is a popular technique. Biatrial interventions to the substrate are needed, so right atrial ablation will be necessary for a complete ablative procedure. The current practice of AF ablation involves long, demanding, and often repetitive procedures; complications in widespread practice; and disappointing efficacy. The current drugs are not effective enough, and more choices for treatment are needed to deal with rotors and focal tachycardia in the right atrium.

There were three potential concerns about using the catheter for atrial ablation. First, ablation orientation influences lesion depth. However, the atrium is only 2 or 3 mm thick, so deep lesions are not desired. Second, the atrium has variations in topography. However, transmural lesions are unlikely. Transmural lesions are only produced with a knife in surgery. No catheter lesions have a complete linear block and complete transmural lesions. Catheter-induced lesions are merely conduction blocks. The third potential objection is that the right atrium is a mere bystander in AF. This view is outdated and is refuted by human AF mapping and ablation.

Alternatives to current treatment allow for tailored ablation and hybrid approaches. The sponsor has developed a right atrial maze to be used as an alternative to pulmonary vein isolation, resulting in a single-stage abbreviated procedure with improved safety and wide patient applicability. Right atrial ablation is clinically relevant to AF ablation and is associated with conduction block in 3D mapping. The device produces right atrial compartmentalization quicker, shortening procedure time.

Abraham Kocheril, MD, FACC, FACP, presented on the phase III clinical study, for which he was the principal investigator. In his 1998 single-center study, lesions were created during AF, and lesion delivery continued until sinus rhythm was restored or until organized electrical activity was achieved throughout the right atrium. Long term success, maintaining sinus rhythm off of AADs (anti arrhythmic drugs), was observed in 79 percent of the patients (23 of 29 patients). Follow-up averaged 19 months.

He joined the Cardima multi-center trial looking at right atrial linear lesions. The study design followed the 1998 Panel recommendations. It was a single-arm and non-randomized, using the patient as the control. The patient population had 2 failed AADs or amiodarone and a baseline of two episodes over three months. Long-term success was defined as a 50 to 75 percent reduction in frequency of symptomatic AF episodes with a six-month evaluation of effectiveness. Major complications were monitored to establish safety, and quality of life was included as an outcome. This was all in accordance with the panel recommendations.

The primary study outcome consisted of frequency of spontaneous symptomatic episodes of AF experienced by the patient and incidence of adverse events. The secondary outcome was quality of life (QOL) measured by SF-36 and Atrial Fibrillation Severity Scale (AFSSS). For the primary endpoint, success was defined as a reduction in the number of symptomatic AF episodes at 6 months compared to baseline, a 50 percent or greater reduction in patients with 5 or more episodes at baseline, a 75 percent reduction in patients with 3 or 4 at baseline. Success for the secondary endpoint was a change of ten points or more per subscale of the QOL instruments compared to baseline. The inclusion criteria was 3 or more symptomatic AF episodes per 30 days, failure to respond to two AADs or amiodarone, absence of significant structural heart disease, a left atrial heart size of 5 cm or less, and absence of echocardiographic evidence of intra-atrial thrombosis, PFO, or atrial septal defect. Patients were excluded for acute ablation failure within 2 months, MI (myocardial infarction) within 6 weeks, CVA or TIA within 6 months, pregnancy, coagulopathy, or bleeding diathesis.

There were 14 sites that screened 178 patients. After informed consent, there was 30 days of baseline monitoring. After screening, 98 patients received the procedure; 84 completed the pre-discharge evaluation and followup at 1, 3, 6, 12, and 24 months. A physical examination and 12-lead EKG was given at baseline, during office visits, and at 1, 3, 6, and 12 months. Echocardiogram and stress tests were done at baseline and 3 months. Patients were given cardiac event monitors and transmitted weekly and with symptoms at baseline, 1 month, 3 months, and 6 months. QOL questionnaires were completed at baseline, 3 and 6 months, and a telephone interview was conducted at 24 months.

Of the 178 patients, 19 were withdrawn due to failed monitoring or withdrawal and 61 failed the screening, so 98 underwent the procedure, 5 of which had ablation 4 months or less before the procedure. The ablation procedure cohort was 93 patients. Of these, 88 completed the 6-month follow-up, but an independent cardiologist excluded four for insufficient baseline. The remaining 84 patients were in the effectiveness cohort. The average patient age was 58 years; 74.2 percent were male. The average number of symptomatic episodes at baseline was 9.7, much higher than in the Affirm trials. The average number of AADs was 2.9. Symptomatic characteristics included palpitations, 88 percent; fatigue, 58 percent; and lightheadedness, 36 percent.

The ablation procedure consisted of using the device to deliver posterolateral and septal linear lesions to the right atrium. The procedural endpoint was adequate tissue ablation indicated by reduction of amplitude by 50 percent, widening of the signal, or split potentials. A flutter line was incorporated along the cavotricuspid isthmus to prevent atrial flutter in patients without prior isthmus ablation, but flutter was not a study endpoint.

The primary endpoint showed 49 of the 84 subjects (58 percent) achieved the target-level decrease in episodes. The mean per-subject 6 month reduction in episodes was 62.3 percent, with a highly-significant p value. The average episodes at 3 and 6 months were 3.7 and 3.4, down from 9.7 at baseline. The result is statistically and clinically significant. At 6 months, 34.5 percent of patients experienced a 100 percent reduction in episodes, 78.6 percent experienced some reduction, and 13.1 percent experienced no reduction or an increase. Patients had lower than average quality of life scores at baseline. By the SF-36 instrument, patients showed improvement in all categories but general health at 6 months. By the AFSS instrument, episode frequency, duration, severity, and overall scores improved significantly, and 50 percent of patients improved by more than ten points.

A decrease was also shown in palpitations (53.3 percent) fatigue (54.3 percent), and lightheadedness (62.3 percent). Long term follow-up showed that at 12 months, 43 percent (26 of 64) of patients reported no episodes of AF since the last study visit, indicating durability and possibly indicating positive remodeling.

The safety results showed 6 device-related adverse events, 4 of which were mild. There were no injuries to the phrenic nerve, strokes, deaths, or esophageal fistulas. There were 50 procedure-related adverse events, occurring in 24 percent of the patients. Half of these events were mild. There were 5 serious adverse events in 4 subjects, 5 percent of the procedures. Only one serious adverse event was considered device-related. This safety profile is better than the pulmonary vein isolation profile.

He concluded his presentation by saying that there was a significant reduction in symptomatic AF events, significant, meaningful improvements in QOL, an excellent safety profile, and sufficient data to demonstrate that the benefits outweigh the risks. He concluded that the device is safe and effective.

Daniel Cher, MD, gave an interpretation of the clinical study and addressed FDA's concerns about the study. Though he currently works for an unrelated device company and has no financial interest in Cardima, he was Cardima's medical director from 2003 to 2004 and submitted the January 2004 PMA.

He first addressed FDA's concern that placebo effect may account for the study's effectiveness. Dr. Cher explained that the device was single-arm, but not uncontrolled. Patients served as their own controls in a before and after design, which is an accepted and valid control design. Additionally, this design was recommended by the advisory panel in 1998. An FDA guidance document published in January of 2004 also notes that patients may serve as their own controls. Additionally, of the 19 PMAs that have been submitted for devices using ablation, only 1 was a randomized controlled trial.

He discussed the history of paroxysmal AF, demonstrating that the disease progresses; it does not spontaneously remit. Short term variation in AF episodes tends to be balanced among patients. He referred to the Botto J. *Cardiov* 2007 study as a historical control, since it demonstrated that short term variation in patients tends to balance between those improving and those worsening. The literature indicates that AF events are clustered, but they tend to cluster over periods of hours and days, not months. Event rates are fairly constant over months, so event clustering would not affect the study results. He addressed the participation effect, citing the 2001 Gerstenfeld et al. study. He noted that if there were a significant placebo effect, it would have been demonstrated in patients who received mapping only. In the Cardima study, AF episodes were confirmed by TTM (transtelephonic monitoring) and an independent cardiologist. The threshold of success was high, and the follow-up was long. Placebo effect is unlikely to last six months. The change in QOL correlates with the reduction in episodes, and the procedure was based on a known, effective surgical procedure.

FDA was concerned about the TTM compliance and its effect on the study results. The patients were told to record and transmit when they had episodes and weekly. An independent cardiologist verified the transmissions, and only transmissions showing AF were counted. Compliance is indicated, since 88 percent of patients transmitted three or more rhythm strips in the 6th month of follow-up, and 93 percent of patients with no episodes at 6 months transmitted 3 or more TTMs. Patients with fewer transmissions

were more likely to be failures, so the reported result may be an underestimate. The study had high compliance and high success.

FDA was concerned that patients may over-report baseline events and under-report events during follow-up. To prevent this bias, patients did not know the number of episodes needed to qualify, and every episode was verified by an independent cardiologist. In the follow-up, underreporting would have to be unusually large to produce the study results.

FDA was concerned that episodes close together could have affected reporting. However, episodes are usually separated by more than a day, and a sensitivity analysis shows that removing episodes that occurred close together did not affect effectiveness.

FDA raised concerns about regression to the mean. For that to happen, patients would have to be enrolled during unusually bad months. However, the mean baseline was significantly higher than the threshold. With statistical modeling, he demonstrated that regression to the mean was unlikely to have affected the results and could as easily skew the results in the other direction.

Because some patients in the trial received pacemakers in follow-up, there was a question as to how pacemaker treatment affected trial results. However, the literature shows that pacemakers do not reduce the frequency of AF episodes. Both the American Heart Association and the Heart Rhythm Society say that permanent pacing to prevent AF is not indicated and not supported by the evidence. In the trial, 16 patients had pacemakers placed during follow-up. Of the 10 who had placement following AV node ablation, 9 were considered study failures. Of the 6 who had pacemakers placed for bradycardia, only 2 had episode reduction. Another patient had a pacemaker placed for a complication of ablation. Since most of the patients receiving pacemakers were already counted as failures and pacemakers don't prevent AF episodes, pacemaker use did not affect the study results.

FDA had expressed concern about non-investigational catheters and isthmus ablation. Isthmus ablation is performed for atrial flutter, not atrial fibrillation. Since there was no approved catheter for isthmus ablation, Cardima developed the NavAblator. In about 30 percent of patients, ablation of the isthmus was performed with a noninvestigational catheter. The AF success rate was actually higher in the patients who did not have a successful bi-directional conduction block as a result of isthmus ablation. Successful isthmus ablation did not improve AF success, and which catheter was used did not make a difference.

Quality of life was an important endpoint that was recommended by the 1998 Panel. SF-36 results showed statistically and clinically significant improvements in all areas but general health. AFSS scores also showed significant improvements in frequency, duration, and severity. The improvement in SF-36 scores is consistent with other AF ablation literature and inconsistent with changes due to drugs alone.

In the follow-up to the study, there were some changes in AAD therapy, 12 patients with a new AAD, 22 with a decrease, 3 with an increase. Most changes were due to tolerance, not effectiveness. A 1991 study looked at serial drug therapy in AAD naïve patients and saw minimal improvement. Since the patients had already failed to respond to drugs before, the effect is probably even less.

FDA said that amplitudes were not measured in all of the procedures. The sponsor disagreed. Amplitude was measured by amplitude decrease, which is a standard measurement in ablation procedures, and the data collected may be the largest existing data set on amplitude reduction in RF ablation. The vast majority of the data shows a decrease, a highly statistically significant reduction. This reduction proves that muscle ablation occurred.

He concluded that the study met the regulatory standard, that a randomized controlled trial was not required, that the study was internally consistent, that it was consistent with other ablation literature, and that the biases proposed by the FDA were unproven, overemphasized, and did not impair the ability to interpret the data.

Dr. Saksena returned to discuss endpoints and clinical issues. In trials, there are many measures of acute success. In this case, acute success was measured by freedom from recurrent AF and quality of life. Decreased electrograms was demonstrated. Line of block demonstration was shown. Other measures were not acute endpoints.

The amplitude electrogram measurements were current and relevant, as illustrated by a 2006 Johns Hopkins trial. However, the main issue was detecting AF recurrences. In other trials, there was routine follow-up at 3 to 6 month intervals, and some symptoms prompted a visit. None required TTM. The Sponsor's study exceeds the standards of landmark and current studies. The only way to know ablation results is to increase surveillance, and increased surveillance shows increased recurrences. Patients report and comply poorly with event monitoring.

He concluded by saying that patients need more opportunity for improvement, which can be offered by making tools available for hybrid treatments. The risks of left atrial ablation are well-known and severe. Right atrial ablation is much safer and should be an option.

Dr. Cher asked for time, but Chairman Ramsey could not, due to protocol. Chairman Ramsey opened the floor to clarifying questions from the panel. Dr. Sackner-Bernstein asked about TTM compliance. Dr. Cher said that the majority of asymptomatic transmissions were normal sinus rhythm; roughly half of the patients transmitted weekly throughout the six months. Dr. Browner followed up on TTM rates. Dr. Cher said that the transmissions were not analyzed by week but by month; 43 of the 84 patients submitted 3 or more weekly strips in the sixth month, and 35 patients submitted 4 weekly strips in the sixth month. The success rate was high in the highly compliant patients.

Dr. Browner noted that the Sponsor's data indicated that 16 percent of successes could be explained by regression to the mean. Dr. Cher said that the proportion of patients randomly having reductions consistent with trial success would be small. Since the success rate was 58 percent, 16 or 20 percent due to regression to the mean is not significant. Dr. Sachner-Bernstein asked for confidence intervals for the success rate at six months. Dr. Cher said the confidence limit was plus or minus ten percent.

Dr. Slotwiner asked about amplitude reduction and ablation. Dr. Cher said that the instruction was to ablate for 60 seconds at 50 degrees, 35 watts, with a maximum impedance of 200 ohms. Another ablation was at the physician's discretion, dependent on electrogram amplitude decrease. Dr. Kocheril said the reduction was usually 50 percent, by a visual estimate. Placement was the important issue.

FDA PRESENTATION

Dr. Donna B. Tillman, Director of the Office of Device Evaluation (ODE) introduced the presentation. **Bram Zuckerman, MD**, Director of the Division of Cardiovascular Devices (DCD), gave an overview of the device and its history, including the FDA review. AF is the most common arrhythmia, and it is a very heterogeneous condition that can result in morbidity and mortality. Treatment options include medical therapy, surgical maze, and percutaneous catheter ablation. There are currently no approved catheter systems for AF. To promote development in this area, DCD published a 2004 guidance document on trial design for AF. DCD currently has no preference as to the best type of percutaneous ablation procedure.

Both the NavAblator and Revelation Tx Catheter are integral parts of the Cardima Ablation System, so the safety and effectiveness of both catheters must be considered. The Sponsor asserts that safety and effectiveness have been demonstrated. FDA disagrees. FDA has issued two not approvable letters, one for the original PMA and another after amendment 6. The Sponsor has proposed a new indication statement that removes mention of the NavAblator catheter.

The Cardima trial was a single-arm unblinded trial that relied on patient self-reporting for the chronic clinical effectiveness endpoint. Individual patient success was defined, but there was no predetermined goal for the number of patient successes necessary to declare the trial a success. The trial design was not ideal, but FDA agreed that it was feasible and could produce valid scientific evidence. However, the trial was not conducted well, and the resulting data are insufficient. In 2003, the Circulatory Systems Devices Advisory Panel voted against approving the device, citing lack of appropriately measured acute procedural data, noncompliance with patient reporting, confounding factors such as medications and pacemakers, and excessive protocol deviations. In response to the 2003 not approvable letter, Cardima submitted Amendment 6 in 2004. The amendment focused on the Phase III study patients and included patients who had not completed

follow-up at the time of the PMA submission. The FDA felt the additional data did not address the problems in the first not-approvable letter, so a second was issued in 2004. FDA and the Sponsor have met on several occasions since then to work toward resolution, and FDA has consistently held that new clinical data are necessary.

FDA's key reasons for not approving the device system are threefold. First, acute procedural effectiveness was shown for neither catheter. Second, the study did not show chronic effectiveness. Third, the risk/benefit profile cannot be assessed; there was significant missing data and concerns of bias.

William Maisel, M.D., MPH, of Harvard Medical School is the Chairman of the Circulatory System Panel and was a Panel member for the May 29, 2003 Panel meeting. He discussed treatment of AF and acute procedural endpoints in trial design. Many factors affect how a lesion is made. Lesion size can be affected by power, temperature, electrode size, catheter orientation, irrigation, catheter type, and atrial anatomy. The right atrium is not smooth, and this affects lesion size, temperature of the burn, and the effectiveness of the catheter. Because of all of these variables, acute procedural endpoints are needed to ensure safe and effective ablation, and their use is standard electrophysiological practice.

Many acute procedural endpoints are used: decrease in electrogram size, increased pacing threshold, creation of a line of electrical block, fragmentation or widening of the local electrogram, or inability to induce arrhythmia following ablation. Reduced electrogram can be automatically recorded continuously by EP recording systems. The challenge with right atrium ablations is to balance creating a lesion large enough to be effective with not making the lesion so large as to cause problems such as phrenic nerve injury and diaphragmatic paralysis, thrombus formation, tamponade or perforation, superior vena cava stenosis, and charring on the catheter, which can embolize.

According to the Cappato worldwide survey, right atrial ablation was popular in the 1990s due to the relative ease of the procedure, but it has fallen out of favor as a stand-alone procedure, due to low success rates compared to biatrial ablation and left atrial ablation. He concluded by reiterating the importance of acute procedural endpoints.

Lesley Ewing, MD, clinical reviewer for the PMA, presented the FDA's clinical review. The trial was a single-arm unblinded investigation in three phases. Phase II (a) and (b) were feasibility studies, and Phase III was a pivotal trial. Each patient was given a transtelephonic event recorder to track and transmit episodes of symptoms. A 30-day period at baseline was compared to a 30-day period six months after ablation. The most important protocol difference between the Phase II(b) and Phase III was the addition of the NavAblator Catheter. The procedures and endpoints were the same. An anterior line, which was optional in Phase II (a) and (b) was removed during Phase III due to risk of sinus node damage. All lesions were first attempted with Revelation Tx, and if the isthmus lesion was not successfully created, NavAblator was used.

During the protocol development, FDA and the Sponsor agreed that decreasing the size of the atrial electrogram would be recorded as the proxy endpoint for documenting a line of block created by Revelation Tx. Animal models showed 50 percent decrease in atrial electrogram amplitude to be the second best indication of an ablation. Increased pacing threshold was the best. Atrial electrogram measurements were recorded and sent to a core lab for blinded review. For NavAblator, a procedural success endpoint was demonstration of bi-directional conduction block at the cavotricuspid isthmus, with the goal of 90 percent of patients having a bi-directional conduction block with a lower bound of 80 percent. Any patient treated with a non-protocol catheter was considered an acute and chronic failure.

The chronic effectiveness endpoint was a 75 percent decrease in the number of self-reported systematic AF episodes at 6 months compared to baseline while on the same medication or a reduced dose, 50 percent decrease in episodes for patients with 5 or more episodes at baseline. To ensure compliance, patients were required to report weekly during the third and sixth months, in addition to transmitting symptomatic episodes. At baseline, there was no mechanism in place to ensure that all episodes were discrete. Because a normal rhythm was not documented between episodes, patients could report one episode of AF multiple times.

The secondary endpoint was clinically meaningful improvement in the quality of life measured by Short Form 36 and the AFSS questionnaires compared to baseline. The forms were completed at baseline, three months, and six months. The safety endpoint was incidence of complications in the first week after ablation in the 24 months of follow-up.

In amendment 6, the safety cohort was 93 patients, and the effectiveness cohort was 84 with six months of follow-up data. Including data from Phase II(b), 178 patients were screened, 98 received the procedure, 93 had verified data in time for Amendment 6. Of Phase III patients, 84 had 6-month follow-up data, and they are the effectiveness cohort. 64 patients had 12 month follow-up, 30 had 24 months. The total safety group was 131.

In 93 patients, 95 procedures were performed, 2 repeat ablations for atrial flutter. Revelation Tx was used alone in 15 percent of the patients, Revelation and NavAblator in 57 percent, and 28 percent of procedures used a nonprotocol catheter because the Cardima System failed to produce the desired lesion or electrophysiologic effect.

FDA is concerned with the procedural effectiveness of the trial. Acute procedural effectiveness was demonstrated by neither of Cardima's catheters. For Revelation Tx, the complete data needed to show success is missing in all study patients. For NavAblator, the data was collected, but the results demonstrate that the catheter was not successful in a sufficient number of patients. The data on the acute procedural endpoint of the Revelation Tx Catheter was not collected so that individual patients could be identified as having met the endpoint. The Revelation Tx Catheter has 8 electrodes, each of which is used individually. The protocol specifies that electrodes are all to be fired sequentially, then the catheter is moved to overlap the gap. Since electrogram is

measured before and after energy delivery, there would be 16 total measurements if all 8 electrodes were used. A large amount of atrial electrogram data is missing, and all patients are missing measurements. Cardima submitted 504 measurements for the posterior lateral line and 424 for the septal line. The measurements were averaged instead of being provided for per-patient effectiveness. Since the pre and post ablation electrogram measurements were not collected and 100 percent of patients were missing atrial electrogram data, it is impossible to determine acute patient success.

Because procedural success can be demonstrated in no individual patient, chronic clinical success cannot be attributed to the use of the system. Even were it accepted that chronic effectiveness could be evaluated, only 25 percent of patients reached the protocol success endpoint. Due to nonprotocol catheter use, pacemaker implantation, or changed medication regimen, FDA disputes 28 of the 49 patients Cardima claimed reached chronic clinical success. Because there was no placebo group, it is unknown whether or not 25 percent would have exceeded the placebo rate.

The extent of over-reporting and under-reporting of the subjective endpoint is also unknown. Patients varied widely in their ability to distinguish atrial fibrillation from other causes of symptoms, and they had different thresholds for recording and transmitting rhythm strips. Patient compliance is critical for this kind of data collection. In the original PMA, 22 of the 83 patients did not transmit in the sixth month and 31 had between 1 and 3 transmissions, a total of 63.8 percent poor compliance. For Amendment 6, Cardima reinterpreted month 6 to overlap with the time of the most event recordings. The new data showed 24 of 84 patients with less than 4 transmissions, 28.5 percent poor compliance.

FDA feels that QOL data is supportive, but it is a secondary endpoint, and there is no placebo rate to compare it to. Additionally, intervening treatment affects QOL interpretation.

FDA's third main concern was the ability to weigh risk and benefit, since the effectiveness cannot be determined. Since 5 patients had complications in the first week after ablation and 4 required a pacemaker within 2 weeks, 6.9 percent of patients had a major complication. In Phases II(b) and III, 27 patients had a pacemaker implanted and 14 had AV node ablation.

Hang Li, PhD, presented a statistical approach to the FDA's position that the study did not show chronic clinical effectiveness. One major obstacle to evaluating the device system is that there is no data on chronic success for a completely ineffective therapy in a similar study. Any difference between frequency of AF episodes between baseline and follow-up with a completely ineffective therapy can be due to three components: inpatient variability, confounding factors, and reporting bias. If the frequency of episodes fluctuates randomly over the next 6 months, there is a probability that the patient will reach the target reduction in frequency. With the beneficial effect of confounding factors and reporting bias, the probability of reaching target level is increased. He demonstrated that a reference population with no systemic change would follow a

bivariate or joint distribution with the marginal distribution equal at baseline and 6 months. However, with enough spread, a non-negligible proportion of patients would reach the target reduction point. With baseline selection, this proportion grows.

Even in a reference population, without confounding factors or reporting bias, many patients would meet the target level of reduction due to baseline selection and patient variability. Without selection, the mean frequency of events is 4 at baseline and 6 months. After selection, the baseline is 4.77 and the mean at six months is 4. The expected proportion reaching target reduction is 21.5 percent. With confounding factors such as medication, changing medication, pacemaker use, and nonprotocol catheters, and placebo effect, the rate is higher. To mitigate confounding factors, patients with medication changes or increases and those with noninvestigational catheters should be classified as failures. Still, this addresses only some of the confounding factors.

Reporting bias is the last confounding factor. Patients may overreport due to desire to be included in the study and underreport in followup due to lack of motivation, enthusiasm, or compliance or due to placebo effect. When reporting bias is included, the probability of meeting target reduction is increased.

Reporting compliance was another factor. In the original PMA, 63.8 percent of patients had poor compliance. In Amendment 6, 28.5 percent had poor compliance. The sponsor used a different definition to reach this percentage. The new definition is based on a sliding 30-day window and is guaranteed to find better compliance than a fixed window. A sensitivity analysis also reduced the number of episodes. Since no useful data on reporting is available, no useful sensitivity analysis is possible. Due to a lack of data on a control or confounding factors, the data are inconclusive.

There is disagreement between the FDA's calculations and the sponsor's on chronic success. Of the 84 patients the Sponsor calls successes, the FDA recognizes 21 as successful under the definition in the protocol, 25 percent. Due to irregularities and the use of other catheters, many analyses are uninterpretable.

The QOL data is also uninterpretable, since there is no control QOL data. Lack of independence between frequency of episode data and QOL data makes it likely that QOL would be better at six months than at baseline, just due to selection and intra-patient variability. Confounding factors would create the illusion of success. The same factors causing reporting bias would create bias in QOL measurement. The appropriate null hypotheses are unknown and the p-values are questionable. Chronic effectiveness cannot be determined.

Dr. Maisel returned to summarize the May 29, 2003 panel meeting as a Panel member and primary reviewer at that meeting. These comments do not address any post-meeting amendments. The Panel voted that the application was not approvable, primarily due to lack of consistently-measured acute procedural endpoints, failure to demonstrate effectiveness, safety concerns, and other issues.

The protocol required acute procedural endpoints that were not demonstrated, since they were not consistently measured or recorded. There was significant missing data, and the procedural endpoints were not well-defined. The Panel said that temperature goals and amplitude reduction specifics were not properly recorded. There is no data on how many or what patients received the recommended amount of RF.

Patients were supposed to transmit a recording of their symptoms, but of the available 83 patients, 22 did not report at all in the sixth month, and 31 did not report weekly. It was difficult to determine who was reporting, and the Panel could not assume that the subjects not reporting were asymptomatic. The whole collection process was called into question.

Additionally, AAD use was a confounding factor that violated the protocol. He noted other confounding factors, such as nonprotocol catheter use and pacemaker implantation. The Panel concluded that effectiveness was not demonstrated, that the data supporting acute procedural endpoints was inconsistent, and that significant data was missing due to poor compliance, use of multiple catheters, and low rate of isthmus block with investigational catheters. There were issues of AV junction ablation, confounding symptom assessment, and concerns with the high pacemaker implantation rate.

Dr. Tillman noted that the Division of Biostatistics had reviewed the data objectively. FDA continues to have problems with the data on the device. She reviewed the FDA concerns. Considerable data is missing for Revelation Rx. For NavAblator, the data is there, but it does not support effectiveness. Acute success was never shown in any individual patient, so chronic clinical effectiveness cannot be attributed either. Even if chronic effectiveness were granted, it could only be granted in 25 percent of patients. The extent of biases at baseline and endpoint are unknown, and the risk-benefit profile cannot be assessed. The lack of a control could have been mitigated by a well-executed trial, but the lack of control over concomitant medication use and poor patient compliance makes the study invalid. There is not enough data to write useful labeling, and it is impossible to determine a risk/benefit profile with the available evidence. Since the evidence does not support safety and effectiveness, she recommended that the Sponsor and the FDA work interactively on an additional premarket study.

Chairman Ramsey opened the floor for questions. Dr. Hirshfeld asked whether the flaws in the trial design were voiced at the time of launch. Dr. Zuckerman said there was a special meeting of the Circulatory Systems Advisory Panel in 1998, at which trial design was discussed at length. The Panel accepted a self-controlled study, provided that the trial be superbly executed. Were this trial performed exceptionally well, it would have been acceptable.

Dr. Sackner-Bernstein asked about the 5 ablated subjects without verified data. Dr. Ewing said that the Sponsor did not have study monitors check the data and put it in the databases. The data went through the standard audit process.

Dr. Schmid asked if 16 percent of patients being treatment successes by chance might be an overestimate. Dr. Li responded that without confounding factors and reporting bias

the expected proportion of successes was 21 percent in the reference population. With confounding factors and reporting bias, the number is higher. With a Poisson distribution with a mean of four episodes per month, it is closer to the trial results. Dr. Sackner-Bernstein followed up on the question, and Dr. Li said that the projection was based a target level of reduction driven by two-dimensional variability in the bivariate or joint distribution. By his model, the bivariate variability corresponds to two independent Poisson distributions with a mean of four episodes per month. The correct joint distribution correction is unknown. The population was created to illustrate the FDA's concerns. It was not intended to reflect an actual population, just to reflect how no treatment could attain results similar to those in the trial.

SPONSOR FOLLOW-UP/ REBUTTAL

Dr. Cher started by objecting to the presentation of Phase II data, saying that data presented in the Panel meeting in May of 2003 were not relevant to the issue at hand. He asked that only Phase III data be considered. He reiterated that the acute procedural endpoint was designed in concert with the 1998 Panel, and it is still in use. He pointed out that measurement in every electrode is impossible. He said the acute procedural data are substantially sufficient to provide reasonable evidence that cardiac tissue was ablated.

Dr. Saksena addressed the FDA's assertion that acute procedural endpoint data was not sufficiently collected in 100 percent of the patients. He said the study produced the largest body of electrogram data he had seen on cardiac ablation. Because the heart is moving during the procedure, it would be impossible to obtain data from every electrode on every catheter, but there is more than enough data to show a decrease in electrogram amplitude across every electrode. Pacing is no longer done. Fragmentation is undefined. Arrhythmia induction is a non-specific endpoint, and isthmus block was not an endpoint of the trial. **Dr. Cher** said there is substantial data to show that cardiac tissue was ablated in the subjects.

Dr. Kocheril said that the major issue was to make the ablation line complete. Sometimes that required overlap. In people with small atria, fewer electrodes were used. The instructions to the clinicians were very specific, and the same procedures were done at the different study sites. Dr. Cher pointed out that a BIMO audit occurred at several sites, and the FDA did not think the study was poorly conducted.

He said FDA's under-reporting and over-reporting hypothesis was not correct and that the Sponsor had been cautious to prevent that. He stressed that the nonprotocol catheters were used only to prevent atrial flutter and that the catheter used was not important to the results.

He said he was confused by the FDA's assertion that the data were insufficient to evaluate risk/benefit. There was only one device-related serious adverse event, and the

benefit was demonstrated by the study. The pacemaker and AAD issues did not affect the results. Without treatment, none of the subjects would have got better and many would have progressed to chronic AF. The trial demonstrated safety and effectiveness.

He said that Dr. Li's modeling made an unrealistic assumption: that patients had a relatively low occurrence rate of underlying atrial fibrillation. This assumption caused exaggeration of the odds of patients getting better by chance. He said that the data was sufficient, the effectiveness exceeded placebo or bias effects, and that a risk/benefit judgment can be made.

FDA FOLLOW-UP/REBUTTAL

Mr. Mallis reiterated that Cardima has not provided sufficient clinical data to demonstrate safety and effectiveness. The FDA was concerned that key procedural effectiveness was not demonstrated with Revelation Tx or NavAblator. Consistent use of Revelation Tx was not documented. Successful creation of lines of lesions is unknown, and data necessary to demonstrate acute procedural success is missing. The NavAblator was not successful in producing the ablation lesion line in enough patients.

Second, FDA was concerned that the study did not show chronic clinical effectiveness of the ablation system. Because acute successful use was not shown in any individual patient, chronic clinical effectiveness cannot be attributed to the use of the system. Even if chronic effectiveness could be evaluated, the device would have a 25 percent success rate. There is risk of bias of over-reporting at baseline and under-reporting at follow-up.

Because neither safety nor effectiveness can be accurately determined, FDA cannot assess the risk/benefit profile. FDA cannot confirm how the device was used, if it was used consistently, or if the data from the study sites are comparable.

FDA disagreed with Cardima's assertion that paroxysmal AF occurs predictably. It is a heterogeneous disease with episodes occurring at different times for different patients. FDA also asserted that the trial contains a number of confounding factors, especially pacemaker implants, which could affect both AF symptoms and perception of symptoms.

While FDA approved a valid study design, the sponsor did not collect the important safety and effectiveness data per its own protocols. There were data collection flaws at baseline, during ablation, and during follow-up. The QOL data was a secondary endpoint, not a primary measure.

Existing data is fundamentally incomplete, making a safety/effectiveness determination impossible. The additional Phase III data added by Amendment 6 did not impact the overall conclusion. The FDA has clearly and consistently communicated these fundamental deficiencies and the need for new clinical data.

Dr. Zuckerman added that Dr. Li's and Dr. Cher's statistical modeling should be closely examined by the Panel's statistical consultants.

OPEN PUBLIC HEARING

Chairman Ramsey opened the public hearing, urging all speakers to disclose any conflicts of interest.

Dr. Jon E. Block, a sponsor consultant and shareholder, spoke on right atrial ablation. After the first Panel meeting, he was hired by the sponsor to synthesize the world literature on right atrial ablation and to write on the results of the clinical trial. The paper on the clinical trial passed peer review. Dr. Jim Cox's studies on the maze procedure showed clinical success rates over 95 percent. However, the success rates lowered as the procedure became more widespread. The median success rate using cut and sew or RF ablation is 85 percent. The median success rate for left atrium procedures is 84 percent. Much of this success is with the continued addition of AADs. For right atrial catheter ablation, the median success rate is 58 percent, the same rate as in the Sponsor's trial. A trial in Japan did an open right-only open maze procedure and achieved a 50 percent success rate. The Sponsor's results are consistent with a right atrial maze procedure.

With placebo effect, subjective outcomes are the most suspect, not objective outcomes. Two reviews from the New England Journal of Medicine indicate that observational trials do not inflate treatment effects over randomized control trials. The 58 percent success rate is real. Since it is an easy and safe procedure, especially compared to open maze procedure, the findings are reasonable. He said the FDA's issues are unreasonable in light of the evidence.

Dr. Jaswinder Gill said he had no financial relationship with the Sponsor. He said that Cardima products are licensed in Europe; they are used for ablation in Britain. He noted that there are rotors and triggers of AF in the right side. Simple pulmonary ablation is rarely successful for persistent atrial fibrillation. Usually, extensive ablation is needed over the left atrium, and often the right as well.

Dr. Gill has been ablating for atrial fibrillation since 2000. Originally, he isolated the pulmonary vein with a right atrial maze, a procedure similar to the sponsor's. This was using drag and burn catheters. These catheters requires that the physician localize the catheter in the right place and provide continuous burns. Various technologies have been used to assess the catheter locations. Ensite has been used to assess the completeness of the line. He noted that diminution of electrogram, split potentials, and fractionated potentials are surrogates, and 3D mapping or propagation analysis are more useful.

He showed data on 25 patients who had atrial fibrillations and had failed pulmonary vein isolation and AADs. They were treated with 2 right atrial lines, one across the anterior wall, one across the septum. All the patients are followed up on, and 13 maintained sinus rhythm long term. The patients require less medication. There is also a reduction in DC cardioversions following ablation.

Possible complications include phrenic nerve damage, AV nodal damage, embolization, and perforation. One patient developed tamponade. There was no AV nodal damage, strokes, TIAs, or atrial flutter. He concluded that right atrial maze is a safe and effective procedure. He concluded that the advantage of linear ablating technology is that it is easy to place, does not leave gaps in the line, and is safe.

Dr. Slotwiner asked how line of block is confirmed without Ensite. Dr. Gill said the Navix system makes it possible to mark the catheter's position. Electrogram amplitude is not a very useful measure. Measuring propagation or pacing either side of the line and measuring timing intervals will show whether there is a block or not.

Dr. Sackner-Bernstein noted that the procedure Dr. Gill used was different from that in the trial. Dr. Gill agreed that he did not do a flutter line unless it was necessary. His goal was just to compartmentalize the atrium.

OPEN COMMITTEE DISCUSSION

Chairman Ramsey stated the Panel's charge. The question to the Panel was, "Does the PMA, as amended, provide valid scientific evidence that demonstrates a reasonable assurance of the safety and effectiveness of the Revelation Tx microcatheter ablation system for its intended use in the specified patient population?" He opened the floor for Panel members to ask questions of the sponsor and FDA.

Ms. Walker noted that the indications for use statement was different between the panel pack and the executive summary. Dr. Cher said that the more recent of the two was intended, the one indicating drug refractory symptomatic paroxysmal atrial fibrillation. For the FDA, Dr. Zuckerman noted that the indications for use statement differed from those in the not approvable decisions. Any future development of the technology or device system does not apply to the questions at hand.

Dr. Slotwiner pointed out that Dr. Gill's presentation was on patients who had pulmonary vein ablation and then right atrial ablation. Dr. Sackner-Bernstein noted that the procedure was compared to the Cox maze but that the lesions do not follow the same pattern. Dr. Slotwiner said the maze was the gold standard, but it cannot be reproduced with catheters.

Dr. Hirshfeld asked why there were so few measurements per patient. Dr. Saksena said that the focus was on creating a conduction block and that there was a large set of electrogram diminution data. Dr. Cher said that electrograms were not collected for every electrode but that sufficient data had been collected to show ablation. Dr. Ewing said that 67 percent of the electrogram data was missing, that mapping data was not submitted, and that the Sponsor had not presented a number of patients with an effective procedure.

Dr. Slotwiner asked further about amplitude reductions data. Dr. Cher said it was not necessary data and that it is not possible to collect in every electrode. Dr. Kocheril added that the electrogram amplitude measurements do not equate to complete lines and that clinical success is the important endpoint. Dr. Saksena said that many lesions do not show electrogram reduction but do form a complete line of block. Dr. Ewing said that the protocol specified that electrograms were to be measured per energy delivery. Dr. Schmid asked further about the paired measurements. Dr. Cher said that 78 percent of the patients had at least one paired measurement, but size of the heart and placement of the catheter prevents 16 measurements. Dr. Ewing said that the average number of burns per line was 20, so there should have been 40 measurements.

Ms. Whittington commented that she was having trouble understanding why there would not be explicit data point collection and asked why FDA did not notice the missing data during the site visits. Dr. Saksena said the FDA's expectations of clinical data were unrealistic. Dr. Ewing said the BIMO inspections would not audit the information.

Dr. Hirshfeld asked how a few data points along the catheter indicate a complete line of lesion. Dr. Saksena said that even when the ablation line is not complete, electrical propagation is altered. The data from all the electrodes could not be measured due to the dynamic nature of the procedure. Dr. Ewing said that assessing the effectiveness of the device would require knowing which patients had successful procedures and looking at those patients' outcomes.

Dr. Browner asked whether acute efficacy was based on the investigator's judgment or objective criteria. Dr. Cher said that at the 1998 panel meeting, the panel recommended that success be judged by ablating according to instructions and doing chronic follow-up, since there was no available endpoint to predict success. Dr. Ewing said that electrogram measurement was supposed to go to a core lab for independent review.

Dr. Slotwiner agreed that amplitude reduction does not always indicate ablation but wanted to know the device's endpoint. Dr. Saksena said the study was done when less was known about catheter ablation. However, he said that success is shown in long-term chronic follow-up. Dr. Kocheril said that the investigators were told to put down complete lines and took care to do so.

Dr. Schmid wondered if there was enough data to reanalyze it. Dr. Cher said there was. Dr. Ewing said the data did not show whether or not any patient had a successful line of lesions or which patients had successful procedures. Dr. Cher said that all patients

received ablations and that the successful procedures can be identified by the clinical outcomes.

Dr. Browner asked about the disputed chronic clinical success patients. Dr. Cher said that he looked at the patients with new AADs and those with pacemakers, but he could not address the patients individually. Dr. Saksena said it would be impossible to withdraw patients from AADs. He said amiodarone might have had an effect. The use of non-protocol catheters or pacing, he said, did not make a difference. Pacemakers were technically exclusions, but they did not interfere with interpretation of clinical success. Dr. Ewing said the FDA analyzed the trial by its protocol, and patients were required to be on the same medication or a reduced dosage. Increased or different treatments could reduce symptoms and affect reporting. He said it had been agreed that use of a non-protocol catheter would render the patient a non-success.

Dr. Sackner-Bernstein expressed concerns about many operational issues. He sought reassurance that the data were collected according to protocol and handled correctly. Dr. Cher said that electrogram measurements were made in Phase III. The lab doing TTM monitoring had a database problem, but Cardima employees were able to reconstruct the database. Some subjects were lost to follow-up before 6 months. Some patients were excluded due to insufficient events at baseline. This was a result of a retrospective analysis by an independent cardiologist. There were several QA measures. Dr. Ewing noted that the electrograms were not sent to a core lab, as the protocol specified.

Dr. Sackner-Bernstein expressed concern that the data was read in an unblinded fashion and that the Sponsor had a shadow database and access to the data throughout the study. He was also concerned by the lack of a control. Dr. Slotwiner commented that objective control groups are hard to find in electrophysiology, and there is considerable placebo effect. If the patient serves as his own control, data must be collected meticulously and objectively and evaluated in a blinded, objective manner. Ms. Whittington agreed, saying that inconsistent data does not serve the consumer or the physician. Ms. Walker said that the problem was not study design but study execution and data collection. The question is how to mitigate the bias introduced by the study design. Dr. Browner pointed out the further complication of the sporadic nature of the symptoms. Dr. Cher said that the discussion mischaracterized the quality, consistency, objectivity, and fairness of the trial. Dr. Zuckerman said the FDA agreed with the Panel's discussion of the problems of conduct in the trial. He said that statistical modeling did not mitigate regression to the mean, and the missing data due to poor conduct in the trial could not be mitigated.

Dr. Browner asked how many patients were unambiguously cured by the treatment and of those how many had other treatments. Dr. Cher said 29 patients, 35 percent, reported no symptoms during the 6 months of follow-up. He did not know how many of these patients had other treatments. Dr. Ewing pointed out that the device was not indicated as a cure but as a palliative treatment.

Chairman Ramsey moved the discussion to the FDA's concern that the risk-benefit profile could not be assessed, addressing safety first. Ms. Walker noted that the

sponsor's safety data was Phase III, while the FDA's presentation included some Phase II(b) data as well. Dr. Ewing said the FDA used all the data it had, combining the phases for completeness of the safety profile. Dr. Cher said that combining the data does not affect the safety profile.

Dr. Sackner-Bernstein asked about the post-procedure hospitalization risk. Dr. Kocheril noted that hospitalization varies by the patient and should be compared to hospitalizations six months pre-procedure. Dr. Cher said there were 34 hospitalizations in follow-up in 21 subjects, 30 for arrhythmia and 25 for AF. He said the rate was reasonable. Dr. Ewing said that 30 patients visited the hospital in 24 months, 64 at 12 months. Dr. Sackner-Bernstein further noted that 38.7 percent of the procedures required general anesthesia and intubation. Dr. Kocheril said anesthesia and intubation would vary by site and physician. Often it was done to keep the patient still. Dr. Slotwiner commented that deep conscious sedation is not so different from intubation. Dr. Sackner-Bernstein noted that the patients could simply be shifting from symptomatic to asymptomatic AF due to a placebo effect.

FDA SUMMATION

Dr. Tillman said that the Sponsor had not provided sufficient valid evidence to support approval. To be approvable, the device should be demonstrated to provide clinically significant results in a significant portion of the target population. The results of the primary endpoint were not interpretable, due to reporting issues for the chronic endpoint and lack of data for the acute procedural endpoint. To determine a reasonable assurance of safety, the Panel must find that the probable benefits outweigh the probable risks and that the device does not present an unreasonable risk of illness or injury. Due to lack of data, the safety profile cannot be determined. Additional data provided by Cardima did not resolve the underlying issues of trial conduct. Additional prospective data is needed to demonstrate safety and effectiveness, and this data must be collected pre-market.

SPONSOR SUMMATION

Dr. Cher said that the study design conforms to FDA regulations and guidance. The study was well-controlled, with each patient his own control, which is a valid practice. Placebo effect does not explain the outcomes. The primary endpoint was met in a significant portion of the population. Secondary endpoints were significant and clinically meaningful. The safety profile showed a 5 percent serious adverse event rate, which is clinically reasonable. The benefits outweigh the risks, and the results are consistent with other ablation literature.

Amplitude reduction was the procedural endpoint, and investigators followed the protocol to create the lesion lines. Chronic clinical effectiveness was demonstrated in the population of highly symptomatic, highly drug refractory patients who would not be getting better on their own. TTM transmissions were independently verified. Study sites underwent FDA auditing. There was a 58 percent success rate, and the risk/benefit profile is favorable. Right atrial ablation is an important treatment strategy for AF and should be available to physicians.

Dr. Cher suggested as a condition of approval that the acute procedural endpoint be addressed in a small study using Ensite mapping to confirm the block.

PANEL DELIBERATION AND VOTE

Ms. Whittington, Consumer Representative, expressed concerns with the lack of early endpoint and chronic effectiveness data. She said that potential patients must be made aware that this treatment will not stop the need for other treatments. Patients would also have to be informed of the success rate.

Ms. Walker, Industry Representative, urged the panel to look at what the study shows and to suggest modifications to the intended use that would allow the device to be approved with a post-approval study to address lingering questions.

Executive Secretary Collazo-Braier read the panel recommendation options for pre-market approval into the record, and Chairman Ramsey opened the floor for a motion.

Dr. Sackner-Bernstein moved that the application was not approvable, prefacing his motion with an understanding of the difficulties facing the sponsor at the time of the study. **Dr. Hirshfeld seconded the motion.** Chairman Ramsey opened discussion of the motion. Dr. Schmid wondered if there was more information to be had and noted the disconnect between the Sponsor's and the FDA's interpretations of the data. He said that there was not sufficient data. Dr. Slotwiner said there were many attractive aspects of the technology, but he would not know how to use it without additional equipment. Dr. Hirshfeld said there were questions as to the value of right atrial fibrillation as a stand-alone procedure or as an adjunct to left atrial pulmonary vein isolation and as to whether the data supports efficacy. While some patients may have benefited, he does not know which patients, so he would not know how to select patients for the procedure. **The motion carried unanimously.**

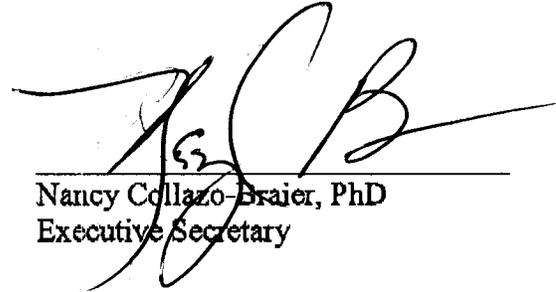
Chairman Ramsey asked the members to explain their votes. Dr. Schmid said the data did not prove the device's efficacy. Dr. Slotwiner said that the catheter was shown to be safe, but its effectiveness is unknown because AF was not well understood when the study started. Dr. Browner said that the data did not support effectiveness. Dr. Sackner-

Bernstein said that the data did not meet the regulatory standard of safety and effectiveness.

Chairman Ramsey asked the Panel to identify what would make the PMA approvable. Dr. Schmid said he wanted to see convincing data, and he urged the sponsor and FDA to work together on conditions under which the application would be approvable. Dr. Hirshfeld noted that there are better techniques now available to assess acute and chronic efficacy, and he recommended that a redesigned trial use them. Dr. Slotwiner said more evidence was needed and expressed doubt about the benefits of right atrium ablation alone. He said it was an excellent catheter, and correct study can find a use for it. Dr. Browner said careful attention must be paid to what constitutes success and failure to avoid ambiguous outcomes. Dr. Sackner-Bernstein expressed appreciation that the sponsor was already looking at how to collect more information. He said the next study should be multi-centered and that acute success should be demonstrated. Outcomes data should account for placebo effect. New devices can be used to track total time in AF, up to two weeks at a time, and the material can be handled in a blinded fashion. Data can be collected in a way that is all-encompassing, minimizes placebo effect, and shows internal consistency, blinding, and multiple assessment time points.

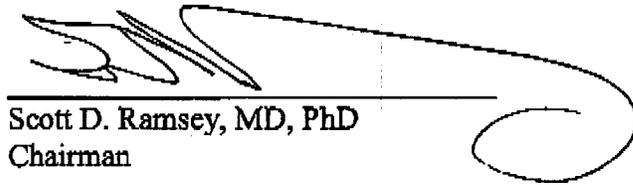
Chairman Ramsey thanked the Sponsor, FDA, Panel, and participants. Mr. Weinstein thanked the Chairman and participants. **Chairman Ramsey adjourned the meeting at 4:42 p.m.**

I certify that I attended this meeting
of the Medical Devices Dispute
Resolution Panel on April 19, 2007
and that these minutes accurately
reflect what transpired.



Nancy Collazo-Braier, PhD
Executive Secretary

I approve the minutes of this meeting
as recorded in this summary.



Scott D. Ramsey, MD, PhD
Chairman

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