

SUMMARY MINUTES

MEETING OF THE CIRCULATORY SYSTEM DEVICES

ADVISORY PANEL

MEETING

June 27, 2007

**Hilton Washington D.C. North
Gaithersburg, Maryland**

Circulatory System Devices Advisory Panel Meeting

June 27, 2007

Attendees

Chairperson

William H. Maisel, M.D., M.P.H.
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Voting Members

Sharon-Lise Normand, Ph.D.
Harvard School of Public Health
Boston, Massachusetts

John C. Somberg, M.D.
Rush University Medical Center
Lake Bluff, Illinois

Clyde Yancy, M.D.
Baylor Heart and Vascular Institute
Dallas, Texas

Consultants

Jeffrey A. Brinker, M.D.
The Johns Hopkins Hospital
Baltimore, Maryland

Michael J. Domanski, M.D.
National Institute of Health
Bethesda, Maryland

Pamela Karasik, M.D.
Veteran's Administration Hospital
Washington, D.C.

Norman S. Kato, M.D.
Cardiac Care Medical Group
Encino, California

Adam Lottick, M.D.
St. Vincent's Hospital
Bridgeport, Connecticut

David Milan, M.D.
Massachusetts General Hospital
Boston, Massachusetts

David Slotwiner, M.D.
Long Island Jewish Medical Center
New Hyde Park, New York

Industry Representative

Marcia S. Yaross, Ph.D.
Biosense Webster, Inc.
Diamond Bar, California

Consumer Representative

Linda Mottle, M.S.M., R.
Director Clinical Trials Research
Arizona State University, Arizona

Executive Secretary

James P. Swink
Food and Drug Administration
Rockville, Maryland

FDA Participants

Bram Zuckerman, M.D.
Director, Division of Cardiovascular Devices

Owen Faris, Ph.D.
Division of Cardiovascular Devices

Randall Brockman, M.D.
Medical Officer, Division of Cardiovascular Devices

Shanti Gomadam, Ph.D.
Statistician, Office of Surveillance and Biometrics

Dale Tavis, M.D., M.P.H.
Medical Officer / Epidemiologist
Division of Postmarket Surveillance
Office of Surveillance and Biometrics

CALL TO ORDER

Chairperson William H. Maisel, M.D, M.P.H., called the meeting to order at 8:03 a.m. He noted that the voting members present constitute a quorum.

Bram Zuckerman, M.D., Director, Division of Cardiovascular Devices, honored Sharon Lise-Normand and William H. Maisel, who are participating in their final panel meeting.

Panel Executive Secretary James P. Swink read the conflict of interest statement. No waivers were issued in connection with the meeting. He then read the appointment of temporary voting members.

Dr. Maisel stated the panel would be making a recommendation regarding premarket approval application P050024 for the CryoCor Cryoablation System. He then asked the panel members to introduce themselves.

FIRST OPEN PUBLIC HEARING

No members of the public came forward to speak.

SPONSOR PRESENTATION

Helen Barold, Chief Medical Officer, CryoCor, stated that the intended use for the CryoCor Cryoablation system is in treatment of isthmus-dependent atrial flutter in patients 18 years of age and older. She then outlined the sponsor's presentation.

Eric Ryba, Director of Intellectual Property, CryoCor, provided an overview of the system. Cryoablation involves use of extreme cold to ablate tissue and is

performed through controlled delivery of nitrous oxide to the tip of a catheter to reliably and consistently produce temperatures of minus 85 to 90 degrees Celsius.

Gregory Feld, Professor of Medicine and Director of the Cardiac Electrophysiology Program, University of California-San Diego, Principal Investigator, and member of CryoCor's Scientific Advisory Board, presented preclinical data on cryoablation. He stated that cryoablation is able to produce larger lesions than standard radio frequency and as large as irrigated RF catheters and that the CryoCor system appears to be able to make lesions large enough to treat atrial flutter.

Hein Wellens, former head of cardiology, Academic Medical Center of the University of Maastricht, The Netherlands, and member of CryoCor's Scientific Advisory Board, discussed data comparing cryoablation to RF in creation of permanent bidirectional isthmus conduction block in dogs. He concluded that cryoablation is able to produce chronic bidirectional block with histologic evidence of full sickness lesions and that, compared to RF, cryoablation adheres well to the endocardial surface in that the tip freezes to the surface, which may be beneficial especially with a trabeculated isthmus area.

Hugh Calkins, Professor of Medicine and Director of Electrophysiology, Johns Hopkins, and member of CryoCor's Scientific Advisory Board, discussed the objective performance criteria (OPCs) as well as published literature on catheter ablation of atrial flutter. He concluded that since 96 percent of prior studies of catheter ablation of atrial flutter used clinical endpoints to determine success and did not employ event monitoring, the published literature underestimates the true recurrence rate of atrial flutter following radio frequency catheter ablation.

Dr. Feld presented the study design and endpoints for the pivotal study.

Al Waldo, Professor of Cardiology, Medicine, and Biomedical Engineering, Case Western Reserve University School of Medicine, and member of CryoCor's Scientific Advisory Board, discussed the initial submission issues and the need for an unbiased and blinded expert to interpret the event recordings.

Mel Scheinman, University of California-San Francisco, headed the core lab which reviewed the event recordings. He said they had no clinical information on the patients and were completely blinded. He emphasized that event recordings alone can be difficult to interpret and that every event that could possibly have been a flutter was considered a flutter.

James Daubert, Associate Professor of Medicine and Director of the Electrophysiology Service, University of Rochester Medical Center, and consultant to CryoCor, presented the study results. He concluded that the system is safe based on the low seven-day serious adverse event rate and chronically effective at achieving bidirectional cavo-tricuspid isthmus block. He suggested the chronic effectiveness rate may be even higher than the 81.6 percent shown in the primary analysis.

Dr. Wellens presented data from the University of Maastricht on treatment of atrial flutter using CryoCor. He concluded by stating that all ablations of atrial flutter performed at Maastricht use the CryoCor system because of the excellent results and that it is significantly less painful than RF.

Dr. Waldo concluded the sponsor presentation by stating that the study demonstrated a reasonable level of safety and effectiveness.

Dr. Normand asked for clarification of the OPCs. Dr. Calkins said they were developed for the approval of RF ablation catheters for various arrhythmias. Dr. Normand asked if only medication refractory patients were included in the trial, and Dr. Barold said no. Dr. Normand asked whether the Kaplan-Meier plot for chronic effectiveness used time to first recurrence of flutter, and Dr. Barold said yes.

Dr. Zuckerman clarified that with regard to FDA the OPC or point estimate should apply to all catheter therapies meant to treat atrial flutter.

Dr. Yancy asked whether the analysis of device and procedure-related adverse events was pre-specified. Dr. Barold said it was not an endpoint in the protocol but that the protocol specified that the Data and Safety Monitoring Board would adjudicate serious adverse events. Dr. Yancy then asked if the post hoc analysis of chronic effectiveness performed by a separate investigator who incorporated clinical information was available, and Dr. Barold said it was.

Dr. Domanski asked how anti-coagulation was handled in the differently adjudicated groups. Dr. Barold said they recorded whether or not patients were taking coumadin but did not specifically follow it.

Dr. Maisel asked about patient compliance with weekly transmissions. Dr. Barold said there were only five patients who were non-compliant at some point and reiterated that compliance was defined as at least three out of four transmissions per month for at least five of the six months.

Dr. Karasik asked how many patients ended up on anti-arrhythmic drug therapy following ablation. Dr. Barold said approximately three patients were started on anti-arrhythmics.

Dr. Domanski asked for further information on the post hoc analysis. Dr. Barold said it was an attempt to compare the data to the published literature. Dr. Calkins emphasized an appropriate interpretation of their very aggressive event monitoring strategy.

Dr. Lottick asked why the sponsor changed the acute success time determination from 60 to 30 minutes. Dr. Barold said the investigators requested a shorter time period and that after an extensive literature review the sponsor felt that 30 minutes would be adequate. The original time length was also a strong impediment to recruitment. Dr. Lottick noted that the procedure looks much more successful at the 60 minute time point, but Dr. Barold said there is no statistical difference.

Dr. Karasik asked about the catheter design change that was made during the study. Dr. Barold said the changes were made for ease of manufacturing and that extensive study demonstrated the catheters are equivalent.

Dr. Maisel asked about the single device malfunction observed. Dr. Barold said it was the earlier model and that they have not seen any problems with the redesigned catheter.

FDA PRESENTATION

Owen Faris, Ph.D., Division of Cardiovascular Devices, described the history of FDA's review of the PMA. He said the readjudication by Dr. Scheinman's lab of the event recorder tracings forms the primary basis for the amended submission currently under review and that FDA considers the revised chronic effectiveness patient classifications to be scientifically valid.

Randall Brockman, M.D., presented FDA's clinical review and discussed atrial flutter and atrial flutter ablation. He concluded that although the safety endpoint was not met, FDA believes the safety events that occurred would be expected for an atrial flutter ablation population. The acute effectiveness endpoint was met, but the chronic effectiveness endpoint was not.

Shanti Gomatam, Ph.D., provided FDA's statistical review. Dr. Gomatam concluded that the performance goal for the acute effectiveness endpoint was met, but the performance goals for the safety and chronic effectiveness endpoints were not met.

Dale Tavris, M.D., M.P.H., discussed post-approval issues. He noted that FDA and the sponsor have not discussed the need for a post-approval study. He identified four important components for a possible post-approval study: fundamental study questions or hypotheses; safety endpoints and methods of assessing them; both acute and chronic effectiveness endpoints and their evaluation; and the length of follow-up.

Dr. Normand asked about the two patients who had prior ablations, and Dr. Maisel said the sponsor had stated one was WPW and the other was perhaps PDI. Dr. Normand asked about using an endpoint of conditional probability of chronic effectiveness rather than an endpoint of the probability of both acute and chronic effectiveness. Dr. Brockman agreed that long-term success is what matters to patients but said it is important for FDA to characterize the difference. Dr. Normand suggested it is misleading to look at the conditional rather than the whole probability. Dr. Somberg suggested the acute effectiveness serves as a surrogate for whether the system works and may have predictive value later on.

Dr. Somberg asked if FDA and the sponsor had discussed what is really meant by chronic effectiveness in that the question is really whether the system prevents recurrent atrial flutter coming from the isthmus. Dr. Brockman said that discussions about chronic effectiveness dealt with recurrent atrial flutter documented on event monitor recordings. Dr. Somberg said that is not clinical chronic effectiveness.

Dr. Domanski asked how the safety and effectiveness endpoints were arrived at, whether those for safety were appropriate, and whether they had contemplated a post hoc analysis by a CryoCor physician to try to meet the endpoints. Dr. Brockman said the endpoints were derived from a 1998 panel meeting and based largely on a literature review and that they had entertained the idea of a post hoc analysis but had not suggested it.

Dr. Slotwiner said acute efficacy is important in the laboratory and that interpretation would be difficult without it. Dr. Normand agreed it is important but said doctors would not give potential patients the conditional estimate. Dr. Maisel said the labeling could provide the correct probability to patients.

Ms. Mottle expressed concern about the different outcomes between the pivotal study and the foreign data and also raised the issue of increased procedure time. Dr. Yaross emphasized the importance of consistency across applications with regard to the OPC.

Dr. Gomatam said patients would really want to know all three numbers and that they had done an analysis of unconditional six-month recurrence with an estimate of 71.4 percent with a lower bound of 64 percent.

Dr. Kato asked whether the six months for chronic effectiveness was defined by the sponsor or FDA. Dr. Gomatam said it was specified in the protocol and was defined as such in the OPC by FDA. Dr. Barold said it was not defined as six months in the protocol. Dr. Kato noted it was three months. Dr. Brockman said the relevant guidance document specifies six months for the OPCs.

Dr. Normand, noting the study was done in the past, asked about how current information can be brought into the discussion. Dr. Zuckerman said they convened a distinguished panel to answer these questions though they also want to be sensitive that the agency and sponsor did agree to a certain protocol.

Dr. Yaross asked if the intensive event monitoring strategy was put in place at FDA's request. Dr. Zuckerman said it was fairly standard for a catheter ablation protocol.

Dr. Lottick asked if the original OPC endpoints were determined based on other SVTs. Dr. Brockman said the OPCs for atrial flutter are the same as those for other super-ventricular arrhythmias, which came from a literature review of those types of arrhythmias, but the atrial flutter OPCs also incorporated a review of literature specific to atrial flutter ablation.

Dr. Yancy asked if there is a revised OPC to use when only looking at device and procedural related complications, and Dr. Brockman was not aware of one. Dr. Somberg said clinicians would decide which device to use based on relative incidence but that it would have been nice to have had a control. Dr. Yaross noted that OPC control trials are considered as valid scientific evidence.

Dr. Domanski said a level playing field is not relevant to deliberations about a particular device and that one must be very careful in selecting OPCs for a non-randomized trial.

Dr. Slotwiner asked how the criteria for serious adverse events within the first seven days were derived given the lack of a control arm. Dr. Brockman said individual events may be evaluated to determine whether they are device related.

Dr. Barold said that according to the guidance document chronic success is three months with no recurrence of the target arrhythmia, and major complications are defined as procedure or device related adverse events requiring any intervention.

Elias Mallis, FDA, said the document referred to was a generic indications guidance published in 2002 while the goals for this study were derived from an advisory panel meeting in 1998 specific to atrial flutter. He also said they have seen both three and six month chronic endpoints in studies and that FDA does not have a position on one versus the other.

Dr. Normand asked if the OPC in this study is based on a three or six month endpoint. Dr. Zuckerman said there would be an explanation later. Dr. Milan emphasized the need for clarification of whether the safety endpoint is all adverse events.

Dr. Maisel asked for comments on what constitutes clinical effectiveness for an atrial flutter ablation catheter. Dr. Somber said chronic effectiveness at six months, if not longer, is the key. He also asked the sponsor for data comparing their retrospective analysis to current therapies as a possible substitute for clinical effectiveness.

Dr. Domanski wondered if the sponsor might make the case why the numbers used in the OPC are historical and not the right ones. Dr. Milan emphasized the

importance of getting rid of symptomatic atrial flutter and making patients feel better as well as how one manages patients who do have a recurrence.

Dr. Slotwiner did not think it reasonable to compare atrial flutter to other SVTs and stated that the OPCs are probably not the correct measure. Dr. Normand asked for clarification of Dr. Maisel's question, and Dr. Maisel said he should have said clinical effectiveness based on symptoms and physician assessment versus event monitoring looking for EKG evidence of recurrence.

Dr. Slotwiner asked how many of the tracings were not interpretable. Dr. Scheinman said that for patients for whom there was only one documented flutter but the clinician reported the patient was asymptomatic, it is more likely to have been an artifact rather than flutter. Dr. Barold said that 79 out of 4,465 tracings were indeterminate.

Dr. Yancy asked if it is true that the designation for 22 of the tracings were changed following the analysis by Dr. Scheinman. Dr. Barold said that if multiple tracings for a single patient were reversed it was only counted as one reclassification and that the decisions went in both directions. Dr. Yancy asked for the error rate with the protocol specified approach. Dr. Barold did not have the number but said that of the 179 recordings initially interpreted as atrial flutter, Dr. Scheinman reversed 103. He did not have the number of reclassifications in the negative direction.

Dr. Maisel asked if anyone on the panel felt that the post hoc clinical assessment is the appropriate endpoint to be looking at. Dr. Domanski said he would not use it because it is a post hoc analysis conducted by someone employed by the sponsor. Dr. Slotwiner was also uncomfortable with the post hoc but also recognized the limitations of the electrograms alone. Dr. Somberg also had concerns but thought a careful clinical

review would be more meaningful than the electrograms. Dr. Normand also expressed concerns with the retrospective analysis, particularly with regard to the censoring of missing data. Dr. Lottick said another problem with the clinical data is the lack of clinical baseline data.

Dr. Brinker asked how many of the monitored strips were initiated by the patients themselves as a result of symptoms. Dr. Barold said they had not collected that data but that it could be gathered by looking at each strip individually. Dr. Yancy agreed that the core lab analysis is probably the best metric available to the panel. Dr. Maisel said the consensus seems to be that the post hoc clinical assessment is not high enough quality data on which to make a determination. He then asked if anyone felt that the OPCs are perfect and that there should not be any wiggle room.

Dr. Domanski asked for views on the reasonableness of the OPCs from the sponsors' experts. Dr. Calkins said the OPCs were based on four studies with only clinical follow-up and no event recording and noted that the more one looks with event monitors, the more one tends to see. He mentioned a 2004 study with comparable efficacy rates and a nearly identical rate of device and procedure related complications.

Dr. Normand asked about the time to endpoint in the four studies, and Dr. Calkins said they varied from short to long. He said the strength of the study is in the intensive event monitoring and discussed the difficulties inherent in that monitoring.

Dr. Waldo agreed and discussed the difficulty in separating atrial fibrillation from atrial flutter, which also makes the anticoagulation problem difficult since it is the atrial fibrillation that determines when anticoagulation should be used.

Dr. Domanski asked why the sponsor had agreed to use the wrong metric. Dr. Barold said they had decided on the study design after working closely with FDA. Dr. Calkins said the interplay between some atrial fibrillation and atrial flutter was not recognized when the study was designed.

Dr. Yancy asked if there is registry data on early complication rates and long-term effectiveness for RF. Dr. Scheinman said he had published results from a voluntary U.S. registry, as was also done in Europe, showing efficacy around 80 percent and about a five percent rate of acute adverse events. He also noted that in studies where patients get implantable recorders, there is clearly a much higher incidence of asymptomatic atrial flutter. He also highlighted the Maastricht data and the benefits to patients. Dr. Somberg noted it was a limited number and not a study with a protocol.

Dr. Wellens took issue with FDA's criticism of the lack of blinding of the operators in Maastricht and of the use of the subjective FOS measure of pain, which is well accepted among pain experts, and of the lack of a p-value, which he said could be determined. He said the number of subjects had been limited by the hospital's ethical committee since they did not know whether the cryoablation patients would experience pain. Dr. Wellens also said that in clinical medicine following ablation, the patient will come back if they experience a symptomatic episode and also for follow-up but that continuous monitoring is not used.

Dr. Normand said that independent evaluators can assess pain if the operators cannot be blinded. She then asked if the times were also changed when strips were readjudicated. Dr. Barold said that strips from obvious failures were not readjudicated and that the time and date identified by Dr. Scheinman in the readjudication were used.

Dr. Somberg asked Dr. Wellens about the pain assessment, and he said it was done by an unblinded independent psychologist. Dr. Somberg asked if the IRB had approved the study without a protocol, and Dr. Wellens said there was indeed a protocol. He noted that the pain study was accepted for publication in *Circulation*.

Donna-Bea Tillman, Ph.D., Director, Office of Device Evaluation, discussed some of the history of the agency's consideration of catheter ablation and the 1998 panel meeting. She said the OPC was a six month endpoint and the safety endpoint was all adverse events within seven days of the procedure. She said for a single-arm trial with OPCs, it is neither assured that meeting the OPCs will garner approval nor that failure to meet them will result in a determination of not approvable.

PANEL DELIBERATIONS

Dr. Slotwiner presented his primary review of the panel pack. He asked whether there was a statistical difference in acute effectiveness when the waiting period was reduced. Dr. Barold said there was a change, though not significant, but chronic effectiveness was not affected.

Dr. Brinker asked Dr. Wellens if there was a difference in fluoroscopy or procedure time compared to RF in the human data as there was in the animal data. Dr. Wellens said the number of applications per site and length of application have been gradually decreasing, but he did not have any comparison data. Dr. Calkins noted that because with cryoablation the catheter adheres to the tissue, the fluoroscopy can be turned off whereas with RF fluoroscopy is typically used for the entire burn.

Dr. Brinker next asked whether the increased catheter size changes anything about its positioning. Dr. Calkins said it performs remarkably similar to a standard 7 or 8

French RF catheter in terms of deflectability. Dr. Brinker asked whether the longer time to produce the injury with cryoablation means that one has some warning about heart AV block and can stop before that. Dr. Calkins said operator error was responsible for the one case of heart block, and he said that if you see heart block and turn off right away, the block is reversible in most cases. Dr. Daubert agreed that the larger catheter handles well.

Dr. Somberg asked if there is a downside to the catheter's adhesion to the tissue and about the best comparator to use. Dr. Feld said one potential issue is that one must be careful not to move the catheter until it has clearly reached a positive temperature. He said he feels the clinical outcome is the most important measure. He also said with regard to the single episodes of flutter early on that the atrial fibrillation trials showed that for the first month or so there is a blanking period during which a recurrence may not be clinically important and suggested the same thing may occur with atrial flutter.

Dr. Karasik asked about groin complications with regular use of 10 French catheters. Dr. Daubert said they had not seen a higher risk compared to a 8 French and that there had only been one hematoma in the study. Dr. Karasik next asked about the labeling's mention of placing the catheter in the left atrium. Dr. Barold said it was draft labeling and said that anything related to the left atrium would be removed from the labeling. Dr. Barold said the wording had been taken from another approved catheter. Finally, Dr. Karasik asked if there is a need for physician training. Dr. Barold said they do training when setting up clinical sites but have not come up with any formal plan.

Dr. Kato asked about the use of medical therapy and whether the sponsor is advocating the device as primary therapy. Dr. Barold said the study does not intend to

advocate ablation over medications and that it is up to the physician how to manage the patient. Dr. Calkins said that many centers are performing catheter ablation of atrial flutter as first line therapy and discussed Type I drug-induced atrial flutter, which is treated with ablation and antiarrhythmic drugs to control the original atrial fibrillation.

Dr. Yancy asked about the clinical utilization of cryoablation versus RF given the lack of signals that cryo is more safe and effective. Dr. Scheinman talked about patients with pulmonary insufficiency, morbid obesity, and severe heart failure where one does not want to use anesthetic. Dr. Yancy asked how many of the study patients fit that profile, and Dr. Barold admitted they were excluded and that her comments would not necessarily pertain to the study population. Dr. Calkins said that different institutions will develop their own preferences.

Dr. Lottick inquired about the fact that waiting for an additional 30 minutes one sees a 25 percent reduction in acute efficacy but no change in the chronic outcome. Dr. Barold suggested it is a statistical/sample size issue. Dr. Lottick said that if the populations had a low recurrence rate to begin with then one would not see a significant difference in the chronic outcome. Dr. Barold admitted it is difficult without knowing the prior amount of arrhythmia burden. Dr. Gomatam said that an unconditional six month analysis showed chronic effectiveness was different across protocols.

Dr. Normand asked if readjudication was not performed for evaluations deemed successes, and Dr. Slotwiner said that was only for the clinical assessments. Dr. Normand then asked about analyses that would treat missing data in a statistically valid manner. Dr. Barold said the plan was developed with FDA and that censoring of noncompliant patients was felt to be appropriate for the survival analysis. Dr. Gomatam

made the distinction that there was censoring of individual indeterminate event recordings and that patients did not have to perform every transmission to be counted as compliant. Dr. Barold said there was information in the panel pack on the patients who were censored. Dr. Normand said the censoring makes the confidence intervals for chronic effectiveness a little wider. Dr. Normand also said that the data was not used such that each subject served as his or her own control as stated by the sponsor in the design.

Dr. Maisel asked about instructions for physicians regarding duration of a freeze. Dr. Barold said they recommend two minutes although there is preclinical data suggesting the lesion size is created at 30 seconds. Dr. Maisel then asked about two apparently defective devices. Dr. Barold said it was actually an issue with nitrous plugging of the console and that the issue has been resolved.

Ed Brennan, President and CEO, CryoCor, said the problem that occurred in Europe was with a prior model and that a physician trapped the catheter in the sheath, applied too much torque, and tore the catheter. He said they have not been able to reproduce the problem in that particular catheter but admitted the catheter will tear if the tip is trapped and torque is applied.

Dr. Maisel asked if FDA has any outstanding issues with device or catheter performance. Dr. Faris said they do not have outstanding engineering concerns and that the nitrous plugging was the result of a supplier issue.

FDA QUESTIONS

1. Please discuss whether the safety results demonstrate that there is a reasonable assurance that the device is safe for the treatment of isthmus-dependent atrial flutter.

The panel was divided with regard to safety. Some panel members were not concerned with safety even though the OPC was not met given that the majority of adverse events were not device or procedure related and given the small sample size. One panel member stressed the need for a comprehensive training program. Dr. Maisel suggested that FDA revisit the OPCs for atrial flutter ablation.

2. Please discuss whether the chronic effectiveness results based upon the core lab determination demonstrate that there is a reasonable assurance that the device is effective for the chronic treatment of isthmus-dependent atrial flutter.

Some members felt the OPC was not appropriate because it was not based on the same type of core lab analysis. One panel member stressed that the efficacy is likely somewhat above what was determined in the core lab analysis since lots of tracings were included that probably were not isthmus-dependent flutter. Some members felt the chronic effectiveness endpoint was not met. One member pointed out there is data from a comparable study with monthly event recordings that showed higher efficacy.

3. Please discuss the value of the chronic effectiveness results based upon the post hoc clinical determination.

Dr. Maisel said the general consensus based on earlier discussions is that while a clinical determination is extremely valuable, the study design and the quality of the data are such that the post hoc analysis in this case is not particularly helpful in assessing the chronic effectiveness endpoint.

4. Please discuss the value of the OUS results in assessing the chronic effectiveness of the device.

Dr. Maisel stated that while the results from Maastricht are reassuring with regard to effectiveness, it is hard to extrapolate the results to the real world.

5. Please discuss the value of the pain study results.

Some members were impressed with the results but thought more work would need to be done before recommending that the procedure be performed without sedation. There was discussion of the importance of sedation to a patient's overall comfort and ability to lie still for three hours or so. Panel members emphasized the potential benefit for patients at high risk for any type of sedation.

6. Please comment on whether the Indications section identifies the appropriate patient population for treatment with the device. Please comment on the remainder of the device labeling as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse outcomes. Please discuss any additional recommendations regarding the device labeling.

Dr. Maisel emphasized that the comments regarding the left atrium must be removed. There is a need for a patient manual. One member thought the labeling needed a more rigorous explanation of use. There was discussion regarding whether there should be a contraindication for use other than in the right atrium. One member suggested the inclusion/exclusion criteria from the study should be reflected in the indications and noted that agency guidelines state that medical management is first line therapy. The panel felt that "right atrial isthmus" should be added to the indication statement. There was also discussion about inclusion of unconditional chronic effectiveness.

With regard to training, one member suggested an audio-visual presentation to avoid the site visit required in the study. Another member thought a site visit would be necessary to set up the console. Another member suggested having trainers present for the first several procedures.

7. Please provide your overall assessment of the risks and benefits of the CryoCor Cryoablation System for the treatment of isthmus-dependent atrial flutter as demonstrated in the premarket approval application.

One member stated that there is reasonable assurance of safety and efficacy. There was a question whether the indication would be patients who don't have congestive heart failure and an EF less than 35 percent, and Dr. Maisel said the risk and benefit assessment should be based on the entry criteria for the trial. One member emphasized that tamponade should be specifically included as a risk.

8. If you recommend approval, please discuss whether a post-approval study should be performed to address any issues that are unresolved but not essential to the approval of the device. If so, please comment on the major components of such a study.

Some members said that a concurrent control group, non-randomized, would be vital to see how the device performs in the broader population over the long term. Some members suggested an endpoint at twelve months. One member was concerned that events occurring after six months would not necessarily be related to the procedure. Another member was not sure a post market study was really necessary. Another member thought it would be useful to look at unusual adverse events, subgroup issues, and real world performance. One member did not think it would be possible to power a control group to look for rare events. One member said a post approval study would be particularly important in looking at safety.

Dr. Maisel said for safety they would want to look at seven day outcomes and to look at real world clinical performance there would need to be rigorously collected effectiveness and clinical data for a duration of at least six months, but weekly or monthly monitoring would not be necessary.

SECOND OPEN PUBLIC HEARING

No members of the public came forward to speak.

FDA AND SPONSOR SUMMATIONS

The FDA had no comments at this time.

Dr. Barold acknowledged the difficulty in evaluating the device without more data on comparable devices and stated her belief that there is a role for the device in the marketplace.

PANEL VOTE

Dr. Slotwiner made a motion to approve with conditions. Dr. Somberg seconded the motion.

Dr. Somberg proposed a condition that the labeling should include a clinical trial section with inclusion and exclusion criteria; acute, conditional and unconditional chronic effectiveness; no wording on left atrium; and that right atrial be added to the indication statement. Dr. Milan seconded the condition. The motion passed unanimously.

Dr. Somberg made a motion for another condition that there should be face-to-face training. Dr. Slotwiner seconded the motion. The vote was nine to zero with one abstention.

Dr. Yancy proposed a condition for a post-market observational study or registry of those treated with the device according to the label indication as well as all others treated for a similar illness followed longitudinally with a focus on near-term safety events, longer term adverse events as well as evidence of clinical utility. Dr. Domanski seconded the motion, but then attempted to amend the motion to a registry of all comers,

both on and off-label. Dr. Yancy resisted the idea of collecting data on a population about which there is currently no data, and Dr. Domanski withdrew his second.

Dr. Somberg made a similar motion but specified that the registry would include all patients who undergo the procedure. Dr. Domanski seconded the motion. Dr. Slotwiner asked if it would include patients treated with a different catheter, and Dr. Somberg said there would be a comparator group with follow-up at twelve months. Dr. Domanski withdrew his second. Dr. Normand seconded the motion. The motion passed seven to two with one abstention.

Dr. Maisel called the question on the motion of approvable with the conditions specified, and the motion passed eight to two.

FINAL PANEL COMMENTS

Dr. Domanski was convinced of reasonable safety and effectiveness but suggested that FDA use a controlled trial for similar studies in the future.

Dr. Brinker suggested there should be a mechanism to evaluate OPCs prior to a study to evaluate how much wiggle room there should be.

Dr. Somberg voted yes because there was fairly good efficacy data. He also suggested the use of a controlled study, preferably randomized, or comparator group would have been helpful. He felt that appropriate training, an appropriate IFU description, and a detailed real world post-marketing study will allow FDA to ensure public safety.

Dr. Karasik agreed with the previous comments.

Dr. Kato voted no due to the failure to satisfy the mutually agreed upon OPCs and felt the panel's decision was not evidence-based.

Dr. Yancy voted yes because there was no strong signal that it is harmful and there was sufficient evidence that it is likely beneficial. He was also sensitive to issues of patient comfort and freedom from distress. He expressed concern that the trial was represented today differently than it was constructed and asked for special focus on heart failure patients.

Dr. Lottick voted yes because the OPCs were developed for a different context.

Dr. Slotwiner voted yes because he felt the device is safe and effective and did not feel the OPCs were appropriate for the device.

Dr. Normand voted no because the safety endpoint was twice that of the OPC and the effectiveness endpoint was not reached. She was concerned that subjective opinions had determined the vote.

Dr. Milan voted yes because the OPC for effectiveness was probably too strict and the majority of the safety events were not procedure or device related.

Ms. Mottle agreed with the comments made by Dr. Normand and felt the PMA was not judged on its own merits.

Dr. Yaross commended the panel and said there is a role for clinical judgment in assessing study outcomes.

Dr. Maisel commended the sponsor for the conduct of the trial in casting a wide net with regard to safety issues. He said there is flexibility in interpretation of OPCs.

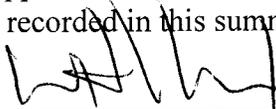
ADJOURNMENT

Dr. Maisel adjourned the meeting at 4:32 p.m.

I certify that I attended this meeting of the Circulatory System Devices Advisory Panel on June 27, 2007, and that these minutes accurately reflect what transpired.


James P. Swink
Executive Secretary

I approve the minutes of the June 27, 2007, meeting as recorded in this summary.


William H. Maisel, M.D., M.P.H.
Chairperson

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