

SUMMARY MINUTES

MEETING OF THE CIRCULATORY SYSTEM DEVICES ADVISORY PANEL

OPEN SESSION

April 22, 2005

**Gaithersburg Holiday Inn
Gaithersburg, MD**

**Circulatory System Devices Advisory Panel Meeting
April 22, 2005**

Attendees

Chairperson

William H. Maisel, M.D., M.P.H.
Brigham & Women's Hospital
Boston, MA

Voting Members

Mitchell Krucoff, M.D.
Duke University Medical Center
Durham, NC

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

Richard L. Page, M.D.
University of Washington School of Medicine
Seattle, WA

John Somberg, M.D.
American Institute of Therapeutics
Lake Forest, IL

Clyde Yancy, M.D.
University of Texas Southwestern Medical
Center
Dallas, TX

Consultants

Eugene Hubert Blackstone
Cleveland Clinic
Cleveland, OH

Jeffrey Borer, M.D.
Weill Medical College
New York, NY

Thomas Ferguson, M.D.
Washington University School of Medicine
St. Louis, MO

John W. Hirshfeld, M.D.
University of Pennsylvania Medical Center
Philadelphia, PA

Valluvan Jeevanandam, M.D.
University of Chicago
Chicago, IL

Normal S. Kato, M.D.
Cardiac Care Medical Group
Encino, CA

Industry Representative

Deborah Moore
Proxima Therapeutics, Inc.
Phoenix, AZ

Consumer Representative

Linda Mottle, MSM-HSA, RN, CCRP
GateWay Community College
Phoenix, AZ

Executive Secretary

Geretta Wood
Food and Drug Administration
Rockville, MD

CALL TO ORDER

Panel Chair William H. Maisel, M.D., MPH called the meeting to order at 8:05 a.m. to discuss and recommend a 501(k) premarket notification for the Cardica™ PAS-Port™ System, K030434. **Panel Executive Secretary Geretta Wood** read the conflict of interest statement. She noted that waivers had been granted for Drs. Krucoff, Somberg, and Yancy for their interest in firms that could be affected by the Panel's recommendations. Dr. Krucoff's waiver was for consulting interest on two unrelated matters; Dr. Somberg's waiver involved a mutual fund and holdings with competing firms; Dr. Yancy's waiver involved services for a competing firm on unrelated products. The waivers allowed these individuals to participate fully in the day's deliberations. The Panel also took into consideration other activities by Drs. Krucoff, Yancy, Borer, and Ferguson. They reported past or current interest with firms involving firms at issue but in matter unrelated to the day's agenda. They participated fully in the day's deliberations. Dr. Blackstone reported his institution's interest with a firm at issue, but because he has no continuing financial interest in the firm, the agency determined that he could participate fully in the day's deliberations.

FDA PRESENTATION: Condition of Approval Studies: Recent CDRH Changes

Susan Gardner, Ph.D., Director, Office of Surveillance and Biometrics, reported on a major programmatic change in CDRH condition of approval studies, including the move of Condition of Approval Studies Program to her office. She noted that her office plays a role not only in post-market but also in premarket reviews. They also conduct signal detection to monitor the postmarket arena. They are responsible for

characterizing device risk by reviewing postmarket data, as well as interpretation of the medical device reporting regulations.

This shift began a few years when CDRH decided to evaluate its COA program, initially to look at the quality of the studies required for condition of approval. They noted that 45 of the 127 PMA studies approved between 1998 and 2000 had condition of approval studies. This led them to discover that they had no standardized tracking process for this area. They also noted that they had not received results for 22 percent of studies.

The official move from ODE to OSB was January 1, 2005, preceded by a 3-year pilot program. One of their first steps was to develop an automated tracking system, which will also help them acknowledge to industry that they have received the report and to conduct any necessary follow-up. The second change added an epidemiologist to PMA team to develop the postmarket plan during the premarket review, and developed a postmarket question when they expect a conditional of approval study.

Dr. Gardner posited that if her office does a good job, she expected this to provide industry with increased motivation to carry out the studies. She added that feedback to industry is an important part of the new way of doing business in the past. The office will post the status of these studies on the CDRH website. As well, under Section 522, they have the ability to mandate postmarket studies; this will allow them to apply penalties to incomplete studies.

FDA PRESENTATION: Panel Update

David Buckles, Ph.D., FACC, Branch Chief, Peripheral Vascular Devices Branch, reviewed the January 13, 2005 Cardiovascular Devices Advisory Panel meeting,

in which the Gore TAG Thoracic Endoprosthesis was discussed. The original PMA was submitted October 4, 2004, and was granted expedited review status; because the device is first-of-its-kind, it had a compressed review schedule. The Cardiovascular Devices Panel voted on January 13, 2005 8-2 to recommend approval of the device; it was approved March 23, 2005. The device's indication was modified to include anatomic specifications, consistent with Panel advice. This device had a condition of approval study; the panel recommended a postapproval study out to 5 years, with specific endpoints consistent with IDE studies. The Panel also recommended a training program, and labeling with inclusion and exclusion criteria and anatomic criteria from ongoing studies. These were all included in the FDA approval order. The final disposition of the PMA application was consistent with the Panel recommendations to approve the device.

Consistent with strategy for change mentioned in Dr. Gardner's presentation, the postapproval study provides for continuing evaluation and periodic reporting on the device's safety, effectiveness, and reliability for its intended use, as well as providing information on the effectiveness of the company's training program.

OPEN PUBLIC HEARING SESSION

There were no speakers during this session.

SPONSOR'S PRESENTATION

Bernard A. Hausen, M.D., Ph.D., President and CEO, Cardica, Inc., began the sponsor's presentation by reviewing his company's history and the development of the PAS-Port system, noting that it was designed before the Symmetry device. He

stressed that Cardica has two products approved for use in Europe—the PAS-Port device and the C-Port Distal Anastomosis System—and that the PAS-Port product has also received approval in Japan.

Dr. Hausen reviewed the clinical need for the device and covered stroke and other complications that commonly occur around coronary artery bypass graft (CABG) surgery. Stroke is responsible for 21 percent of operative mortality, adds to recovery time, and increases hospitalization and rehabilitation costs for these patients. There is an increased chance of peri-operative aortic atherosclerosis and postoperative stroke as a patient's age increases—a growing problem as surgeons are seeing older patients.

Describing the product, Dr. Hausen said that the PAS-Port device replaces hand sewn anastomosis of the proximal anastomosis and features the following: it is an integrated device, providing aortotomy and implant deployment in one action; deployment is completed in seconds with the turning of a knob; use of the device is simple and intuitive; clamping is not required, reducing the risk of embolization; the device has been designed to minimize metal exposure to blood; and it provides a firm attachment to the graft vessel. The package serves as a loading platform.

Dr. Hausen discussed how the PAS-Port device differs from the Symmetry device (which has been removed from the market), recognizing the concern the Panel has expressed in the past about their similarities. According to Dr. Hausen, endothelial trauma and the amount of blood exposed to nonendothelial tissue is considerably more significant in the Symmetry device than in the PAS-Port device (the amount of blood-exposed nonendothelial surface is approximately 350 percent more in the Symmetry device, and there is significant amount of metal protruding into the lumen of the graft

with the Symmetry device). The effective orifice area is approximately 150 percent larger in the PAS-Port device, and chances for graft kinking are reduced by the device's lower profile.

Responding to questions raised by the FDA in the past, Dr. Hausen noted that, while most surgeons perform the distal anastomosis first, there is no necessarily correct order of performance of proximal and distal anastomosis. However, with the advent of beating heart surgery, he noted that there are a number of advantages to first performing a proximal anastomosis.

He addressed the Panel statements during the March 18, 2004 meeting. He also discussed the chronology of Cardica's efforts to secure approval of the device, noting that the Symmetry device was used as a predicate device. Cohort I enrollment for the Pivotal PAS-Port clinical trial was completed in September 2002, and in January 2004 they completed the prospective PAS-Port postmarket study conducted with the Cohort II C-Port clinical trial. (He noted that these two products were never use in the same graft; however, there was concurrent use of both devices in patients requiring multiple vein grafts.) This was two months before the Panel met to determine objective performance criteria in March 2004.

Dr. Hausen next responded to concerns expressed by the March 2004 FDA Panel. The FDA stated that pooling was acceptable if the cohorts were comparable and data homogenous. The clinical protocols to both cohorts were amended to allow for the collection of long-term data: Cohort I now followed patients out to 24 months and Cohort II followed patients out to 12 months. Cohorts I and II were prospective non-randomized, multi-center trials, with similar selection criteria and same endpoints. He noted that the

FDA has stated in its packet that the data were collected retrospectively; however, this is not the case. The data were collected prospectively, primarily to meet European post-market requirements.

In response to the March 2004 Panel concern that there was a bias in target vessels in favor of PAS-Port index grafts, the decision was left to the surgeon's discretion; that 51 percent of the PAS-Port grafts went to the right side versus 13 percent of the C-Port grafts, and that grafts on the right side historically show poorer patency rates than those on the left side. The sponsor's data suggests that if there was a selection bias it was against the PAS-Port index graft, according to Dr. Hausen.

Another question raised by the Panel was whether there were significant device changes between Cohorts I and II motivated by the desire to improve the delivery system reliability. Dr. Hausen said there were small changes made to improve the ergonomics and decrease friction and deployment forces. Additionally, the sponsor removed a chevron feature from the outer flange portion of the implant to improve manufacturability, and small changes were made to the packaging and the pull-through tool. He stated that these changes added precision to the components, and did not negatively affect the device's final shape, function, or integrity, or make any functional change.

Wolfgang Harringer, M.D. Ph.D., Chairman, Department of Cardiothoracic and Vascular Surgery, Braunschweig, Germany, presented the sponsor's clinical trial data. Dr. Harringer began by going over the similar inclusion and exclusion criteria for the two cohort studies. Cohort II allowed for an older population with more comorbidities

and underlying cardiac disease. The follow-up schedule for the two cohorts were identical to each other except for the fact that the additional long-term follow-up differed because enrollment for the first study had been completed a year earlier; therefore, the follow-up was a year longer. He noted that while the FDA materials given to the Panel state that the use of CTs was a protocol violation, this was not the case. They were allowed in both studies if a patient refused an angiogram.

Looking at the endpoint analyses, Dr. Harringer reported that the rates of patency reported by both cohorts compared favorably with the historical controls. Following the last Panel meeting, the endpoints were redefined: per FDA guidance, the primary endpoint had to have an index graft patency of at least 85 percent, with a lower confidence bound of 80 percent, at 95 percent confidence interval at 6 months using angiography as the primary method. He noted that qualitative angiographic Core Lab data was collected before the new FDA guidance was issued. The secondary endpoint was to determine the occurrence of major adverse cardiac events (MACE) at one year. He defined MACE as death, myocardial infarction, and the need for a target vessel revascularization. Patency evaluations were based on the FitzGibbon Grading System.

Dr. Harringer described the study results, beginning with the intraoperative and discharge data. A total of five sites in Germany and Switzerland were involved in either or both of the cohorts. Patient demographics were comparable to the literature. In the two studies, 123 PAS-Port deployments were attempted in 109 patients; 12 deployments failed. A total of 111 deployments were performed in 99 patients; 2 patients died of causes unrelated to the device before discharge. Procedural success was obtained in 83.3 percent of Cohort I patients and in 92.6 percent of Cohort II patients (following minor

device changes and better surgeon training). A total of 109 implants were placed in 97 patients.

He also presented long-term follow-up data (at 12 and 24 months) on the 10 patients who did not receive the implant and were converted to hand sewn anastomosis. One patient refused to re-enroll in the study for follow-up. Because all of these patients were classified as acute procedural failures they were not included in the 6-month analysis, as study protocol defined evaluable patients as those discharged with an implant. All patients who did not receive the implant were successfully converted to hand sewn anastomosis. While discussing bypass statistics, Dr. Harringer stressed that each patient had an average of 3.1 grafts, and that the surgery times were comparable to those seen in standard CABG surgery. Using the FDA definition of patency as less than 50 percent stenosis, the PAS-Port patency rate at discharge was 99 percent. He reported that the one graft rated as FitzGibbon B resolved and the graft was patent without stenosis at 6 months.

When comparing the observed rates of adverse effects for study patients with the literature, Dr. Harringer reported that 40 patients had 47 adverse events and 69 (63.3 percent) had no adverse events; this was comparable to the literature. In addition, the rate of individual events also compared favorably with the literature: 81 patients (74.3 percent) experienced no cardiac events, and 28 patients reported 31 cardiac events.

Dr. Harringer stated that the sponsor was particularly pleased with the completeness of follow-up: at 3 months, the rate was 96.9 percent; at 6 months it was 92.8 percent; and at 12/24 months it was 94.6 percent. These rates compare favorably with the literature on cardiac surgery trials. He presented data from the 3-month follow-

ups. Using a stress EEG, 90 percent of the patients were shown to be negative for myocardial ischemia; 5 of the 9 patients showing evidence of myocardial ischemia had patent index grafts at 6 months which resulted in good long-term outcome. At the 6-month patency evaluation, the overall graft patency rate for the 99 PAS-Port grafts followed was 91.9 percent.

In summarizing the primary efficacy of the studies, Dr. Harringer noted that there were discrepancies because the FDA used a 0.025 level of significance in a two-sided test, while Cardica used a 0.05 significance level in a one-sided test. However, he stated that the differences in lower confidence bound for imputed patency at six months were very small.

Dr. Harringer presented data on adverse effects from patient discharge to 6 months, noting that 32 patients experienced 42 adverse events; 67 patients (71.3 percent) reported no cardiac events, while 27 patients had 33 cardiac complications. He also presented long-term follow-up evaluation data for Cohort I at 24 months and for Cohort II at 12 months. Of the 97 patients discharged with 109 PAS-Port implants, 4 of the 97 died and 5 declined to re-enroll in follow-up. Of the 84 who received a resting ECG evaluation, 100 percent were negative for myocardial infarction; of the 78 who received stress ECG evaluation, 93.6 percent did not show myocardial ischemia; and 100 percent did not require index graft revascularizations. Overall, he noted, the results for the patients in positive stress ECG compared favorably with the published literature.

In response to an FDA request to discuss the need for long-term antiplatelet therapy after the device is cleared for market, he noted that at 6 and 12/14 months, 74 percent of the cohort patients had been treated with aspirin therapy only. In response to

FDA concerns about MACE and the long-term safety of the device, they added three MACE events. In this revised analysis, there were 21 MACE events, 10 of which were index graft stenosis or occlusions. In comparing the two cohorts' MACE rates with the ARTS study published in *Circulation* (2004;109:1114-1120), they discovered that their rates were consistent with the literature.

Dr. Harringer wrapped up his presentation by stating that the results from the two cohorts show a favorable safety and efficacy of the device for CABG patients. He said that the data supports clearance for the Cardica PAS-Port system in the United States.

Daniel Bloch, Ph.D., Professor of Biostatistics, Stanford University, presented the sponsor's evidence supporting pooling of the data from Cohorts I and II. He stressed that both studies operated under predefined protocols, written prior to the studies' findings, with identically defined endpoints, and patency analyses performed by the same Core Lab. He noted that the patency results were all high across all 5 European study sites.

The 26 baseline demographic characteristics were compared for homogeneity, using Fisher's exact test or chi square test for qualitative data, and a two-sample t-test or Wilcoxon's two sample rank test to compare quantitative data. While there were differences among the variables, several are by design, he said: for example, the average age was purposely 3 years older in Cohort I than in Cohort II because the inclusion for the second cohort allowed older patients to be enrolled. As well, there were patients with more co-morbidities and cardiac involvement in the second cohort. Dr. Bloch pointed out, however, that the two cohorts were operating under different protocols, the biggest

difference being that in Cohort II the C-Port and the PAS-Port were both used. This prompted the FDA to ask Cardica for propensity score analyses to compare patency outcomes, adjusted for baseline differences.

In the first analysis using propensity score modeling, after considering all 26 variables, only three variables were found to have had a potential effect on outcome, with p values of less than 0.15.: smoking history, diabetes, and vessel disease. Upon adjustment, the cohort patency rates were found to be not statistically different. After considering this analysis, the FDA expressed concern that the sponsor had not controlled for enough variables. In doing another propensity score analysis, the sponsor identified an additional five variables that differed between the two groups: age, weight, angina, Canadian Cardiac Score, and peripheral vascular disease. Dr. Bloch formed four strata from the propensity scores, then compared patency rates as defined by the four strata for each cohort on a per graft basis. Upon adjustment, he reported, cohort patency rates were still not statistically different, and had little impact on the assessment of the primary endpoint. Therefore, the two cohorts, according to Dr. Bloch, were poolable.

Michael J. Mack, M.D., Director, Cardiothoracic Surgery Associates of North Texas, began by offering a rationale for anastomotic connectors. His interest in anastomotic connectors centers on how they can facilitate less invasive CABG surgery by shortening the time and increasing the accuracy of beating heart CABG surgery; by eliminating endoscopic suturing; and by creating a more uniform, reproducible, and possibly better anastomosis outcome when compared with sutures.

To support his contention that all anastomotic connectors are not the same, Dr.

Mack compared the PAS-Port device with historical suture controls, with current suture outcomes, and with Symmetry device outcomes. He presented a meta-analysis of literature, looking at saphenous vein graft (SVG) patency rates at 30 days, 3 to 6 months, 12 months, and 2 to 5 years. The overall vein graft patency rate was 83.9 percent.

His overview of the outcomes of current SVG patency trials included the Portland Endoscopic SVG Harvest (6-month angiographic patency rate=69.1 percent; arterial grafts patency rate > 90 percent), the Prevent IV Trial (one-year angiographic patency rate=64 percent; arterial grafts patency rate in the 90 percent range), and the Prague-4 Trial (one-year angiographic patency rate=52.5 percent). With these numbers in mind, he suggested that the 91 percent patency rate of the Cardica PAS-Port compares very favorably with the current trials of SVG patency.

According to Dr. Mack, this raises the question as to why current SVG patency rates are so different from historical controls. One answer, he said, is that surgeons currently have inferior target vessels on which to operate. A second answer is that there has been an increased use of arterial grafts, and those arterial grafts go to the best vessels.

Finally, Dr. Mack compared the clinical outcomes of the Symmetry device with the PAS-Port device. At 12 months, the Symmetry device produced a patency rate of 77.4 percent, as compared to 91 percent for both Cardica device cohorts.

He defined MACE as death, myocardial infarction, and target revascularization, and asserted that it does not include graft occlusion or stenosis discovered on surveillance angiography. But, he said, in the FDA packet and previous presentations, grafts discovered on surveillance angiography are inappropriately included in MACE data. The MACE rate using surveillance angiography will typically be about twice as high as a

clinical MACE rate. When he examined the Cardica trial data using his definition of MACE, the MACE rate is 11 percent (12/109 patients). This includes 6 deaths, of which 4 were clearly not cardiac-related but should still be included in MACE. One patient had MI, and 5 patients underwent target vessel revascularization with no clinical events. He stressed that, from his vantage point, the Cardica device is not the same device as the Symmetry device.

PANEL MEMBERS' QUESTIONS

Dr. Hausen responded to a question from the Panel about how patency rates were calculated, stating that the sponsor calculated it on a per graft basis versus for individual patients. There was a question about why the sponsor relied on the withdrawn Symmetry device as a predicate device, yet stated that their device is different than the predicate device. Dr. Hausen answered that they submitted their device for approval before Symmetry had been withdrawn from the market. They did not want to withdraw their submission of the PAS-Port device. Dr. Zuckerman noted that it is legitimate for the sponsor to continue using the Symmetry device as a predicate device because Symmetry's withdrawal was voluntary.

Dr. Hirshfeld asked the sponsors why they stated that one of the primary benefits of the device is to prevent complications of aortic cross clamping, while all implants were done on bypass. He wondered whether the value of the device has been overstated for prevention of aortic cross clamping. Dr. Hausen said he was careful to present this as inference.

The Panel continued along this line of questioning by asking why the sponsor

suggested that one advantage of the implant is to provide greater selection of implantation sites versus freehand. Dr. Hausen responded that with the Cardica device a surgeon can access the descending aorta and other parts that are typically accessible with very limited visibility. Dr. Blackstone expressed concern that while the sponsor is promoting the device for use in more sites, without clamping, the very first contraindication for use of the device is for use in sites that one would not use with clamping. Dr. Hausen stated that they need more data to support his comments about the increased access to additional sites, but they wanted to be conservative in the instructions for the U.S. market.

The Panel discussed how the device, versus a hand sewn anastomosis, may promote kinking. The sponsor's study, according to Dr. Hausen, examined the take-off angles of the vein and found that the device did not increase the probability of kinking, thanks to the low profile of the implant. Additionally, he said that all of the kinks they saw in the study were from hand sewn grafts used with the C-Port device. He stated that in Cohort I the average rate of patency was 82 percent for hand sewn grafts, more like the historical controls.

Dr. Borer asked whether the sponsor's data could be compared with historical controls, given the changes in techniques and patency rates between the 1970s and 2000. He and other Panel members expressed concern about the small size of the two cohorts, and why the sponsor did not randomize initially to the C-Port device versus hand sewn in Cohort I. Dr. Hausen responded that it was a timing problem, noting that the enrollment for the studies was completed before last year's Panel meeting. The objective criteria requirements were presented to the sponsor then, and they had to meet these using

previously designed studies. This prompted pooling of the data for the two cohorts. Randomizing would have been preferable, but they would have needed a sample size of 500-600 patients. Dr. Maisel noted that this issue was raised in last year's Panel meeting. The result of that discussion was that the FDA decided on an 85 percent patency rate with a lower confidence interval of 80 percent.

Dr. Hausen discussed the sponsor's registry that looks at MACE events and the incidence of angina. They now know that 1 percent of patients came back with angina., what one would expect in this patient cohort. Questions about healing arose; Dr. Hausen reported that within 3 months of the procedure the graft is completely healed into the aorta.

The Panel raised a question about whether the device has been adequately tested in the kinds of vessels found in the United States versus Europe, and how this would influence the patency rates presented by the sponsor for the device. Dr. Harringer stated that, looking at the Core Lab information, they believe they are comparable.

FDA PRESENTATION

Kachi Enyinna, M.S., Scientific Reviewer, Circulatory Support and Prosthetics Devices Branch, went over the Cardica device's engineering features. The implant itself is made of laser-cut, medical grade 316L stainless steel tubing, with nine barred prongs designed to penetrate through the vein graft after inversion; the device also includes a delivery system.

He discussed the device's similarities to its predicate, the Symmetry device. Both systems deliver and implant a metal star-shaped connector that provides for hemostatic

anastomosis between the aorta and the saphenous vein during CABG surgery. While it does perform similarly to the Symmetry system, it may include some changes made in response to the problems discovered in the predicate after widespread use. This includes system integration with arteriotomy creation and capture and implant deployment on one step; no conduit cannulation; a reduced profile; and a reduced amount of metal-to-blood contact. However, some of the Symmetry's controversial features remain in the PAS-Port device: exposure of metal to blood is reduced but still present; and a noncompliant annular containment still exists at the circular orifice with stent-like scaffolding conducive to kinking.

Mr. Enyinna summarized the performance testing conducted on the device: the test samples met and passed the set minimum performance criteria. He also noted that the device passed tests for mechanical safety and preclinical testing. He briefly covered the history of the device's approval history, noting that since the last Panel meeting in 2004, the Symmetry device has been withdrawn from the market, the Bypass Maakafim CorLink AAD has not been marketed, and the Coalescent U-Clip is being marketed as a suture—all listed as predicates for the Cardica device.

Mr. Enyinna described the device modifications made between Cohort I and Cohort II. The most recent version of the device was only tested in human tissue models using an aorta and saphenous vein, not considered adequate to address the device malfunction rate. The changes are as follows: at the top of the implant, the part edges were shifted up by 0.0007 inches; the large barbs have been replaced with three small barbs; and the discard section has been changed to a full mesh and slightly lengthened.

He concluded by stating that the sponsor has not performed fatigue testing on the

final version; as well, fatigue lifetime determination should be performed on the final product. The sponsor must provide documented evidence of fatigue testing of one equivalent use under similar physiological conditions on the final product before any type of clearance can be granted.

Barbara Krasnicka, Ph.D., Statistician, Office of Surveillance and Biometrics, focused on concerns the FDA had with the sponsor's study design and statistical analyses. She noted that the sponsor's submission was based on four studies: the Pivotal Study conducted under Investigative Plan CP2001-01 (Study 1); CP2004-03, a prospective, nonrandomized, multi-center follow-up study intended to evaluate patients' long-term health from Study 1; the C-Port study, conducted as the Investigational Plan CP2002-02 (study 2); and a prospective, non-randomized, multi-center follow-up study to evaluate the health of the C-Port patients at about one year.

In Study 1, Dr. Krasnicka noted that lower confidence limits of the 95 percent confidence interval for the patency rates for different methods of assessment are all below the recommended 80 percent level. As well, she highlighted problems with the MACE evaluations in the sponsor's study. The MACE rate at 6 months *plus 15 days* (13 percent) was considerably higher than the sponsor's results at 6 months (4.4 percent). Only 71 percent of the 55 patients enrolled in the study were evaluated by angiography at 6 months. In addition, 7 patients who withdrew at the baseline were re-enrolled for the 2-year evaluation. But only 4 of these patients received the stress ECG test. Despite that, the sponsor qualified all 7 patients as MACE-free after 2 years. She expressed concerns about the study's safety endpoints, noting that 2 patients died during the follow-up period

between 6 and 24 months. As well, there were 10 technical failures of the device in 8 patients that were not included in the adverse events analysis. She noted a number of factors that may have limited analyses in this study, for example, the effectiveness endpoint was not met for the 55 patients, for per protocol, or for the observed populations. In addition, the point estimates and limits of confidence intervals may have been biased.

In comparing the two studies, Dr. Krasnicka noted that the PAS-Port system used in the pivotal study and in Study 2 were not exactly the same due to the improvements made on the device. As well, she asserted that the populations in the two studies were not comparable because of the patients' pre-operative and intra-operative covariates.

As far as the sponsor's propensity score analyses, Dr. Krasnicka stated that these could not provide the needed justification for pooling the two cohorts for three reasons: the scores were based on only three covariates; some important covariates (such as surgery length) were not included in the analysis; and the data sets were very small.

In her conclusion, she stated that the propensity score distributions for the pivotal study and for Cohort II did not support pooling the data. She stressed that a subset of the Cohort II data cannot be considered a separate clinical study. The pivotal study itself did not provide evidence of the device's safety and effectiveness, and that the point estimates for the safety and effectiveness endpoints could be biased because of the *post hoc* nature of the analyses and the considerable lack of information

Wolf Sapirstein, M.D., Medical Officer, Division of Cardiovascular Devices, presented the FDA's clinical review of the device. He began by stressing that for a 510(k)

clearance, the predicate device may be used to demonstrate equivalence in function, but not to provide materials for comparison to the device under consideration. Primarily, he stated, he had questions on how the data provided by the sponsor can be interpreted. He noted that the FDA had no input on the protocols on either Cohort I or Cohort II; they only suggested some of the criteria required for clearance after the studies were conducted. In the Cohort I study, because of failure to comply with a stipulated angiography, the sponsor undertook sensitivity analysis of patients. He noted that their results of the intention to treat analysis did not meet the protocol hypothesis for effectiveness.

In Cohort II, according to Dr. Sapirstein, the selection bias inherent in the patient recruitment process was compounded by the PAS-Port device use being determined by the surgeon. The improvement in effectiveness shown in this study should be viewed with caution, he said, because of the possible effect of a learning curve, the recruitment process, and changes to the device. He reviewed how patency was imputed by the sponsor; the FDA realized that angiography is an invasive evaluation that is difficult to perform one year after the procedure, which is why they insisted on stress ECG as a screening test.

Dr. Sapirstein described the studies' designs limitations. He noted that the first cohort did not meet the prespecified effectiveness hypothesis; that the poolability of the two cohorts' data is suspect; that angiographic follow-up of patients was incomplete because the sponsor relied on imputations of noninvasive technologies to assess patency; and that the sponsor's attributing several adverse events as non-device related is questionable.

PANEL QUESTIONS FOR THE FDA

Dr. Krucoff began the FDA question session by asking about the definition of patients included in the category “intention to treat,” and whether these patients’ outcomes included or excluded from the calculations for the safety and efficacy of the device. Dr. Krasnicka said that they were considered enrolled.

Dr. Blackstone stated that he was concerned about the differences in the results of the two propensity scores. He asked how this can be if they are picking variables from same group. He added that this seemed to be the critical issue for the day, because if the Panel supports the FDA’s analysis that they are not poolable, the data from Cohort II cannot be used.

Panel members raised concerns about the quality of the data and the problem of drawing inferences from the small numbers of patients, as well as using less invasive procedures than angiograms for evaluation. Dr. Sapirstein agreed that the sponsor’s statistics for safety and efficacy were not sufficient given the public health impact this device could have.

Discussion ensued about whether or not the differences in patency between Cohort I and II could be explained by the fact that Cohort II deployed the Cardica device with improvements and changes. The FDA noted that changes and improvements are a positive thing but these must be validated and the sponsor must have documented evaluations of the new device before it is released to market. Dr. Zuckerman, however, urged the Panel to leave the engineering concerns to the FDA and focus on the clinical issues.

Dr. Hirshfeld expressed a desire for some historical guidance on how to make sure the case of the Symmetry device—in which the problems were discovered only on the postmarket surveillance period—does not repeat itself here. He raised the question of whether the Panel and the FDA currently have the correct data needed to be more confident about this device than the Symmetry device. Dr. Sapirstein noted that only 6-month data was available for the Symmetry device. However, he said that the FDA does not feel that MRI or computer technology is adequate to demonstrate significant obstruction in an anastomosis device. Dr. Zuckerman assured the Panel that the FDA has learned from prior device experience in this arena and they have attempted to convey that experience to industry. As well, if there is a concern about the post-market period with this class of device, the Agency, as per the presentations this morning, is assuming a new approach during the pre- and postmarket periods.

Dr. Yancy raised the question of whether there were any overt advantages of some of the changes made to the device, and whether these changes were instrumental in changing outcomes. Mr. Enyinna stated that he could not say with certainty whether the changes improved the outcomes of the second study. However, he asserted that this should be evaluated before clinical trials begin to determine if the device is safe enough to be implanted into patients. The sponsor's data, however, was post-implantation, and the proper procedure for performance testing was not applied, he said. Dr. Sapirstein stated that from a clinical point of view there seemed to be a clear advantage in using the newer device, but it remained unclear to what the improvement in outcomes can be attributed.

Panel members sought confirmation that sponsor conversations with the FDA

took place after the both cohorts had been enrolled. The first study had been completed and the second cohort had already been commenced. Both studies were undertaken without FDA input.

OPEN COMMITTEE DISCUSSION

Dr. Krucoff presented his primary review. He stated that the concept and ingeniousness of this device is apparent, but the fundamental question is whether there is data in humans to show it to be safe and effective. He noted that the study is working with not only small numbers of patients but also small numbers of events, as the failure rate for grafts from proximal anastomosis is very low when compared to hand sewn. The other unresolved issue is whether it can be known if events observed 5 centimeters distal to the proximal anastomosis are unrelated to the device. He also mentioned that angiographic evaluation is still the best way to understand how a device such as this one behaves anatomically. He stated that imputing from very small patient numbers may not necessarily be reasonable when combining assessment modalities.

Dr. Krucoff asked Dr. Mack about which graft is suitable for this device, versus a graft that should be hand sewn. Dr. Mack described the hierarchy of grafts. A surgeon would defer a saphenous vein graft to the least important vessel, for example. From his experience with the Symmetry device, he would use the device in both veins, but in the least important graft. He would use the Heartstream device that allows surgeons to do a clampless suture—although he stated that this would be cumbersome.

Dr. Krucoff asked the sponsors about the approval time line. Dr. Hausen stated that they met with the FDA in 1999, well before the first trial. They then submitted the

510(k) with 3 months of data well before the start of the second trial. There was some uncertainty on both sides as to what the data requirements would be, he said, as this was while the Symmetry device was coming under fire. The sponsors had to start the second cohort before the Panel met to maintain their CE mark in Europe. During all of this time, Dr. Hausen stated, there was an active correspondence, but not always with Dr. Sapirstein.

The sponsor related that the volume of bypass surgeries in the German centers was very high and very experienced: Hamburg was doing about 800 coronary bypasses annually, for example, and Dresden was completing between 2300 and 2500. Dr. Krucoff asked why, then, were there such small patient numbers for Cohorts I and II. Dr. Hausen said that the fact that these were invasive studies, including the follow-up angiogram, reduced the enrollment. He said that, in fact, they were very pleased with an 80 percent follow-up. The sponsors assumed that these numbers would suffice, following the example of the predicate device.

Dr. Borer presented his review. He expressed concerns about drawing conclusions from the small number of observations and the fact that long-term effects of the device could not be assessed. In addition, the sponsors provided no comparison of the population that actually received the device with an appropriate, historical control. He asked for clarification on the adverse effects as noted in the Panel's materials (page 17). Dr. Hausen responded that the adverse events listed are correct but the associations are not known in all of those patients with ischemia. Dr. Borer said that this sounds reasonable but that the sponsor is still inferring that there is no relationship; maybe the more conservative method would be to look at the worst case.

Dr. Maisel asked that the other Panel Members speak for a few minutes about their concerns about the device, and asking questions of the of the FDA or the sponsor. Dr. Hirshfeld asked whether the sponsor had a more quantitative analyses than the FitzGibbon scale to describe the percent stenosis within these devices. Dr. Hausen responded that in the first cohort, there were two devices with 32 percent stenosis, and the others were below 20 percent. In second cohort, the distribution was very similar.

Dr. Yancy asked for more clarification on the patency rates between Cohorts I and II. He wondered whether the patency rate was difference between the two cohorts because of surgeon decision in what device to use. He also wondered if the learning curve had an effect. Dr. Hausen answered that there was no real difference in the patency rates between the two cohorts. He believes, as well, that the surgeons actually decided with a negative bias, retrospectively.

Dr. Norman expressed concern about three areas: whether the data results from studies outside of the United States should be used; whether or not to pool the data; and how to construct the confidence intervals. She discussed with Dr. Bloch how he would assess the poolability of data.

Dr. Blackstone suggested that future studies should take into account that there may be multiple grafts per patient. As well, he said that there should be a better way to get wider confidence intervals than the ones seen in this study. He expressed concerns about the safety outcomes with regard to MACE. Dr. Mack restated the definition of MACE, noting that it includes death, MI, and index graft revascularization—not graft occlusion. Dr. Blackstone mentioned that some of the features of the Cardica device should have been compared with the hand sewn anastomosis, not with the Symmetry; the

Cardica device actually guarantees the narrowest vein, he asserted. Dr. Hausen responded that this is partially correct.

Dr. Ferguson asked about which group fell out in the “intent to treat” group. Dr. Hausen answered that 92 percent of vein grafts that were measured in the operating room were within these ranges, and that very few were excluded for being too small.

Dr. Somberg asked about whether the difference between PAS-Port device and Symmetry device MACE was significant. Dr. Hausen answered that the first year differences between the two devices were not significant. Dr. Hausen also shared some data from the registry in Japan and Europe.

Dr. Kato asked the sponsor why they enrolled such a small proportion of their patients in Europe in their study. Dr. Hausen noted that they submitted their study to the ethics committee as an observational study, which allowed them to expose only 50 to 60 patients to the risks associated with angiograms. Dr. Kato asked how the sponsor intended to improve on their follow-up rate in their U.S. registry. Dr. Hausen stated that it should be easier in the United States to gather this information, thanks to language and procedure familiarity.

Dr. Page expressed concerns that the next generation of surgeons may not be as well trained in CABG surgery as is the current generation. Dr. Mack acknowledged that the number of CABG surgeries is dropping, as is the number of cardiac surgeons. Devices such as the PAS-Port, in a sense, make the procedures more reproducible however. Dr. Hausen suggested that such procedures may even be on an outpatient basis in the near future.

Dr. Jeevanandam stated that anastomotic devices such as the Cardica device are

very important. However, he would have liked to have seen longer-term data given how the Symmetry device turned out.

FDA QUESTIONS

- 1. The sponsor did not achieve the patency objective in pivotal Study I and is attempting to pool data from a subset of Study 2 to remedy this failure. Please comment on the acceptability of pooling data from Study 1 and Cohort 2, discussing any limitations of this approach.**

Most Panel members expressed the sense that the data from both cohorts could be pooled, but not in the way undertaken by the sponsor; a stratified analysis of the pooled data would have made more sense and would have helped with the interpretation. While members appreciated the value of the data, they acknowledged that the data was not interpretable as presented. A few Panel members believed that the pooling of the data was acceptable, and Dr. Ferguson stated that he believed the sponsor did what was asked of them. Dr. Zimmer noted that these studies were not performed under IDE, and the FDA does prefer to interact with the sponsor during the IDE process to help define these issues.

- 2. Modifications were made to the PAS-Port device between Study 1 and Cohort 2. These modifications were made to address failures in device deployment. Do you have any concerns with the use of the combined data set given the changes in device design?**

Dr. Maisel stated that the Panel had concerns about the use of the data set given the device changes, but the data are potentially poolable.

- 3. The primary effectiveness endpoint for the combined data was the proportion of patent grafts at 6 months. Definition of patency is less than 50% stenosis. FDA recommends that the lower confidence limit of the 95% confidence interval for the proportion of patent grafts be greater than 80%.**

a. In the per protocol analysis, patency for 20 of 97 (20%) device patients who failed to have an angiogram was imputed from MRI (5), CT (5), Stress ECG (4),

and absence of symptoms (3). One patient lost to follow-up and 2 deaths were listed as occluded grafts. Please discuss whether this is a sufficiently robust assessment for this device.

Dr. Maisel said that most of the Panel, from last year's discussion, recognized angiograms as the "gold standard" for evaluation, but most seemed willing to potentially accept MRIs and CTs for this purpose. He did note, however, that he has some concerns about the fact that the MRIs and the CTs were not analyzed at a Core Lab, and that these modalities are not equivalent to angiograms; other Panel members echoed this concern.

b. In the intent to treat analysis, 9 of the 12 patients who converted to hand-sewn anastomoses following failed deployment of the device, had "patency" imputed with data from stress-ECG in 7 cases and from absence of cardiac symptoms in 2 cases. Insufficient follow-up data were available for three patients and for that reason imputed as "occluded." Please discuss whether this is an acceptable assessment of outcome for 12 of the 109 patients that constitutes the intent to treat cohort analyzed?

Dr. Maisel noted that it was "very generous" of the FDA to call a hand sewn vein patent.

Dr. Somberg stated that an 80 percent follow-up with angiographic studies is the best that can be expected. Dr. Jeevanandam stated that there are safety implications related to this device working improperly not expressed in this study, because the patients were on pump and cross-clamped.

c. Is device effectiveness adequately demonstrated by the multiple angiographic and clinical analyses?

Most Panel members stated that while this may be a very attractive device, they did not believe that device effectiveness had been demonstrated by the multiple angiographic and clinical analyses. They specifically expressed concern about the small study size. A few other Panel members disagreed, noting that the sponsor fulfilled what the FDA asked it to do, and that the device did show efficacy and a patency rate; whoever, this was not necessarily the optimal way to accomplish it and randomized trials would have been better. In fact, the angiographic portion did demonstrate efficacy.

Dr. Zuckerman asked for clarification from the Panel as to what is the most important effectiveness data available. Dr. Krucoff stated that the available data is not adequate to assess the device, because clinical events may not provide evidence of what an angiogram can provide. Dr. Borer stressed that the study's numbers were very small, and that those patients lost to follow-up erode the Panel's ability to understand the endpoint. Dr. Hirshfeld said that the Cardica device could be a wonderful device but that the Panel does not have the data to support this; alternately, he feels that the data do not provide enough information to highlight any problems.

4. **Please discuss whether you believe the data provides reasonable assurance of safety for the proposed indications. In your discussion consider the critical importance of the aortic anastomosis to the patency of the CABG conduit that requires careful scrutiny of adverse events as they relate to the anastomotic device. Do you concur with the sponsor's assessment that the following adverse events were not device related:**

- a. **ECG ischemia assessed as unrelated to the device solely based on interpretation that the index graft did not supply the region of myocardial ischemia;**
- b. **Ischemia related to the index graft that resolved over the course of the study was not considered significant for conduit patency irrespective of coronary vessel bypassed;**
- c. **Hypokinesia in one case and inferior myocardial infarction in a second case were assessed as not device related although occurring in the region of index graft perfusion.**

Dr. Maisel noted that ischemia in territory unrelated to index graft doesn't seem related to the device. Any ischemia, hypokinesia, or MI in the territory of a graft would have to be evaluated, he added. Most of the Panel members agreed. One panel member suggested that these events may be actually procedure-related, as there are multiple processes involved in using this device. This may be the more conservative approach. Dr. Maisel stated that he was not personally comfortable with the number of adverse events.

5. **Taking into account all pertinent clinical information available as well as your responses to the above questions, please comment on whether you believe the data provides an overall risk/benefit ratio which supports marketing clearance of the device in the United States for the proposed indication.**

The Panel generally agreed that the data does not provide an overall risk/benefit ratio supporting the marketing clearance of the Cardica device in the United States for the proposed indication. Drs. Hirshfeld, Yancy, Krucoff, Normand, Borer, Ferguson, Kato, Page, Jeevanandam, and Maisel stated no. Members did wish to commend the sponsor, however, on designing an ingenious device and they expressed the hope that the outcome of this Panel would not halt the eventual development of the device, given sufficient data provided. Dr. Somberg stated that he believed the device could be approved with an adequate and mandatory registry. Dr. Maisel commended the sponsor for changing the device in midstream.

6. **The indications state that the PAS-Port System is intended to create an everting anastomosis between the aorta and an autologous vein graft. The PAS-Port System has only been studied in CABG procedures involving the unique coronary circulatory system. Please comment whether the indication should be restricted solely to this use which is consistent with their instructions for use (IFU)?**

Dr. Maisel said that the indication for the device should state that it must be used only for CABG, with no expansion of use.

7. **The anastomosis created with the PAS-Port device has many characteristics of endovascular stenting, i.e., circumferential splinting and exposure of subintimal tissue and of blood stream to bare metal. The report of adverse events noted two episodes of conduit thrombosis and the occurrence of distal anastomotic obstructions that could reflect embolic episodes. Should a regimen of antiplatelet coverage be advised with use of this device?**

The Panel agreed that there is not enough data to comment on this. Dr. Maisel suggested that anticoagulant studies be included in any future studies requested by the FDA. One member noted that nearly all of the patients were on a some sort of an antiplatelet regimen, and this fact should be reflected in the device indications.

8. **The IFU indicates that a mean arterial pressure of at least 50mmHg for deployment of the device. This suggests the use during beating heart or off pump CABG or the performance of all proximal anastomotic use before cross-clamping the aorta. This will require estimation of conduit lengths for multiple CABG procedures at an early stage of the operation, possibly compromising bypass grafting performed. Should this potential problem be indicated with a warning in the labeling?**

Dr. Jeevanandam stated that most surgeons would know to measure the conduit length before they do their bypasses; Dr. Kato concurred.

9. **The stented circular anastomosis created with the device has an inherent propensity for kinking. This is addressed generically in the precaution section of labeling. This complication is particularly problematic with right coronary revascularization. Should use of the device be restricted for CABG procedures for the circumflex area of myocardial perfusion?**

Dr. Maisel stated that there was nothing in the Cardica device that suggested that right coronary arteries should be excluded from its indications. Dr. Krucoff suggested that there be a focus on training to avoid kinking instead of labeling in this area.

10. **Please provide any other recommendations or comments regarding the labeling of this device.**

Dr. Maisel suggested that the labeling should reflect the patient selection criteria as seen in the cohorts so physicians know what to expect. As well, the training should be opened up beyond formal Cardica training. Dr. Kato said that the label should warn that the mere use of this device will not reduce the risk of stroke in patients.

11. **If the data provided are not adequate to support safety and/or effectiveness, what additional data, analyses, or studies would you recommend?**

Dr. Krucoff stressed that this device is a step in the advance of medicine, but it is an invasive procedure and requires a “real” clinical trial. He would encourage U.S. enrollment; urge careful attention to the anatomic characteristics of the aortas that are included or excluded; draw attention to the structure of the endpoints that reflect the anatomic behavior of anastomosis; and be very systematic as to adjunctive therapy. He said he would like to see power calculations to create as complete characterizations of the

patient group as possible. This may require hundreds of patients on the safety side of the calculations because this device could potentially be used in as many as 300,000 humans.

Dr. Zuckerman asked Dr. Norman to expand on the pooling of data and her earlier suggestion of a stratified analysis. Dr. Norman responded that additional data are definitely needed. Dr. Zuckerman asked Dr. Krucoff about the need for U.S. data. Dr. Krucoff said this is very important, otherwise there are too many assumptions that would have to be made. Dr. Hirshfeld said that any future trials should be done on beating heart operations and not bypass operations. Dr. Borer stated that he would favor randomized control trials, but the key issues to be answered are necessarily appropriately done with a randomized control trial. A randomized control trial would give the Panel and the sponsor a better sense of whether the data were comparable with hand sewn grafts. If such a trial is not feasible, he would be pleased to see an additional study performed with stringent enrollment, analysis, and procedure criteria.

OPEN PUBLIC HEARING

There were no speakers during this session.

ADDITIONAL FDA COMMENTS

Dr. Sapirstein stated that the FDA did have an interaction with Cardica about the study in April 2003, in which they made clear their feelings about the confidence bounds. The FDA sees any anastomotic device as a replacement for suturing and as such relies on patency.

ADDITIONAL SPONSOR COMMENTS

There were no additional comments from the sponsor.

COMMENTS FROM INDUSTRY AND CONSUMER REPRESENTATIVES

Industry Representative Deborah Moore, Proxima Therapeutics, Inc., stated that because this device study was not conducted under an IDE doesn't mean that good clinical protocols were not in place. She said that the data may be salvageable, and that she believed the safety of the device was demonstrated; the registry speaks to the safety issue and this should be taken into consideration. These issues could be addressed in the postmarket study.

Consumer Representative Linda Mottle, MSM-HSA, RN, CCRP, GateWay Community College, said that she would want more safety data and tighter indications on labeling consistent with the clinical trails. She added that she would like to see the device approved and implemented after gathering additional data.

FINAL PANEL COMMENTS

Dr. Krucoff said that this situation is a good case in point that patients are better off when issues are resolved before the device is on the market.

Dr. Maisel adjourned the meeting at 4:29 p.m.

I certify that I attended this meeting
of the Circulatory System Devices
Advisory Panel Meeting on April 22,

2005, and that these minutes accurately reflect what transpired.

Geretta Wood
Executive Secretary

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

William H. Maisel, M.D.
Chairperson

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