

SUMMARY MINUTES

MEETING OF THE CIRCULATORY SYSTEM DEVICES ADVISORY PANEL

OPEN SESSION

October 2, 2003

**Gaithersburg Hilton
Gaithersburg, MD**

**Circulatory System Devices Advisory Panel Meeting
October 2, 2003**

Attendees

Acting Chairperson

Warren K. Laskey, M.D.
National Naval Medical Center

Executive Secretary

Geretta Wood
Food and Drug Administration

Voting Members

Salim Aziz, M.D.
University of Colorado

Cynthia Tracy, M.D.
Georgetown University Hospital

Consultants

Thomas Ferguson, M.D.
Washington University School of Medicine

Mitchell W. Krucoff, M.D.
Duke University Medical Center

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

Douglas A. Morrison, M.D.
University of Arizona

Gary G. Nicholas, M.D.
Lehigh Valley Hospital
Allentown, PA

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

John C. Somberg, M.D.
Rush University

Christopher J. White, M.D.
Ochsner Clinic Foundation

Industry Representative

Michael C. Morton
CarboMedics, Inc.

Consumer Representative

Allen Hughes, Ph.D.
George Mason University

FDA Participants

Bram Zuckerman
Director
Division of Cardiovascular Devices

John P. Holden, Ph.D.
Lead Reviewer

Wolf Sapirstein, M.D.
Clinical Review

Barbara Krasnicka, Ph.D.
Statistical Review

CALL TO ORDER

Acting Panel Chair Warren Laskey, M.D., called the meeting to order at 9:01 a.m. and stated that the purpose of the meeting was to discuss and make recommendations on PMA P910001/S022 for the Spectranetics CVX-300[®] Excimer Laser System to treat critical limb ischemia (CLI). **Executive Secretary Geretta Wood** read the conflict of interest statement. Mitchell Krucoff, M.D., and Christopher J. White, M.D., were given full waivers for their interests in firms for matters that could be affected by the panel's recommendations. She added that FDA took into consideration other matters regarding Dr. Krucoff's and Cynthia M. Tracey's, M.D., past or current interest involving firms at issue but in matters not related to the day's agenda. She also noted that Industry Representative Michael Morton has reported interest in firms at issue. Dr. Laskey then asked the panel members to introduce themselves.

Ms. Wood read the appointment to temporary voting status. Panel consultants Thomas Ferguson, M.D., Sharon-Lise Normand, Ph.D., Mitchell W. Krucoff, M.D., William Maisel, M.D., M.P.H., Douglass A. Morrison, M.D., Gary G. Nicholas, M.D., John C. Somberg, M.D., and Christopher J. White, M.D. were appointed to temporary voting status for the duration of the meeting. Dr. Laskey was appointed as acting chair for the duration of meeting.

OPEN PUBLIC HEARING

No comments were made.

SPONSOR PRESENTATION: PMA P910001/S022

Chris Reiser, Ph.D., vice president for Technology and Clinical Research at Spectranetics, introduced the sponsor presenters and gave a brief background of the

development of the excimer laser. The CVX-300[®] uses a XeCl laser that emits a pulse of ultraviolet light at 308 nanometers through fiber optic catheters, and was first approved in 1993 by the FDA for use in coronary arteries. Dr. Reiser noted that this system is currently being used in the United States for coronary atherectomies and pacing lead removal, and in Europe for peripheral atherectomies. The fibers deliver the UV light directly to the tissue, directly penetrating about 50 microns into the tissue.

Dr. Reiser said that they became interested in using the system for peripheral arterial disease (PAD) when they noticed that PAD shared some of the same indications as cardiac disease. In February 1999, FDA approved the Laser Angioplasty for Critical Limb Ischemia (LACI) Phase 1 Registry. LACI Phase 1 was a 25-limb study using excimer laser atherectomy to open blocked arteries near or below the knee in patients presenting non-healing ulcers or gangrene. This study resulted in limb salvage for 70 percent of patients who were poor surgical candidates. Based on this and other data, FDA approved a pivotal trial, LACI Phase 2, in January 2001.

John Laird, M.D., Washington Hospital Center, presented the protocol and results of the LACI Phase 2 Registry. He said that the patients in this study had CLI with advanced PAD, and classified in the literature as Fontaine III or IV, or Rutherford 4, 5, or 6. Only a minority of patients presented with lesions suitable for balloon angioplasty. Dr. Laird referred to the patients chosen for the study as “no option” patients.

Dr. Laird discussed why the LACI 2 study was not randomized. The investigators decided to include patients in the trial that were poor surgical candidates, which removed surgical by-pass from the randomization scheme. Percutaneous transluminal angioplasty (PTA, or balloon angioplasty, was rejected as an appropriate randomization strategy for

these patients because the results of previous trials in the literature were variable, retrospective single-center studies; in addition, there have been no randomized trials comparing PTA with other therapies in the past 15 years. He added that the TransAtlantic Inter-Society Consensus (TASC) Working Group document recommends PTA for CLI only in simple lesions. In fact, Dr. Laird noted, about 88 percent of patients in the LACI 2 trial had TASC lesion types C and D, with complex patterns and long diffuse disease. He added that that no study in the literature has made balloon angioplasty the “gold standard” in treating CLI.

Given these limitations, Dr. Laird said that the investigators decided that their best option was to use historical controls for the LACI 2 study. They decided to use an Italian multi-center randomized study of prostaglandin E1 in CLI patients, published in *Annals of Internal Medicine* in 1999, by the Ischemia Cronca Critica degli Arti Inferiori Study Group, or ICAI. The study conformed to the TASC definitions and good clinical practices, he noted. Dr. Laird discussed the details of the Italian study, stressing that ICAI statistics set a high benchmark for the standard of care in CLI patients, with lower or expected levels of mortality compared to the published literature for CLI, and a low frequency of major amputation.

Dr. Laird next presented the LACI 2 study design. He noted that LACI 2 is the first study of its kind, being a prospective, multi-center study evaluating a device for the treatment of CLI. LACI 2 patients had CLI with a Rutherford category of 4 through 6, and were felt to be poor surgical candidates because they had at least one of the following conditions: poor or absent vessel for outflow anastomosis; absence of a venous conduit; American Society of Anesthesiology (ASA) classification of 4 or higher for high risk of

surgical morbidity. The treatment consisted of ELA of the superficial femoral artery (SFA), popliteal and/or infrapopliteal arteries with adjunctive balloon angioplasty and optional stenting. The study used laser catheters no larger than 2.5 mm in diameter. The primary effectiveness endpoint of the trial was limb salvage (freedom from amputation at or above the ankle) at 6 months, and the primary safety endpoint was death within 6 months following the procedure.

A total of 145 patients with 155 legs were enrolled in the study between April 2001 and April 2002 at 14 sites, including three German sites. In general, according to Dr. Laird, there were significant differences in patient morbidities between the LACI trial and the control group; for example, nearly half of the patients in the LACI group were women, compared to 28 percent in the control group, and 66 percent of the LACI patients suffered from diabetes mellitus versus 39 percent in the control group.

Dr. Laird presented two case profiles of patients enrolled in the LACI 2 study, and also viewed several sets of patient photographs that documented baseline conditions and follow-up at three and 6 months, using digital morphography to measure the area of the ulcers. Dr. Laird noted that they have collected a large library of such photographs.

Dr. Laird provided the panel with results from the LACI 2 trial, including information about lesion types, LACI procedure results, and angiographic results. Stent implantation was performed in 45 percent of cases and adjunctive PTA was performed in 96 percent of cases. Procedure success, defined as less than 50 percent residual stenosis in all of the lesions treated in a given limb was 85 percent. Straight line flow to the foot was established in 89 percent of the cases. Half of the improvement in luminal gain

following intervention was a result of ELA. The median hospital stay was 1 day; mean was 3 days. He also presented representative angiograms from the study.

Dr. Laird discussed the treatments performed in the ICAI control study, noting that 43 percent of patients underwent some kind of surgery or angioplasty, while 57 percent underwent more conservative supportive care with such treatments as analgesics, oxygen therapy, etc.

Comparing the two study groups for serious adverse events, Dr. Laird asserted there was no difference in terms of mortality or major amputation, and nonfatal myocardial infarction (MI) or stroke. However, he noted a higher re-intervention rate in the LACI 2 group, 17 percent versus 4 percent. He explained this by noting that the 4 percent reflects the entire control study, and that among the 43 percent of control patients who underwent some surgical or angioplasty treatment, the re-intervention rate is 11 percent. He said that this makes the 17 percent in the LACI 2 group compare favorably with the control and any other study. Dr. Laird added that the incidence of LACI patients with acute limb ischemia or the need for bypass surgery or endarterectomy was low during the follow-up time period.

Dr. Laird went over the study's 6-month results. The data can be analyzed several ways, he said. Looking at the data on a per patient basis, the study enrolled 145 patients; 15 patients died during the follow-up period, with 2 dying after having gone through major amputation. Eleven patients were lost to follow-up, leaving 119 patients who reached their 6-month endpoint. Major amputation was required in 9 of the 119, so 110 patients survived with limb salvage. Approaching the data using an "intent-to-treat analysis," considering all deaths and the loss-to-follow-up patients as treatment failure,

the limb salvage rate is 76 percent (110 patients with limb salvage out of the original 145 patients). Dr. Laird, asserted, however, that the more accurate way to analyze the data is to consider the numbers who survived: 110 patients (92 percent) survived with limb salvage out of the 119 patients who reached their 6-month endpoint. The results are similar when looking at the data on a per limb basis.

According to Dr. Laird, there was no difference between the LACI group and the control group when comparing the main endpoints at 6 months, so he feels that the study did not negatively alter the natural history of the LACI patients. He presented an analysis of the ulcer healing success and functional outcomes. He also looked at the impact of stenting in the study, noting that there was no statistical difference in the limb salvage rate between those limbs that were stented and those that were not.

Dr. Laird ended his presentation by noting that the outcomes met all of the hypotheses in the study protocol, and the statistics met the benchmarks of safety and effectiveness. He also covered the clinical benefits of the LACI treatment, including limb salvage without affecting patients' chances of survival or significantly increasing their risk of serious adverse events.

Panel Questions for the Sponsor

Dr. Krucoff asked Dr. Laird about the learning curve in applying this technology to CLI. Dr. Laird said that he had no data but that he sensed that the learning curve was relatively short. Dr. Somberg asked what would happen to these patients, given that they were not good surgical candidates, if they had not received ELA. Dr. Laird thought that a significant percentage might have been treated with amputation, while some would have

been referred to surgery and received a distal bypass with synthetic grafts, and others may have undergone PTA or other modalities.

Dr. Laskey suggested that some of the statistics had been glossed over in the sponsor's presentation, and asked why a delta of 10 was chosen. Dr. Reiser responded that [his response is not on the microphone so it's unintelligible]. Dr. Normand asked what the delta would have been if the two populations had been randomized, but Dr. Reiser said that this issue never came up. Other questions about the study included those regarding perforation of vessels, the definition of "inadequate venous conduit," the number of ASA class 4 patients, and problems resulting from the lack of raw data from the Italian study.

FDA PRESENTATION

John P. Holden, Ph.D., Division of Cardiovascular Devices, FDA lead reviewer, presented the FDA Review Team for this PMA and provided a history of the clinical trial and the PMA application. He read the proposed indications for using the CVX-300[®] Excimer Laser System in treating CLI, as well as the device description. He noted that the device description also includes 15 models of the Spectranetics ELA catheters. The three types of catheters evaluated in the LACI trial included over-the wire (Extreme and Extreme II), rapid exchange (Vitesse), and eccentric (Vitesse E). He noted that the peripheral catheters underwent preclinical testing, and that there were not additional questions about this from FDA. Dr. Holden included in his history of the trial portions of the FDA conditional approval letter for the pivotal trial covering risk-benefit analysis and the necessity of showing that stenting did not confound the analysis of the study endpoints.

Wolf Sapirstein, M.D., Division of Cardiovascular Devices, provided the FDA's clinical summary. Dr. Sapirstein went over the LACI 2 study's design and a description of the patient population. He said that, because of the study's single-arm design and historical control, the outcomes from this study were open to conflicting interpretations. However, he added that the study was well-conducted and monitored. Dr. Sapirstein discussed the problems faced by the sponsor because of their choice to use an historical control, including lack of access to the original ICAI data, which made it difficult to compare many important secondary endpoints for the treatment of CLI in the two studies. He noted that the sponsor justified the nonrandomized design because there were no suitable alternative treatments for these patients. Dr. Sapirstein, however, asserted that a literature review shows that these patients can be managed with a variety of alternative treatments.

Dr. Sapirstein discussed the standards used to include patients in the LACI 2 study, and determined that significant differences exist between the study's planned criteria and its actual criteria. For example, only 46 percent were classed at ASA 4 or above, and only 32 percent did not have a suitable autogenous vein. Moreover, he noted that the sponsor's claim that the LACI patients were more comorbid and at a greater risk for poor outcomes than the ICAI patients can be disputed. In examining the LACI procedure, Dr. Sapirstein concluded that, because PTA was used in all of the LACI cases, the angioplasty alone might have been effective without ELA. Use of stents in 45 percent of the cases obscures the issue of successful treatment with ELA, as well, he said. He also noted that the incidence of required re-intervention was significantly higher in the LACI group versus the ICAI group, and persisting CLI was about 30 percent in both groups.

In the final analysis, Dr. Sapirstein said that while LACI did achieve equivalent patient survival with limb salvage as compared with the ICAI group, any benefit from this treatment was diminished by the high incidence of re-intervention and by CLI persistence. As well, the value of balloon angioplasty in the management of CLI remains unclear.

Barbara Krasnicka, Ph.D., Division of Biostatistics, said that her presentation would focus primarily on the problems with the LACI study's design and statistical analysis. She discussed the statistical analysis issues related to the study's primary effectiveness endpoint and for one of the secondary endpoints, survival time in 6 months of the follow-up. She expressed concern that there was no data at the individual patient level for the control group, only summary statistics.

Dr. Krasnicka discussed the sponsor's objective of showing that the results in the LACI group would be at least as successful as those in the control group. The FDA agreed to the study's equivalence design assuming that the LACI patients were sicker than the control patients. The primary effectiveness endpoint was met in 75.9 percent of the LACI patients and in 73.4 percent of the control group patients, with a 95 percent confidence interval (-5.3 percent, 10.2 percent). Dr. Krasnicka said that these results show no statistical difference between the two groups.

Limitations to an analysis of the primary endpoint included the fact that the study was not randomized, making the treatment results uncertain, she said. The results may have been affected by the fact that the LACI patients and the control group patients were not comparable, and the two studies took place in different hospitals and countries.

Additional factors affecting the results included the unavailability of raw data from the control group, missing data, and differing treatment modalities in the two groups.

Dr. Krasnicka examined one of the secondary endpoints, the survival time in 6 months, using Kaplan-Meier estimates. The visual impression of the Kaplan-Meier estimates suggested that the LACI patients could survive longer than the control patients. However, according to the Wilcoxon test, the difference between the two groups is not significant at the .05 level, where the P value is .1728. Dr. Krasnicka also looked at the limitations to an analysis of the secondary endpoint. These limitations included the heterogeneity of the LACI patients, which could affect treatment comparisons; non-stratified comparison of survival times; the interactions of covariates that could have influenced treatment effects; the differences between the LACI and control groups; and the use of ELA with adjunctive PTA. These limitations contributed to questionable survival analyses, she said.

Dr. Sapirstein concluded the FDA's presentation by providing the panel with a summary of their review.

Panel Questions for FDA

The questions for the FDA focused on the study's use of an equivalency hypothesis and the choice of a control group that differed with the LACI group in significant ways. A number of panel members expressed doubt as to whether equivalency proved treatment effectiveness in this trial.

Dr. Sapirstein noted that an equivalency hypothesis was accepted for effectiveness but not safety reasons, because the patients in the LACI group were facing inevitable limb loss. He said that the FDA believed the control group statistics to be

sufficiently robust. Dr. Zuckerman noted that FDA gave only conditional approval to the study design, and not a total endorsement of the trial.

Several panel members expressed concern about FDA guidance in this trial, the sponsor's reading of the literature, what the laser treatment added to other interventions and therapies, and whether the results of the ELA treatment could truly be understood given the study's design.

OPEN COMMITTEE DISCUSSION

After providing a brief summary of the study protocol, **Panel Member Gary G. Nicholas, M.D.**, presented his concerns about the LACI protocol. A stronger control group, he noted, would have received only balloon angioplasty and stenting without ELA. The lack of such a control group, Dr. Nicholas said, made it difficult to see the actual benefits of ELA. As well, the assumption that the LACI patients were less sick than the ICAI patients does not contribute toward the sponsor's argument of equivalency.

Dr. Nicholas continued his discussion of concerns by noting that the rates of patients reaching the primary safety endpoint in the two groups were not significantly different, and cast doubt on the medical fitness difference in the two groups. The multiple comparisons of the LACI group to the surgical and medical literature failed to achieve Level 1 or Level 2 evidence. For example, the control group contained a significantly larger number of men and current smokers than did the LACI group. In addition, the control group did not use the Rutherford classification for chronic lower limb ischemia. As well, the LACI study's inclusion of patients classified as Rutherford category 6 was questionable, as the stated protocol was limb salvage. Dr. Nicholas noted that the

sponsors indicated that they measured ankle indices upon patients' entry into the study and at regular intervals, but these data are not included in the proposal.

The effectiveness of the procedure is unclear, he said, because 6 months after the procedure 39 percent of the LACI patients remained in Rutherford class 4, 5, or 6; 43 percent in the control population also had continuing CLI. The information for the occurrence of adverse effects stops at 6 months, but Dr. Nicholas said he would be interested in knowing what happened to these patients after that period.

Dr. Nicholas asserted that the "gold standard" for care of CLI is distal bypass grafting with a venous conduit, and he expressed concern that the investigators did not evaluate their patients for alternate sites for venous conduits. He added that ASA classification 4, used by the study to include patients, is common among the patients of vascular surgeons.

LACI Investigator Venkatesh Ramaiah, M.D., Arizona Heart Hospital, responded to questions from the panel about the possibility of graftable vessels and the prominence of renal therapy in LACI patients. He stressed that the primary purpose of the study was to evaluate patients not appropriate for surgery.

Bruce Gray, D.O., Greenville Memorial Hospital and LACI investigator, addressed a panel question about the avoidance and use of stents in the study's patients. He noted that using a laser through an occlusion removes the chronic thrombus there, changing the conditions such that using a stent and a balloon becomes safer. Also, the number and length of stents are decreased with this method.

Dr. Reiser responded to a panel question about how the ICAI study was selected as the control study. He said that they did an extensive search in the balloon angioplasty

literature and in other modalities to find the standard of care for this particular patient group. Between LACI 1 and LACI 2 the ICIA study paper appeared, fulfilling the sponsor's desire to set a high benchmark and find a standard of care against which the LACI study could compete.

Dr. Reiser also responded to **Panel Member William Maisel's, M.D.**, question about the 128 patients who were screened out of the study, noting that no follow-up was done on these patients. Dr. Maisel suggested that this data would have been helpful. Dr. Laird also responded to Dr. Maisel's questions about the pace of re-intervention and whether 6 months was too short for a follow-up period, by noting that pace of serious adverse effects did not seem to increase as time progressed.

Christopher White, M.D., panel member, added his voice to the other panel members who commended the investigators for the execution of the trial, despite the disappointing design of the trial. He asked the sponsors about the average fluence per lesion, and Dr. Reiser said that the mean maximum fluence was 51 mJ/mm², mean repetition rate was 32 pulse per second, and mean laser pulses per limb were 5,371. Dr. White said he was concerned that angioplasty was not chosen as the design for this trial because he believes that the laser is actually an adjunctive treatment. He added that the data do not allow him to determine what the laser adds to the treatment of CLI. As well, he said that he does not believe that the treatment in the ICAI study is the standard of care for CLI patients.

Panel members brought up the issue that there are numerous studies in the literature that show good results with PTA, despite the sponsor's argument that many of the studies showed poor results. Dr. Laird discussed some of the literature, but stated that

the study showed excellent results, especially considering the difficult patient population, by using a strategy of laser first followed by other modalities. He noted that investigators did not want to randomize against a treatment they did not believe would work for these patients, such as PTA.

John C. Somberg, M.D., panel member, brought up the issue of the various techniques involved in using the ELA, and what could be learned from the fact that in about 13 percent of the LACI patients, investigators were not able to cross the lesion with a guide wire. Dr. Ramaiah noted that an important feature of the device was that being able to initiate the procedure with the laser still helped these patients. Dr. Somberg suggested that this possibly indicated a subset of patients to whom the laser should be made available, but that the weaknesses in the study's design precluded a complete understanding of this.

Dr. Krucoff, panel member, acknowledged that the investigators and sponsors were "passionate" about the work they undertook. He referred back to the FDA conditional approval letter and discussed with Dr. Reiser the possibility of the confounding effect of stents on the study's results and whether the sponsors looked at any quality of life measurements. Dr. Reiser said that the study did provide ISO standard risk analysis, but that was different than the traditional qualitative risk/benefit analysis. Dr. Krucoff said he believed that this patient population could be randomized against standard care, opening the door to other ways to gather information on risks and benefits that are not death or amputation.

Panel member Sharon-Lise Normand, Ph.D., asked about the appropriateness, from a statistical standpoint, of having less than 50 percent of the LACI patients ASA

class 4, or high surgical risk. Dr. Reiser said that this was a marker of expected mortality under surgical conditions. She noted that if she looked at the variables one at a time the LACI group appeared sicker and at other times the ICAI group seemed sicker. This made it impossible, according to Dr. Normand, to analyze the statistics and find the delta for these two groups, because they are not comparable. She also addressed the study's safety endpoint. The sponsor's contention that the LACI group is sicker prompts concern, she noted, about the lack of information related to this group's larger number of patients lost to follow-up. Dr. Normand also questioned whether the variables used to characterize the two cohorts, as well as the endpoint, are measured the same way for the two groups.

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No comments were made.

PANEL QUESTIONS

1(a) Please comment on whether or not the characteristics of patients in the LACI trial and the control group demonstrate an increased risk for limb loss in LACI, sufficient to justify the 10 percent difference for the primary effectiveness endpoint.

The panel concurred that there is not enough evidence to justify the 10 percent difference for the primary effectiveness endpoint and the entire concept of the study design because of the inability to compare the two groups.

1(b) An active intervention for limb salvage in LACI is compared to a control arm of non-intervention. Please comment on whether the outcomes for this endovascular procedure can be satisfactorily assessed without comparisons to balloon percutaneous transluminal angioplasty (PTA).

The panel concurred that the outcomes cannot be assessed or compared without more in-depth knowledge of the LACI patient population and the Italian study.

2. Re-interventions were significantly higher in the LACI study than the control group. Please comment on whether the adverse event data from the LACI study provide reasonable assurance of the safety of ELA used to treat CLI.

The panel concurred that the adverse event data from the LACI study provide reasonable assurance of the ELA safety to treat CLI, when compared to the literature. Two panel members expressed concern, however, about the upward trend of adverse effects, and whether that continued after the 6-month follow-up period.

- 3. The clinical objectives of the study were stated as: (i) protection from acute amputation; (ii) limb salvage; (iii) resolution of CLI; and (iv) preservation of surgical options. Please comment on whether the outcomes for the LACI study demonstrate that these objectives have been achieved.**

The panel concurred that the study provided a measure of safety but no convincing measure of efficacy.

- 4. Please comment on the added value provided by the laser therapy, which is used as an adjunct prior to the PTA required for final resolution of the lesion obstruction.**

The panel concurred that the study did not present enough data to understand clearly the added value provided by the laser therapy.

- 5. Please comment on whether the benefit demonstrated in this study, particularly with respect to quality of life-years, outweighs the adverse events that occurred and the persistence of CLI documented.**

The panel members commented that the sponsor did not provide enough information to make a judgment on whether the benefit of the treatment outweighs the adverse events.

- 6. Labeling for a new device should indicate which patients are appropriate for treatment, identify potential device-related adverse events, and explain how the device should be used to optimize its risk/benefit profile. If you recommend device approval, please address the following:**

- (a) Do the Indications for Use, as stated below, adequately define the patient population and procedural use for which the device will be marketed?**

The Spectranetics CVX-300[®] Excimer Laser System is indicated for facilitation of limb salvage in patients with critical limb ischemia (associated with Rutherford Categories 4, 5, and 6) who have angiographically evident culprit stenosis and/or occlusions in the SFA, popliteal and/or infrapopliteal arteries, who are poor surgical candidates, and who are acceptable candidates for revascularization.

The panel concurred that they could not address this question based on the continuing questions about the device's efficacy.

(b) Based on the study results, please discuss whether the proposed warnings, precautions, and contraindications are acceptable.

The panel concurred that the Indications for Use are well-written, given the questions about the device's efficacy.

(c) Please discuss whether the instructions for use adequately describe how the device should be used.

The panel concurred that the instructions for use should be clearer on nonprotocol approaches and technical nuances in the area of stents and guide wires.

7. Please indicate if the following findings are sufficiently robust to warrant incorporation in the label:

(a) The 110 LACI patients in Rutherford Clinical Categories 5 and 6 experienced 15 percent mortality and an amputation rate of 7 percent. This contrasted with 1 percent mortality rate and 2 percent amputation rate in 45 Category 4 patients.

(b) Seventy limbs in the LACI study also required stent placement. Stents were placed in 56 superficial femoral arteries (SFAs) in the 104 limbs with SFA lesions. Forty-nine (87.5 percent) of the SFAs with stents remained amputation-free at six months.

The panel concurred that both statements should stand as written.

8. The sponsor has proposed the following training requirements in the draft Instructions for Use:

The use of the CVX-300[®] Excimer Laser System is restricted to physicians who are trained in atherectomy, Percutaneous Transluminal Coronary Angioplasty (PTCA) and who meet the training requirements listed below. These requirements include, but are not limited to:

- 1. Training of laser safety and physics.*
- 2. Review of patient films of lesions that meet the indications for use.*
- 3. A review of cases demonstrating the CLiRpath catheters in lesions that meet the indications for use.*
- 4. A review of laser operation followed by a demonstration of the CVX-300[®] Excimer Laser System.*
- 5. Hands-on training with the CVX-300[®] Excimer Laser System and appropriate model.*
- 6. A fully-trained Spectranetics representative will be present to assist for a minimum of the first three cases.*
- 7. Following the formal training session, Spectranetics will make available additional training if so requested by the physician, support personnel, the institution or Spectranetics.*

Please comment on whether these training requirements are adequate.

Panel members requested that the use be restricted to physicians trained in peripheral

vascular intervention, not PTCA; that the qualifications for use include a physician

credentialed in angioplasty. Panel members discussed who would be best to assist with

training—a proctor, a company representative, or other. Dr. Laskey suggested that a patient information brochure be added to the materials.

Additional Comments

Dr. Laskey asked if the FDA has any additional comments. Dr. Zuckerman said they did not have any additional comments. He asked the sponsors if they had any additional comments. Dr. Laird acknowledged that there were limitations to the study's design. He also noted the challenges in trying to demonstrate efficacy against an historical control in which a majority of the patients did not receive an intervention. However, he said that he was confident that the sponsors had demonstrated safety and excellent results in this device in a population of very sick people.

Dr. Laskey solicited comments from the panel's industry representative. Mr. Morton recognized the work that went into the day's presentations and thanked FDA for clarifying the requirements for valid, scientific evidence.

Dr. Laskey then asked the panel's consumer representative, **Allen Hughes, Ph.D., of George Mason University**, for any comments. Dr. Hughes also commended the meeting participants for their presentations. He asked if the sponsors knew whether any of the LACI patients who had a limb amputated were good candidates for prosthetic devices. Dr. Ramaiah said that studies have shown that patients who undergo revascularization experience a much higher quality of life when compared with patients who must undergo amputation. Dr. Hughes also asked about alternative treatments and whether the ELA treatment is considered the last option before amputation. Dr. Laird responded that this was generally the case.

VOTE

Ms. Wood read the voting options. Dr. Nicholas moved to deny approval of the PMA; the motion was seconded. The panel voted 9 to 1 in favor of denying approval of the PMA. Dr. Laskey asked each panel member to state their vote and the reasons for their vote.

Several panel members stated that they felt that while there was a need for such a product, the sponsors must design a study with an appropriate control group that would allow the panel to approve this device. One panel member suggested that additional data supporting efficacy be presented, and that a human device exemption (HDE) path might be discussed for extremely sick patients. Another member suggested that a technical endpoint be used, and one suggested that the follow-up data be longer than 6 months.

ADJOURNMENT

Dr. Laskey thanked the participants and adjourned the meeting at 3:28 p.m.

I certify that I attended this meeting of the Circulatory System Devices Advisory Panel Meeting on October 2, 2003, and that these minutes accurately reflect what transpired.

Geretta Wood
Executive Secretary

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

Warren K. Laskey, M.D.
Chairperson

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