

SUMMARY MINUTES

MEETING OF THE CIRCULATORY SYSTEM DEVICES ADVISORY PANEL

OPEN SESSION

June 8, 2004

**Gaithersburg Hilton
Gaithersburg, MD**

**Circulatory System Devices Advisory Panel Meeting
June 8, 2004**

Attendees

Chairperson

Warren K. Laskey, M.D.
George Washington University

Voting Members

Salim Aziz, M.D.
Capitol Cardiovascular & Thoracic Surgery
Association

Mitchell Krucoff, M.D.
Duke University Medical Center

Cindy Tracy, M.D.
George Washington University

Consultants

Kent R. Bailey, Ph.D.
Rochester, MN

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

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

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

Joanne Lindenfeld
University of Colorado Health Sciences
Center

John C. Somberg, M.D.
Rush University

Judah Z. Weinberger, M.D., Ph.D.
Columbia University

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

Industry Representative

Michael Morton
Carbomedics, Inc.

Consumer Representative

Christine Moore
Baltimore, MD

Food and Drug Administration

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

Geretta Wood
Executive Secretary

Chul H. Ahn, Ph.D.
Biostatistician

Michael Berman, Ph.D.
Lead Reviewer

Ileana L. Piña, M.D.
Case Western Reserve University
Consultant

CALL TO ORDER

Panel Chair Warren K. Laskey, M.D., called the meeting to order at 8:07 a.m. **Panel Executive Secretary Geretta Wood** read the conflict of interest statement. A full waiver had been granted for Kent R. Bailey, Ph.D., for his interest in a firm that could be affected by the panel's recommendations. The Agency also took into consideration certain matters concerning Clyde Yancy, M.D., who reported current involvement with a firm at issue but in matters not related to the day's agenda; he could participate fully in the panel's deliberations. Dr. Laskey then asked the panel members to introduce themselves.

Ms. Wood read the appointment to temporary voting status. Panel consultants Kent R. Bailey, Ph.D., John W. Hirshfeld, M.D., Thomas B. Ferguson, M.D., Norman S. Kato, M.D., Joanne Lindenfeld, M.D., John C. Somberg, M.D., Clyde Yancy, M.D., and Judah Z. Weinberger, M.D., Ph.D., had been appointed voting members for the duration of the meeting.

OPEN PUBLIC HEARING

Dr. Laskey read the Agency's statement on transparency of the device approval process. No other comments were made.

SPONSOR PRESENTATION

Roderick M. Bryden, President and CEO, World Heart Incorporated, provided an overview of the sponsor's presentation and introduced the sponsor speakers and consultants. The sponsor had requested that the indication for the Novacor left ventricular assist system (LVAS) be expanded so that its intended use is for short- or long-term bridge to transplantation in cardiac transplant candidates and in patients with relative contraindication to transplantation who are

expected to become transplant candidates with mechanical circulatory support. Judgments about patient readiness for transplant will be made by transplant centers. World Heart is conducting a randomized controlled trial (RELIANT) and will submit data for a PMA for destination therapy when complete. The proposed indication, however, is distinct from a destination therapy indication. The goal is to help a class of end-stage heart failure patients who have relative contraindications to treatment but are expected to be listed for treatment.

A clear and substantial patient group within the Novacor bridge-to-transplant (BTT) study, a prospective, controlled, pivotal trial, had one or more relative contraindications at the time of enrollment. These patients became part of the trial despite those contraindications because criteria for transplant eligibility are defined by each center. Enrollment was completed in September 1998; the evolution and experience during the enrollment period resulted in adjustments in enrollment criteria.

The data support the proposed indication. The Novacor LVAS provides clear benefit to patients who have relative contraindications (RCIs), particularly reduction in mortality risk and improved transplant rate. The evidence is clear that those who had RCIs had substantially the same results as those who did not have them.

Patients with relative contraindications face a highly uncertain prospect of receiving LVAS support. Almost all would be excluded from transplant listing at least one center, and some would be excluded at all centers. It is inappropriate for clinicians to bend the rules for these patients.

In the proposed indication, the term “short- and long-term” is intended to clarify the potential range of implant duration. The BTT study includes durations to 3.4 years, and waiting

time for donor organs is highly variable. Some relative contraindications may resolve slowly. It might be preferable to state “short- or longer-term.”

Jal S. Jassawalla, M.S.M.E., M.B.A., Executive Vice President, World Heart, presented an illustration of the Novacor LVAS as implanted and explained its operation. The device is an implanted, pulsatile electromechanical ventricular assist device that has a percutaneous lead. It is totally self-regulating and responsive to flow from the left ventricle. The recipient simply needs to manage power sources. The device has an extensive clinical history consisting of more than 1,500 implants worldwide to date, totaling more than 500 patient years of experience. The current device received the CE Mark in Europe in 1993, and FDA approved the BTT indication in 1998. A total of 1,077 devices had been implanted as of April 15, 2003.

As Mr. Jassawalla presented slides 17 and 18, Ms. Wood stated that the data on 1,077 implants were not in the PMA supplement submission and could not be discussed. She later clarified that the data were submitted but not included in the panel pack.

The Novacor LVAS BTT study was conducted in NYHA Class IV end-stage heart failure patients who were at risk of imminent death. Enrollment consisted of 190 LVAS patients and 35 control patients who did not receive LVAS. The longest period a patient was on support was 3.4 years. Mortality and adverse event rates decreased substantially after the postoperative period. Sixty-eight percent of LVAS recipients received a transplant; median survival on LVAS was 10.8 months. Thirty-seven percent of control patients received a transplant, and median survival pretransplant was 0.4 month. LVAS support provided a sevenfold reduction in mortality,¹ which was statistically significant.

James B. Young, M.D., Cleveland Clinic Foundation, consultant to World Heart, presented the Novacor BTT study results. Patients were divided into two groups. Group I

¹ Note: the sponsor later stated that the device provided a sixfold reduction in mortality.

consisted of patients without contraindications; Group II consisted of patients with one or more RCIs that would preclude transplant listing at some centers. The sponsor focused on seven RCIs, the rationale for which was based on literature review and the advice of experienced heart failure and transplant clinicians. The RCIs were the most clinically relevant of 59 variables for which data were available in BTT study.

Thresholds are consistent with current consensus guidelines for transplant listing and with payer guidelines. These relative contraindications are consistent with clinical practice and data. References on RCIs provide robust information about how they contribute to excess risk posttransplantation. The Novacor LVAS can help patients resolve the RCIs.

The control group was the basis of BTT approval—its comparability was accepted by FDA. The same criteria were used to select Group II control patients and Group II test patients. The advantage (test vs. control) remained highly significant after multivariate analysis correcting for covariates. Even though RCIs lead to worse outcomes after transplant a Kaplan-Meier graph comparing survival in Group I and Group II showed no statistically significant difference between the Group I and Group II patients who received the device. Survival observations were censored at transplantation. The transplant rate in Group II (RCI) patients was similar to that of Group I patients. The results suggest that hemodynamic support “pulls patients back from the brink.” LVAS in patients with RCIs provided improved survival while awaiting transplant, improved rate of transplantation, and posttransplant survival similar to patients without RCIs.

Ms. Wood noted that the information on slide 31 was not presented in the PMA supplement submission and could not be discussed.

Analysis was performed to examine the effects of preimplant patient covariates on survival. The reduction in mortality risk remains virtually unchanged when considering any

differences in individual patient covariates. LVAS therapy provided a sixfold reduction in mortality risk in patients with RCIs. The incidence of adverse events in Group I and Group II LVAS was similar.

Ms. Wood stated that the data on slides 35 and 36 were not part of the submission and could not be discussed.

Dr. Young discussed the characteristics of end-stage heart failure patients. Such patients have varying risk factors, and transplant listing practice varies from center to center. There is a clinical need for an indication of the sort proposed. Retrospective analysis in this case is appropriate. The data presented are from a prospective, controlled study and show a sixfold reduction in mortality. A prospective randomized trial would be impractical and raise ethical issues. Postmarket surveillance could confirm BTT study results.

In summary, a population currently exists with RCIs to transplant that has no assured access to ventricular assist devices and transplant. The Novacor BTT study included a significant number of such patients. Approval of the expanded indication will provide uniform access to LVAS therapy for these patients, with demonstrated survival benefits. LVAS recipients who survive to transplant have the opportunity to benefit from the current therapy gold standard. Approval of the revised indication will increase effective utilization of scarce donor organs.

Panel members asked for information on the number and type of RCIs in each patient; recruitment of control and test patients; reasons for the relatively short median survival of the control patients; the number of patients on inotropic therapy; reversibility of pulmonary hypertension in the patient population; the proportion of patients who had had prior heart surgery; other clinical characteristics of the control group; and methods the sponsor used to address the weaknesses of the retrospective analysis.

FDA PRESENTATION

Michael Berman, Ph.D., lead reviewer, listed the review team and reviewed the proposed expanded indication for use and the regulatory meaning of “indications for use.” He noted that the description of the patient population changes in the new indication. As part of the review process, FDA must determine whether there is a reasonable assurance of safety and effectiveness for the device with respect to the patients for whose use the device is intended, the conditions of use, and the probable benefit versus probable injury.

If the device were being presented de novo, the Agency would assess multiple characteristics of the device system from bench testing data. None of those matters are at issue in the day’s discussion.

The Agency has several clinical concerns. (1) The patients evaluated are not the same as the patients indicated: The patients in the analysis data subset were transplant eligible, but additional patients may not be. (2) A total of 160 of 190 patients were on the device for 6 months or less; of the 30 LVAS patients, 15 were on for more than 1 year and 4 were on for 2 years or more. (3) It is not clear why the seven RCIs and the corresponding thresholds were chosen. (4) The term “expected to become” is problematic because all patients were transplant patients. (5) No objective evidence of reversal or normalization of the RCIs was provided in the submission, nor was objective evidence that one can determine a priori whether a patient with a specific RCI will become a transplant patient. (6) The subgroup analysis may not be extendable to patient population. In addition, the subgroups may not be comparable because the subgroups were not matched.

Chul H. Ahn, Ph.D., Biostatistician, reviewed the BTT clinical study in the original submission. The intended patient population is different from the patient population. He

presented an animation showing no overlap between the BTT population and the population with RCIs who are expected to become transplant candidates.

The patients with RCIs were eligible for transplant when they entered the study. Even if the patients were technically not eligible, no evidence demonstrates that the 75 LVAS patients became eligible while on support. No outcome data for the seven RCI criteria were provided. Therefore, the data do not directly address how effective the device will be for the intended patient population.

The 75 LVAS patients may not be comparable to the control patients because of differences in year of implant, baseline covariates, and propensity scores. The year of implant differed considerably between the two groups: All LVAS patients were enrolled in the last half of the 1990s. The year of implant is important because of changes in treatment. Little overlap exists in the time of enrollment in the two groups. In addition, imbalances in baseline covariates make direct comparisons problematic; all p values from direct treatment comparisons are therefore not comparable. Treatment comparisons cannot be used to adjust for imbalanced covariates because the treatment group has healthier patients. In addition, the overlap between the treatment groups is insufficient to do a propensity score analysis, and survival curves are problematic because the groups are not comparable. Even if we assume that the two treatment groups are comparable, a subgroup with significant differences in survival curves may exist. The sponsor's data censoring was also problematic. Any sample from the BTT study will likely show a significant difference between the two treatment groups.

Ileana L. Piña, M.D., Case Western Reserve University, Consultant to FDA, reviewed the proposed indications and the composition of the dataset. She noted that there is currently no accepted definition of short or long term in the context of using left-side mechanical

circulatory support as a bridge to transplantation. Many traditional contraindications have become “relative” contraindications over time. It is unclear why the sponsor chose the seven RCIs described in the submission. It is also unclear how the thresholds for the RCIs were chosen. For example, renal function can be a marker of poor outcome; but it is not possible to tell a priori who will reverse and who will not. No patients were excluded from transplant listing due to renal dysfunction. Even if patients fail to recover renal function, they can undergo dialysis safely and undergo transplant. Similarly, one cannot predict a priori which patients will reverse on pulmonary artery pressures. Sometimes hepatic function temporarily worsens, then resolves.

In summary, RCIs are relative; including some and not others is not justified. From the dataset presented, there is no way to predict which patients with the RCIs identified by the sponsor will become transplant candidates if they are not candidates prior to device placement. Writing an FDA-approved label would be difficult.

Panel members asked for additional information on the propensity score analysis, the durability of the device, the meaning of “long term” in the indications; the noncomparability of the groups, impact of reversibility of RCIs on survival posttransplant, whether any of the groups had a tendency for a particular RCI, and relation of RCIs to mortality.

Panel Reviews

Mitchell Krucoff, M.D., panel clinical reviewer, raised several questions for the sponsor. Because the dataset was not built on a prospective hypothesis, the findings might be more useful for developing hypotheses to be tested in randomized clinical trials. In addition, the number of study participants is so small as to make the groups noncomparable and the study statistically suspect. The ethical issues regarding randomized trials can be overcome and may not be the barrier the sponsor says they are. The problem is a practice of medicine issue, not a

regulatory issue. Reversibility is an issue; whether or not the RCIs abate or improve, a practice of medicine element plays a role. The fact that the patients all were in the BTT trial means that they were considered transplant candidates.

Dr. Krucoff asked the sponsor for information on patients in other countries; how the cutoff values were determined; safety relative to timing of adverse events; and contraindications for patients with other RCIs not listed.

John C. Somberg, M.D., panel statistical reviewer, noted that he had submitted his review in writing to the Agency. He stated that even though the sponsor pointed to 20 years of experience with more than 1,500 implants, the data consist of a small BTT trial. The study has statistical problems. Treatment of these patients changed significantly during the course of the trial, and the data suggest that the control population was considerably sicker. One cannot tell whether the device is what makes the difference. Many patients are awaiting transplant who never get one and who do not have many interventions. The sponsor should have been able to compare several groups of patients with similar outcomes; not doing so is devastating in being able to decide whether long term use is adequate. We know that this device causes some problems, but we do not have anything on which to base a risk–benefit analysis because the control group is inadequate.

The concept the sponsor proposes is interesting—that people with RCIs could become transplant eligible. However, the number of people with each RCI is very small, making it hard to compare them. It is difficult to reach any positive conclusion. The control population consists of 12 patients and was nonconcomitantly recruited, so it is inadequate for comparison. No additional historic controls from any other database were provided to validate the sponsor's recommendation. Finally, the most disturbing conclusion is that no evidence demonstrates that

implantation of the device changes the relative contraindications to make the person a better transplant candidate.

It is of concern that the current labeling does not advise physicians as to what to do about RCIs, but it also of concern that we do not have information sufficient to recommend that if the device is implanted, a certain outcome will result. We have a reliable device with little information on how to use it for these questions. It is not possible to make a recommendation.

PANEL DISCUSSION

Panel members asked for information on the rate of right ventricle failure in patients with elevated pulmonary hypertension and discussed the relation of the indication to destination therapy, the relation of the indications to UNOS regulations, the reasons for listing age as an RCI when it is not reversible, the number of patients who had RCIs that reversed, and the role of the device as a “bridge to candidacy.” They also discussed whether the current labeling would preclude patients from receiving an LVAS.

FDA QUESTIONS FOR PANEL

Question 1: The sponsor makes outcome comparisons between the selected subgroups of LVAS and control patients, yet significant covariates of the two groups are not matched. Are such comparisons between groups with unmatched covariates valid?

The panel concurred that the comparisons are not valid.

Question 2a: ... All of the selected patients were transplant eligible and were listed for transplant; the majority were transplanted. Are these patients comparable to patients with these “relative contraindications” who are not transplant eligible and would not be listed or transplanted?

The panel concurred that it is difficult to establish comparability.

Question 2b: ...Is there a sound scientific or clinical rationale for choosing the seven RCIs selected and not including others?

The panel noted that the issue is one of clinical judgment rather than consensus or specific guidelines. No sound scientific evidence exists.

Question 2c: Is there a sound scientific or clinical rationale for choosing the threshold values of the seven selected variables such that these variables, singly or in combination, are RCIs to transplant?

Many panel members felt that the cutpoints were arbitrary. No data presented suggested the incremental utility of a combination of variables. Several panel members, however, felt that in a broad clinical context, the numbers were reasonable. Data on issues of reversibility and multiple comorbidities are missing.

Question 3: Is the data sufficient to demonstrate the effect of the LVAS to “normalize” these seven variables to justify expanding the label . . . ?

The panel concurred that the data are not sufficient. No data suggest normalization or even a change that the panel can evaluate.

Question 4: Does the retrospective subgroup analysis of transplant-eligible patients provide sufficient evidence of safety and effectiveness to expand the labeling to include patients not eligible for transplantation?

The panel generally agreed that the retrospective subgroup analysis does not provide sufficient evidence of safety and effectiveness. It provides no safety data or meaningful data for the time that patients will endure the device, and it provides no long-term effectiveness data. With so few patients, it is difficult to make anything of the Kaplan-Meier curves. One panel member felt that for the duration of device use in the study, the clinical data and bench testing demonstrated that the device is safe. It functions as an LVAS and helps reduce creatinine levels, so it seems effective. Panel members concurred that it was not possible to extrapolate from the transplant-eligible subgroup to the ineligible subgroup. The safety profile of the device for patients who have RCIs is unclear.

Question 5: [Do the data provide] sufficient support to expand the labeling to include “long-term” use?

The panel agreed that the number of patients receiving the device for the long term is not sufficient to provide meaningful information. An unknown number of patients may wind

up with the devices as destination, and many patients will be ineligible for transplant even after getting device.

Question 6: Does the retrospective subgroup analysis of transplant-eligible LVAS patients provide sufficient data to judge whether expanding the label to include patients not eligible for transplant is safe?

The panel concurred that the analysis does not provide sufficient data. The number of patients is insufficient, and the curves do not cover a sufficient amount of time.

Question 7: Does the proposed expanded indication for use meet [the FDA's labeling] requirement[s]?

The consensus of the panel was that it does not.

OPEN PUBLIC HEARING

No comments were made.

CONCLUDING COMMENTS

Bram Zuckerman, M.D., stated that the question facing the panel is whether enough data are in the current application to justify changing the indication for use. In addition, a more general problem faces the left ventricular assist device (LVAD) industry: Many patients have received a particular device and, with study, could have provided additional data. The Agency is committed to continuing support of these devices throughout the approval process in pre and postapproval domains.

Dr. Young thanked the panel for its time and attention and expressed disappointment with the panel's conclusions. He clarified that the sponsor's intention was not to open the door to using the device as destination therapy.

Ms. Moore stated that it was important to have consistency in characteristics that define someone as transplant eligible. Given that physicians have leeway to use their judgment, it does not seem necessary to specify short-term or long-term use in the indications. Mr. Morton stated

that the sponsor did a good job of data presentation and is committed to doing what is best for patients.

VOTE

Ms. Wood read the voting options. The panel voted 10-1 that the PMA was not approvable.

POLL

The panel member voting against the motion stated that some patients fall in between absolute contraindications and indications. Devices like this are generally safe and effective and are needed. The trial was not ideal, but patients nevertheless would benefit.

Panel members voting in support of the motion focused on the inadequacies of the data to support changing the indication. The reality is that premarket evaluation is not identical to what physicians face in the real world. The sponsor can help fill the gap by collecting systematic postmarket information. Professional societies or NIH might be a more appropriate venue for determining how LVADs and other devices could play a role as bridges to transplant candidacy. In the meantime, patients can currently receive the device, so there is no reason to change the labeling. The bridge-to-candidacy concept should be explored further.

ADJOURNMENT

Dr. Laskey thanked the participants and adjourned the meeting at 3:16 p.m.

I certify that I attended this meeting of the
Circulatory System Devices Advisory Panel

Meeting on June 8, 2004, 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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