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SUMMARY MINUTES
OF THE
CIRCULATORY SYSTEM DEVICES PANEL MEETING

July 28-29, 1997

OPEN SESSION

Walker/Whetstone Salons
Gaithersburg Holiday Inn
Gaithersburg, MD

Circulatory System Devices Panel Meeting

July 28, 1997

ATTENDEES

Julie A. Swain, M.D.
Acting Chairperson

John E. Stuhlmuller, M.D.
Executive Secretary

Voting Members

Gulshan K. Sethi, M.D.

Consultants Appointed to Temporary Voting Status

Robert M. Califf, M.D.

Samuel W. Casscells, III, M.D.

Manuel D. Cerqueria, M.D.

L. Henry Edmunds, Jr., M.D.

Thomas B. Ferguson, M.D.

Alfred F. Parisi, M.D.

Cynthia Tracy, M.D.

George W. Vetrovec, M.D.

Ronald M. Weintraub, M.D.

Janet Wittes, Ph.D.

Panel Discussant

Lawrence Friedman, M.D.
(afternoon session)

Industry Representative

Gary Jarvis

ATTENDEES, Cont.

FDA

Thomas J. Callahan, Ph.D.

Paul L. Chaneysson, M.D.

Judy Danielson, B.S.N., M.P.H.

Steven Kurtzman, M.D.

Acting Chairperson Julie A. Swain, M.D., called the meeting to order at 9:30 a.m. Executive Secretary John Stuhlmuller, M.D., read the conflict of interest statement and announced the panelists with temporary voting and discussant status. Panelists introduced themselves, and Dr. Swain noted that there was no old and no new business for the panel to discuss.

Open Public Hearing. Dr. Stuhlmuller said he received two letters opposing the use of transmyocardial revascularization (TMR) for the treatment of coronary artery disease. One author has a "short" position and financial interest opposite to the sponsor; the second author has no financial interest in any laser company. No other comments were made.

Sponsor Presentation on Premarket Notification Application (PMA) P950015. A representative from PLC Medical Systems, Inc., outlined the proposed labeling for TMR using the Heart Laser CO₂ Laser System: It is indicated for treating patients who are refractory to medical therapy and suffer from chronic angina secondary to myocardial ischemia, not treatable by direct coronary revascularization. Discussion followed on the procedure and mechanism, and the study designs, objectives, and results of three studies spanning 1990-1996. He concluded that TMR using the Heart Laser significantly improved myocardial perfusion, angina pectoris, and quality of life (whereas medical management did not). Additionally, he said, TMR using the Heart Laser was associated with similar mortality and less morbidity than medical management.

FDA Review. Lead Reviewer Judy Danielson introduced participants in the PMA review, and Medical Reviewer Steve Kurtzman provided an overview and summary of the data. He said only Phases II and III of the study were to be discussed, and he described the Phase III control analyses and the Phase II and III angina data. He said the treatment successes in three

Phase III control groups were significantly less statistically than the treatment success in the Phase III randomized TMR group. Dr. Kurtzman also explained why the angina treatment success experienced by a majority of TMR patients may have been partly due to the placebo effect. The percentage of deaths was highest in the Phase III unstable angina TMR group (31%) and lowest in the control noncrossover group (13%), he explained. Dr. Kurtzman concluded his presentation with data on the causes of death and nonfatal adverse events. He asked the panel to consider the following points: (1) The clinical investigation was not designed to rule out the placebo effect. (2) Angina and thallium perfusion data are not available for all patients in Phases II and III (angina followup compliance ranged from 72-90%; thallium perfusion data were analyzed for only 32-44%). (3) There was a high percentage of crossovers from medical management to TMR in Phase III.

Medical Officer Paul Chandeysson compared the symptoms and thallium scans to show the change in number of ischemic segments and change in angina class. He asked the panel to consider the following points: (1) The perfusion data are sparse. (2) Correlation with angina data is weak. (3) The scoring method used by the sponsor was not validated.

Ms. Danielson concluded FDA's review. She asked the panel to address a number of issues.

Panel Review. Robert M. Califf, M.D., the first primary reviewer, referred to the panel meeting as an "important hearing," because the number of patients with refractory angina is growing worldwide. He then described a number of concerns. Over 50% of the data on the primary endpoint is missing, he said. He asked for help in determining why so much data are missing, addressing how the statistical values were quoted, and assessing bias (or the potential

for it) in the angina and morbidity data.

The sponsor's representatives provided page numbers and explained the statistics used, attrition rate, nonpreventable deaths, and angina compliance rates. One noted the similarities in the baseline profile for SPECT and non-SPECT patients. He said the perfusion sample is an accurate representation of the general population, two-thirds of the study losses were nonpreventable, and approximately 75% of the patients had angina relief. Because it is not always possible to collect all the data at all times for all patients, he asked the panel to look systematically between the two groups and note that no differences will be found. Nonetheless, Janet Wittes, Ph.D., maintained that selection to any primary endpoint is biased. Dr. Califf said that the study was not blinded, therefore, there was bias in general, and this is his main point of concern.

Representatives responded to questions involving analyses of deaths as failures, worst-case scenario analyses, the procedure for filling out patient questionnaires, the three-fold increase in mortality noted by Dr. Califf, and morbidity.

The second Primary Reviewer L. Henry Edmunds, Jr., M.D., recognized the burden faced by the sponsor and then noted that two of the three endpoints (angina and quality of life) are subjective measures. He wondered if operative mortality data were also included in the analyses (they were). And, he mentioned his concern about the sponsor's methodology and the evaluators' lack of objectivity. After representatives commented on animal and foreign data, Dr. Edmunds concluded that the submitted data are incomplete and the sponsor did not demonstrate efficacy.

Committee Discussion. According to S. Ward Casscells, M.D., the submitted data are difficult to analyze, data are possibly understated, 90% followup was not reached, and there

needed to be predetermined endpoints. Dr. Casscells was also concerned that adjunct therapies were neither identified nor randomized. He acknowledged that the data show dramatic increases after the therapy; however, which ones are directly attributable to the device?

A representative and Dr. Casscells discussed the definition of myocardial infarction, the increased rate in the control group, aggregating treadmill data, and reversible defects. Dr. Casscells maintained that it is important to know what happened after TMR. What was the medical regimen, weight loss, and compliance rate, he asked? A representative responded that an impartial cardiologist, independent of the study, graded the patients. The representative said there were no differences in compliance, weight loss, and cigarette use. Ninety percent of the patients had had bypass surgery and were "in tune with their health," he said. The representative continued: All patients in the trial were taken care of at the tertiary level by one cardiologist, so they received the same medications they had been receiving before the procedure. Certain patients (exact percentage is unknown, but they constituted the biggest group with preinfarction and unstable angina) received Coumadin for 3 months after the procedure and the control group received aspirin. Representatives responded to questions about study termination (it is still ongoing) and enrollment discontinuance.

Committee Discussion, continued. The panel reconvened after lunch, and members posed many questions. Dr. Casscells reiterated his concerns about patients lost to followup and the lack of thallium data. He said the unfiltered "real" scores were needed for the angina questionnaire. A representative insisted that changes in angina pectoris are not necessarily linear with myocardial perfusion. Furthermore, he said, SPECT data are not the gold standard for relief of angina, and investigators did not look for 100% concordance. Rather, he said, discordance

shows the independence of the two.

Dr. Casscells maintained that increased or decreased efficacy rates depend on other therapies. Discussion ensued, with representatives claiming results such as relief of angina was independent of nitrate use. According to the sponsor: investigators restarted medications postoperatively, there were no changes in the use of calcium nitrates and beta blockers, and glucose and cholesterol levels were not followed.

Gulshan Sethi, M.D., asked questions regarding the change in angina classifications in Phases II and III; the small number of patients (15) evaluated at 12 months; and how the procedure differs from another well-known procedure. He was told why the classification "no angina" (class 0) was added; that Phase III was a confirmation of Phase II and the angina data were statistically significant at 12 months; and that the Heart Laser is an elaboration and improvement of the technology. Final comments were made regarding mechanism of action, the placebo effect, and total deaths/open channels.

Thomas Ferguson, M.D., said he is impressed with the way the procedure treats patients who have no alternative. He asked for evidence that the channels are enervating the heart and assurance that there was general regulation of protocols in the 13 institutions. Representatives replied that one animal and a different laser study were conducted. The data on denervation showed 6 patients out of 86 were worse off. There was no variation among sites, angina was looked at independently, and the global outcome was similar at all sites.

According to Manuel Cerqueira, M.D., the sponsor cannot make definitive conclusions about perfusion because of the number of dropouts. He was told no phantoms and no specific tests were run for quality control. In response to his other questions, a representative explained

that there were no specific requirements for following the protocol; the reproducibility of the semiquantitative method used; that investigators did not look for changes in abnormalities; and that their choice of endpoint was not unrealistic, the attrition was expected.

Ronald Weintraub, M.D., greatly appreciated the small submission and congratulated FDA and the sponsor for the randomized trial, despite the problems. He cited missing data, insufficient radionuclide data, and the assessment of "nonpreventable" losses. Dr. Weintraub asked for guidance in assessing statistical significance. Janet Wittes, Ph.D. said there are several different kinds of missing data. The amount of missing data is problematic, and the differential followup is worrisome, she said. Discussion ensued regarding dropouts versus crossovers; improvements versus failures; and additional procedures after TMR (including those contraindicated before TMR).

Alfred Parisi, M.D., made the following observations: the majority of patients don't have a change in perfusion; 20 patients had additional procedures; and on average, patients received 30 punctures. Dr. Wittes then asked for an explanation of how the study randomized subjects, the affect of unstable angina on mortality, and why there were no differences between the treated and nontreated groups.

Issues addressed by George Vetrovec, M.D., included the following: assessing high risk patients, determining if mortality is correlated with left ventricular function, and relating evidence of fibrosis and diastolic function. He said documented consistency is lacking, and a representative said there was no core lab review of angiograms.

Representatives discounted the placebo effect. They cited 2- and 4-year followup data showing that improvements were maintained over the long term and the sponsor's rigorous

definition of angina. Discussion ensued over Dr. Casscells' concern that success rates may reflect patients who quit smoking and changed their diets. A representative replied that only 10% of the patients were smokers and investigators did not counsel patients. Furthermore, he said, it would have been unethical to carry out a sham operation and FDA did not require the company to show the mechanism of action. Dr. Swain concluded the discussion saying the company is responsible for convincing the panel that the quality and quantity of the data are sufficient to prove safety and efficacy.

Cynthia Tracy, M.D., commented on the discordance in data reflecting angina symptoms. A representative acknowledged that a combination of mechanisms were responsible for improvements. Dr. Tracy told the sponsor not to discount heart rate variability. A direct myocardial hit is going to alter the autonomics, she said. Finally, she is worried about sudden death. "It seems high," she said.

A representative answered Dr. Swain's questions regarding no measure of medical compliance, the number of smokers in the TMR and control groups, and the number of TMR and control patients who had cardiac rehabilitation. Another representative said that out of 2,500 of his patients in a span of 2 years, 400 would fit the study protocol. Two panelists restated the concern that the missing data raises serious questions of interpretability. Representatives explained how the intent-to-treat, mortality, and crossover data were plotted.

Panelists were given three options for rendering a recommendation for the PMA and they offered their opinions in round-robin fashion. Dr. Califf said safety could not be ascertained. He said more than 50% of the data are missing, there is a huge crossover rate, and the sponsor made no effort to get unbiased information on subjective status. Dr. Ferguson said the 7 days on drips

in ICU indicates something must be done. Dr. Tracy agreed that too many crossovers took place, and a 6-month wait period should have been instituted. Dr. Weintraub said the sponsor made a good faith effort and accounted for the missing data. He reminded the panel that these patients are without alternatives. Dr. Cerqueira said there is a way to shore up the data. "You won't get 100%, but you could get 80%," he said. According to Dr. Parisi, a number of patients did not change and a number of them worsened; nonetheless, the data say patients got relief from angina. He said he has a problem with self-administered data that are incomplete at 6 months.

Dr. Edmunds acknowledged that the company has a difficult burden given the type of patients in the study. However, he said the study has serious problems regarding compliance, consistency, and data loss. The perfusion data are discordant with angina (except the PET data) and the 6-month followup is too short. He is convinced the device relieves angina, not that it perfuses monocytes. Dr. Sethi said this is a less than 6-month study. Although the device improves angina, angina is affected by different sources, he said.

Dr. Wittes was not concerned with the placebo effect, but rather that the changes had no concomitant effect in mortality and perfusion. Dr. Vetrovec concluded "if treatment affects mortality in low-risk patients, we need to know."

Vote. A motion was made and seconded, and the panel voted 9:2 to recommend PMA P950015 as nonapprovable. Panelists made a number of suggestions and urged a "relatively expedited re-review." Suggestions included: Complete the data on the existing cohort of 200. Correlate ejection fraction with morbidity and mortality data. Use trained interviewers with scripts for quality of life assessments. Obtain 12-month mortality data on late crossovers. Obtain baseline data on all patients. Obtain 1-year patient data using uniform collection

methods. Obtain 1-year of good followup data. Relate risk factors and type of mortality.

Regarding future studies, panelists said the following are needed: consistent, high-quality quantitative data; people whose only role is blind assessment; core laboratories, certified machinery, and training; consistent data collection, quantitative and standardized functional and perfusion measures; and objective measures.

The session was adjourned at 5:10 p.m.

Circulatory System Devices Panel Meeting

July 29, 1997

ATTENDEES

Julie A. Swain, M.D.
Acting Chairperson

John E. Stuhlmuller, M.D.
Executive Secretary

Voting Members

Gulshan K. Sethi, M.D.

Consultants Appointed to Temporary Voting Status

Salim Aziz, M.D.

Thomas B. Ferguson, M.D.

Cynthia M. Tracy, M.D.

George W. Vetovec, M.D.

Ronald M. Weintraub, M.D.

Janet Wittes, Ph.D.

Industry Representative

Gary Jarvis

FDA

Thomas J. Callahan, Ph.D.

Christopher M. Sloan, M.S.

Daniel Spyker, Ph.D., M.D.

Dr. Swain called the meeting to order at 8:30 a.m. Dr. Stuhlmuller read the conflict of interest statement and announced the consultants with temporary voting status. There was no old business or new business to discuss, and no comments were offered during the Open Public Hearing.

Sponsor Presentation on Premarket Notification Application (PMA) P960042.

Spectranetics' representatives provided an overview of the application; described the evolution of the device; and reviewed the clinical data and complication and crossover rates. Investigators of the clinical study, which included 764 patients, 842 procedures, and 1,369 removals, compared standard explant tools to standard tools and a 12 French Laser Sheath. Representatives described the randomization procedure, effectiveness and safety results, analysis of complications, and patient characteristics. The laser group was partially successful 94% and failed 11.2% (versus 64% and 14.2%, respectively, for the nonlaser group).

FDA Review. Christopher Sloan described the device as an adjunct to conventional tools that cuts through tissue binding sites and reduces counter pressure. He outlined several concerns (crossover rates varied across sites; investors had considerable experience, which limits generalizability; limited followup for training patients; the maximum lead diameter is 7.5 French; and the fluoroscopy time was not recorded). He also posed a series of questions to the panel.

Panel Review. The first Primary Reviewer, Dr. Tracy, questioned representatives about lead materials, the tip parameter table, the alternative method of applying direct traction, and the indications section. A representative explained the differences in the complication rates of sheaths precluded in the trial, investigator experiences with pacemakers and fluoroscopy, and

degree of heating. Dr. Tracy's concluding comments were that there appears to be bias toward the crossover group and the procedure time of 4-6 minutes is fairly short.

The second Primary Reviewer, Dr. Sethi, said the sponsor did a "good job in submitting data." He requested explanations on the term "discretionary" as it applied to survivors of breast cancer surgery, how to address emergencies, the extent of laser use and lead removal, and the location and high incidence of complications in the training group and among female patients.

Committee Discussion. In round-robin fashion, panelists asked a series of questions. Salim Aziz, M.D., asked about site differences in the use of anesthesia and patient complications. Dr. Wittes asked a representative to describe the nature of the study's randomization and blinding, how the data were analyzed, and how investigators chose the primary lead. Additional concerns cited by Dr. Wittes included the site-to-site variability, and lack of uniform and followup training. Drs. Ferguson and Vetrovec also congratulated the sponsor and FDA for the high-quality submission. Dr. Ferguson said the laser sheaths, when close to the myocardium, cause VPCs; there is a difference between the laser and standard approaches; and, the instructional material for both approaches should be the same. A representative explained the perspective of the calibration information and the maximum time that energy can be applied (5 seconds followed by a 10-second wait period). Representatives answered Dr. Vetrovec's questions about bubbles at the site and rates of passage, exceeding the limit on pulsing, and training guidelines.

A representative explained the "sweat factor" to Dr. Weintraub, stressing that the device would be used frequently and does not require brute force. Discussion ensued about the practicality of use. Dr. Swain was told there are no data to support the claim of "discretionary

lead removal" in the indications. However, representatives stressed that lead removal is a "touchy" subject, it is increasingly difficult to remove older leads, and there must be a weighing of risk versus benefit over the patient's lifetime. Dr. Swain also requested an explanation for the site differences (40% of the procedures were completed at one site) and the significant failure rate among institutions with no financial interest in the company. Pooling the data is not an option, according to Dr. Swain. Are three sites sufficient for a multi-institutional study, she asked?

Dr. Tracy's comments and questions focused on thermalizing from the laser beam, inadequate training as the source of deaths and high complications, explanations of technique, and the sponsor's success rate compared to the literature. Dr. Wittes focused on the randomization methodology and the small amount of bleeding present during treatment.

The panel's options and requirements were explained. The panel discussed and answered a series of questions for FDA regarding labelling issues. These were later modified as conditions of approvability.

Vote. The motion to vote the PMA P960042 approvable with six conditions passed unanimously. The conditions are as follows. (1) The labelling should be consistent with the Cook instrumentation, since the two techniques are not independent. (2) The issue of calcification should be added as a warning and not a contraindication. (3) Physician trainers should be present for the first two attempts at using the device. (4) A warning for the physician to take care at the right atrial juncture is needed in the labelling. (5) It should be stated in bold that the physician should stop the sheath at the myocardial juncture. (6) Results data should reflect the variability. Panelists discussed the need for a registry. Dr. Swain suggested

that the first 10 cases at each site be monitored for deaths and complications. Dr. Wittes said FDA needs to think about issues of crossover (i.e., when prohibited or discouraged) and sponsors need to set clear definitions in their protocols. There are additional issues to be grappled with, she said, including the relationships between soft endpoints and blinding. Dr. Wittes was invited to help FDA grapple with these and other issues.

The session was adjourned at 11:36 a.m.

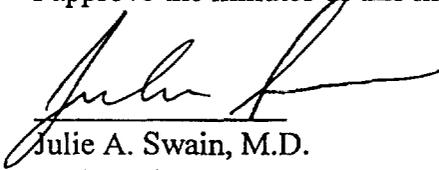
I certify that I attended the Circulatory System Devices Panel meeting on July 28-29, 1997, and that this summary accurately reflects what occurred.



John E. Stuhmuller, M.D.
Executive Secretary

31 Oct 97

I approve the minutes of this meeting as recorded.



Julie A. Swain, M.D.
Acting Chairperson

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