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SUMMARY MINUTES

OF THE

CIRCULATORY SYSTEM DEVICES

ADVISORY PANEL MEETING

OPEN SESSION

APRIL 23, 2001

**Silver Spring Holiday Inn
8777 Georgia Avenue
Silver Spring, Maryland**

CIRCULATORY SYSTEM DEVICES ADVISORY PANEL MEETING**April 23, 2001****ATTENDEES****CHAIRPERSON**

Cynthia M. Tracy, M.D.
Georgetown University Hospital

EXECUTIVE SECRETARY

Megan Moynahan, M.S.
Food and Drug Administration

VOTING MEMBERS

Salim Aziz, M.D.
University of Colorado

Michael D. Crittenden, M.D.
Harvard University

Julie A. Freischlag, M.D.
UCLA School of Medicine

Warren K. Laskey, M.D.
University of Maryland School of Medicine

Janet T. Wittes, Ph.D.
Statistics Collaborative, Inc.

CONSULTANTS

James A. DeWeese, M.D.
University of Rochester

Kenneth Najarian, M.D.
University of Vermont School of Medicine

Anne C. Roberts, M.D.
UCSD Medical Center

Tony W. Simmons, M.D.
Wake Forest University

INDUSTRY REPRESENTATIVE

Gary Jarvis
St. Jude Medical

FOOD AND DRUG ADMINISTRATION

James E. Dillard III
Director, Division of Cardiovascular and Respiratory Devices

Judith Danielson
FDA Reviewer

Paul L. Chandeysson, M.D.
FDA Reviewer

Judy Chen

Donna-Bea Tillman, Ph.D.

OPEN SESSION—APRIL 23, 2001

Cynthia M. Tracy, M.D., Panel Chairperson, called the Open Session to order at 9:05 a.m. and read the charge to the panel, which was to consider a premarket approval (PMA) application for Sulzer IntraTherapeutics' IntraCoil Self-Expanding Peripheral Stent and then to consider clinical study design issues for iliac stenting. **Executive Secretary Megan Moynahan** read the conflict of interest statement, noting that waivers had been granted to Janet T. Wittes, Ph.D., and Anne C. Roberts, M.D., for their interests in firms potentially affected by the day's deliberations and that matters concerning Anne C. Roberts, M.D., Cynthia M. Tracy, M.D., Julie A. Freischlag, M.D., Warren K. Laskey, M.D., Tony W. Simmons, M.D., and Kenneth Najarian, M.D., had been considered but deemed unrelated and their full participation would be allowed. **Dr. Tracy** asked the panel to introduce themselves and state their areas of expertise. **Ms. Moynahan** read appointments to temporary voting status for James A. DeWeese, M.D., Kenneth Najarian, M.D., Anne C. Roberts, M.D., and Tony W. Simmons, M.D., and noted that Mr. Robert Dacey, the Consumer Representative, was unable to attend because of weather-related travel delays.

Open Public Hearing

There were no requests to address the panel.

PMA P00033 FOR SULZER INTRATHERAPEUTICS, INC.'S INTRACOIL SELF-EXPANDING PERIPHERAL STENT

Sponsor Presentation

Maria Brittle, Regulatory Affairs Manager of Sulzer IntraTherapeutics, Inc., introduced the sponsor team. **Kenneth Rosenfield, M.D., of St. Elizabeth's Medical Center and Tufts University School of Medicine,** who stated that he was a compensated member of the sponsor's Medical Advisory Board during the trial but had no connection with or influence over outcomes or data management and no conflicts or financial interests other than travel expenses and compensation for time, provided background on femoropopliteal disease. He stated that the superficial femoral arteries (SFA) and popliteal arteries were a special challenge to the vascular specialist because of their high plaque burden and high prevalence of primary occlusion. Surgical treatment, while effective, has significant morbidity and mortality risks; endovascular treatment methods are subject to high restenosis rates. Noting that the two stents approved for peripheral vascular applications are the balloon expandable Palmaz stent and the self-expanding WallStent, Dr. Rosenfield presented data from the FAST trial on percutaneous transluminal angioplasty (PTA) versus the Palmaz stent in SFA treatment, observing that the trial was discontinued because of restenosis due to stent compression. He also presented findings from the Conroy and Martin studies on the WallStent in the SFA/popliteal arteries and contrasted them with findings from the Henry study showing a potential benefit to the current self-expanding Nitinol stent. He described the IntraCoil Stent characteristics, noting that it is designed for application in tortuous vessels subject to external compression and flexion, and he explained the mechanics of IntraCoil

delivery, noting that it is an over-the wire device that is easy to deliver and visualize while positioning.

Dr. Rosenfield summarized the clinical trial, which initially was designed to compare safety and efficacy of IntraCoil stenting versus PTA alone. Primary endpoints were angiographic restenosis of greater than or equal to 50% narrowing at nine months or major adverse clinical events (MACE) rates at nine months. Secondary endpoints were the major complication rate at 30 days and a change in delta ABI from baseline to nine months. The study design assumed that restenosis for PTA alone would be 50% and for stent would be 37%, with an 80% power. The study was a randomized controlled multicenter trial using 480 patients stratified at randomization for diabetes. Dr. Rosenfield described the major inclusion and exclusion criteria and enrollment and crossover procedures, noting that the trial was initiated in March 1997 but terminated in December 1999 because of slow enrollment based on reluctance to randomize to PTA and on the availability of off-label stents. He presented baseline patient characteristics, noting that this was a typical cohort of very sick peripheral vascular patients, with high numbers of diabetics and smokers.

Dr. Rosenfield noted a high rate of PTA to stent crossover, but no difference in the acute procedure results. The nine-month restenosis rates showed a high rate of restenosis, but Dr. Rosenfield expressed doubts about the validity of the data because they were derived from only 52% of the evaluated lesions. Nine-month clinical follow-up on freedom from MACE and freedom from clinically driven target lesion revascularization (TLR) showed very similar results

in both groups. Secondary endpoints showed outstanding results with a low complication rate and good improvement in ABI.

Dr. Rosenfield summarized that from an acute safety standpoint, there was a lower 30-day major complication rate in the stent group compared to PTA and that the IntraCoil stent was necessary to salvage PTA failure and to avoid emergency surgery. Effectiveness and durability results showed a high freedom from clinically driven TLR of 85% at nine months and an improvement in ABI for the IntraCoil stent superior to that of PTA. He stated that this suggests improved flow characteristics for stented lesions versus PTA lesions. Dr. Rosenfield concluded that the study results demonstrate that femoropopliteal stenting with the IntraCoil stent is effective in preventing clinical restenosis and preserving distal leg blood flow and that study data also demonstrated that IntraCoil stenting is safer than PTA for prevention of acute complications.

Gary Ansel, M.D., presented clinical scenarios and observations, after disclosing that he was compensated as a member of the sponsor's Medical Advisory Board but had no connection with or influence over outcomes or data management and no conflicts or existing financial interests other than travel and time reimbursement. He discussed femoral/popliteal artery stenting in terms of claudication or limb threat, noting that surgical procedures were effective but used sparingly due to morbidity or mortality rates. Comorbid conditions that are possible indications for stenting include advanced age, coronary disease, diabetes, and renal insufficiency. He showed examples of use of the IntraCoil stent across the knee and gave case examples.

Dr. Ansel showed that a subgroup analysis performed during the IntraCoil stent trial on 70 roll-in and randomized IntraCoil stent patients who experienced suboptimal results after initial dilation (defined as a residual stenosis of greater than or equal to 50% before stenting and grade C dissection or greater) showed baseline and overall results similar to the main analysis.

In considering an indication for device use with suboptimal PTA results, Dr. Ansel reminded the panel that conventional PTA could be a first good option, in that if results are optimal, a low rate of TLR can be expected. But when the initial PTA results are suboptimal, continued attempts to optimize the result increase the patient's likelihood of complications. Therefore, he thought that treatment of a suboptimal PTA result with the IntraCoil stent presents fewer complications while providing a low rate of TLR similar to an optimal PTA result. In considering an indication for primary device use, Dr. Ansel noted that the IntraCoil stent trial data also showed a significant improvement in acute safety and no differences in safety and effectiveness at nine months as compared to PTA. He added that specific advantages to this device include its flexibility, durability, and resistance to compression, all of which make it suitable for use in the popliteal artery.

Maria Brittle noted that after consultations with the Food and Drug Administration, sponsors had decided to submit the PMA with a revised indication for use with the suboptimal patient group.

FDA Presentation

Judith Danielson, PMA lead reviewer for the FDA, gave the FDA nonclinical summary and introduced the review team. She stated that nonclinical performance was assessed through biocompatibility, bench, and animal testing in the laboratory. Biocompatibility testing of the stent and delivery catheter produced accepted results, as did bench testing of the stent for material specification and integrity and of the stent /catheter delivery system. Animal testing of 17 stents in the porcine model, the majority of them in the iliac artery, demonstrated the integrity of the device for intended use through histological evaluations at one, three, and six months to assess early and late patency.

Paul Chandeysson, M.D., clinical reviewer for the FDA, gave the clinical summary. He observed that the device was originally tested in a randomized trial of the stent versus PTA, based on a superiority hypothesis of a projected 25% decrease in restenosis with the IntraCoil stent in a patient sample size of 500, half randomized to device and half to PTA. The primary effectiveness endpoint for this trial was a composite endpoint of restenosis of greater than 50% at nine months and MACE rates at nine months. The majority of the lesions treated were less than or equal to three centimeters. Dr. Chandeysson noted, however, that the study was stopped early because patient enrollment was slow. The superiority hypothesis was not demonstrated against PTA alone, but there were no significant safety concerns evident with the stent. At that point, a subgroup of IntraCoil patients were selected prior to stenting, based on the following criteria: residual stenosis of greater than or equal to 50% or Grade C or greater dissection. Retrospective

analysis showed that this group, known as the suboptimal predilatation group in comparison to the PTA control group, had no differences in adverse event rate or effectiveness.

Dr. Chandeysson stated that the indications for use of the device had changed from primary stenting for occlusive disease to stenting for patients meeting the subgroup criteria, a more limited use. Study limitations, in his view, included the retrospectively selected test group, the relatively small sample size, and differences in dilatation technique.

Open Committee Discussion

Anne Roberts, M.D., served as the panel lead discussant. She raised a number of questions about the study design, about selection of patients in the suboptimal predilatation group, about the use of retrospective data, and about reanalyzing data that were not intended to prove the revised study goal.

Other panel concerns included whether risk factors were addressed in this high-risk patient group and whether medical management versus surgical intervention was considered or studied. Length of follow-up time was thought to be insufficient, and one member commented that analysis at a transient point in time was being redefined as a suboptimal result. Several panel members expressed procedural concerns, especially with the small numbers studied. A number of panel members voiced the need for clarity in defining the appropriate patient population for the stent, with one member stating that loosening the definition of entry criteria to suboptimal results could lead to widespread stenting and greater restenting. Investigator bias was also a concern. Some panel members were concerned about a lack of enthusiasm for the PTA group

from the beginning of the study, resulting in small numbers being used to bolster a less than convincing case.

Panel members also asked for clarification on data from a study conducted in the United Kingdom that appeared to support the clinical study results. Sponsors replied that they were bound by a pre-publication agreement with the study investigators not to discuss the study openly. At 2:03 the meeting was adjourned for a Closed Session to clarify this point.

The Open Session resumed at 2:45 p.m. **Mr. James E. Dillard III, Director of the Division of Cardiovascular and Respiratory Devices**, stated for the record that during the Closed Session there had been no discussion of the data from the United Kingdom study or of any other data or substantive issue. The session was purely for clarification purposes.

Sponsor representatives decided that based upon FDA input concerning the rules of order, they would not present the United Kingdom data.

FDA Questions to the Panel

1a. Please discuss the use of the suboptimal pre-dilatation classification as a surrogate for suboptimal results with PTA.

The sense of the panel was that the suboptimal pre-dilatation classification as defined in the study was not clinically equivalent to suboptimal results with PTA.

1b. Please discuss any expected differences in terms of clinical outcomes between patients with suboptimal pre-dilatation and patients with suboptimal results from PTA.

The panel thought that the clinical outcomes of patients with suboptimal pre-dilatation and those with suboptimal results from PTA may not be equivalent and may in fact be quite different because of the severity of disease in the population studied and because of the way in which and the point at which the decision was made to transition to the stent in a clinical bailout effort. Panel members also found this language unclear.

1c. Please discuss whether there are adequate data for a primary stent indication. If not, what additional information would be necessary to support a primary stent indication in the femoral and/or popliteal arteries?

The panel thought that the safety data alone were not sufficient for a primary stent indication. Additional data on additional numbers of patients were needed for a primary stent indication. Helpful information that should be obtained would include a Duplex ultrasound to look at lesions, data on whether there is a falloff in good outcomes at 24 months, and an increased and improved follow-up on the original cohort on ABIs and ultrasound results.

2. Please discuss whether the clinical data are adequate to determine the safety and effectiveness of the IntraCoil stent in the popliteal artery.

The panel's reservations about the lack of data also applied here, with some expressing the same and some greater concern about the popliteal artery. Some members suggested that it might be helpful to break data into above the knee, below the knee, and distal popliteal data, but all agreed that more detail and more numbers are needed in general.

3a. Please comment on the indications for use section as to whether it identifies the appropriate patient population for treatment with this device.

The panel thought the patient population identified was appropriate.

3b. Please comment on the contraindications section as to whether there are conditions under which the device should not be used because the risk clearly outweighs any possible benefit.

The panel thought this question could not be answered until additional information was available.

3c. Please comment on the warnings/precautions section as to whether it identifies all potential hazards regarding device use.

Allergy to nickel should be added in this section.

3d. Please comment on the operator's instructions as to whether they adequately describe how the device should be used to maximize benefits and minimize adverse events.

The need for care regarding stent movement, migration, proper sizing, breakage of the wire and methods to resolve that problem, device breakage, sharp bends, maldeployment, and difficulty in release of the delivery system should all be discussed.

4. Please identify and discuss the items that you believe should be contained in a physician's training program for this device.

In addition to items noted above, the panel recommended that recommendations similar to other types of these devices should be used, including the need for adequate knowledge and

skill of the operator before solo performance, sponsor-provided interventional therapeutic training, and certification by professional societies.

Open Public Hearing

There were no requests to address the panel.

Closing Sponsor Comments

There were no additional comments from the sponsors.

Closing FDA Comments

There were no closing remarks from the FDA representatives.

Recommendations and Voting

Executive Secretary Megan Moynahan read the voting options and instructions.

A motion was made and seconded to recommend the PMA as not approvable. This motion carried unanimously.

The panel suggested the following actions to put the PMA into approvable condition: Better and longer follow-up, larger numbers of patient samples, especially those with popliteal artery problems, reanalysis of existing data and a more sophisticated look at popliteal data, more convincing efficacy data, and a properly conducted study using registry data with a stringent look at closure.

Dr. Tracy thanked the sponsors and wished them well in future submissions.

CLINICAL STUDY DESIGN ISSUES FOR ILIAC STENTING

FDA Presentation

Judith Danielson, FDA reviewer, introduced trial design issues. She noted that there are currently two stent systems that have FDA approval for treatment of iliac arteries following suboptimal PTA. Both of these stents were evaluated in registry trials using a historical control. Subsequent IDE applications for iliac stent trials incorporated a randomized clinical trial design using an approved stent as control. However, patient enrollment is slow because of the randomized trial design, limitations with currently approved stents that are used as controls, and the availability of other stents for off-label use. Ms. Danielson read the FDA questions to the panel.

Open Public Hearing

Christopher White, a clinical cardiologist, spoke on behalf of the **American College of Cardiology**. He defined stent placement as primary or provisional, with primary stenting being with or without balloon predilation and regardless of balloon result, while provisional stenting involved cases where balloon dilatation is not optimal. He suggested a stratification of devices into coronary and non-coronary devices to allow consistent treatment of devices like stents, balloons, and so forth without having to approve each stent for every vessel. Stents could be considered for approval for use in subsets of non-coronary vascular beds and for certain indications. Stratification or grouping of these vessels could be discussed, with some separated out and others grouped for generalized approval. On randomized iliac trials, he stated that these trials are unrealistic when the control is clinically unattractive and when unapproved devices are superior to approved ones. Because the professional literature

supports high success and low complication rates, he suggested that historical controls be used to create objective performance criteria or OPCs. Endpoints for provisional stent placements in the iliac artery should be based on procedural safety and efficacy, with 30-day endpoints of safety and efficacy and postmarket surveillance at one and three years to consider repeat procedure and limb salvage rates. Primary stent placement endpoints should be six-month patency with Duplex ultrasound and safety at 30 days. A fast-track approval process should be in place for life-saving devices, with postmarket surveillance to ensure long-term safety and efficacy. For embolic protection devices, he recommended use of surrogate endpoints and recognition that recovery of debris is a positive finding and equivalent to efficacy.

Gary Ansel of Grant/Riverside Methodist Hospitals/Medical College of Ohio added that long-term patency should be considered as separate from short-term or surgical patency. Survivability and functionability should be looked at as well, as should the complication rate, which he noted is very low.

Kenneth Rosenfield, of St. Elizabeth's Medical Center/Tufts University School of medicine, stated that the real problem for clinicians is how to conduct randomized trials when good new stents are available off-label to salvage suboptimal balloon angioplasties. He stated that randomized controlled trials are not necessary. Provisional stenting for suboptimal balloon angioplasties should be allowed based on historical controls. He thought it probably not reasonable to ask for randomized trials of newer stent technology against old controls.

Therefore, he suggested registries for newer technologies, using OPCs. Indications for primary stenting could be supported by a long-term trial.

Brian Stanken, M.D., University of Maryland Medical System and SCVIR Executive Council Member, spoke on behalf of the **Society for Cardiovascular International Radiology**. He discussed the two approved stents, listing their disadvantages and saying they were obsolete. New stents are not approved because of the financial disincentive and the delay in acquiring approval. Iliac trials to date have used controls or eligibility criteria that do not meet standards of care and are overly complicated. Furthermore, many operators prefer to stent iliac lesions primarily because the intervention is quick, simple, and seen as improving results. Dr. Stanken looked at advantages of randomized trials, literature or historical controls, and objective performance criteria, and he concluded that the development of clearly defined and detailed objective performance criteria for iliac artery stent procedures will simplify clinical trial design and reduce clinical trial cost and risk to the manufacturer. OPCs will also produce more useful comparative data, and by streamlining the approval process will create an opportunity to realign device indications and applications in the iliac arterial system.

Ann Peterson of Sulzer Therapeutics noted that vascular grafts have been reclassified as class two devices after much work from various disciplines and that registries provide valuable information. A number of the speakers suggested a multidisciplinary forum to serve in an advisory capacity to develop OPCs and design a trial.

OPEN COMMITTEE DISCUSSION

FDA Questions

- 1) *Please discuss the need for a randomized control trial to evaluate a new iliac stent system for a suboptimal indication and 2) If randomization is not considered necessary, please discuss the use of a nonrandomized concurrent control, historical control or the development of OPCs in the assessment of stenting following suboptimal angioplasty.*

The panel agreed, with varying degrees of reluctance, that while a randomized controlled trial is good, it is not realistic to demand one when there is no plausible control device. The panel liked the idea of a multidisciplinary forum to decide OPCs, with surgeons and institutions such as the SCVIR a part of the forum. The need for follow-up data and clearly defined indications was stressed, as was the need to demonstrate safety and efficacy. A registry should be loosely enough structured and prospectively set up to follow safety and efficacy over time.

- 3) *In considering stenting in occluded iliac arteries, please discuss the adequacy of a registry trial design, a historical control, or objective performance criteria and please comment on trial endpoints and the appropriate length of study follow-up for these patients.*

The panel thought the same concerns applied for occluded arteries as highly stenotic ones. They added that there should be a limit to the time of follow-up, with mortality and morbidity derived from a statistical analysis. Endograph and other registries should be looked at.

- 4) *Please discuss the following points regarding trial design for a primary stent indication: a randomized trial? Control? Superiority versus equivalence? Endpoints?*

The panel thought most of the points had already been discussed and that similar concerns applied to trial design for a primary stent indication.

- 5) *Do you have any other recommendations regarding the trial design for a primary stent indication in the iliac artery?*

All members of the panel recognized the difficulty in setting up a study. They noted that follow-up is especially critical in any study and suggested also looking at this issue in terms of patency, because of its critical importance to the patient. Very objective criteria should be used such as pulse volume and pressure recordings before and immediately after the procedure to see if the vessel is open. They recommended trying to find ways not to have repeat angioplasty because it is difficult to bring patients back when they feel fine. Surrogate endpoints for angiography should be used.

Mr. Dillard noted that there is a generic issue about the movement away from randomized control trials in all circumstances and toward looking at the knowledge base to see if other clinical trial designs such as registries will provide suitable information. He asked if the panel was expressing its willingness to work on other trial designs and look at data from other designs than a randomized control trial.

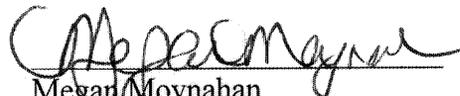
The panel thought that if the data were convincing and complete and the design appropriate, such data would be considered. It was noted, however, that other designs are

often extremely difficult and there is a need to be absolutely meticulous in execution, as well as posing clear and answerable questions. Confounding variables must be considered with care and finite endpoints must be clearly defined. The value of the randomized controlled trial is its clarity.

Mr. Dillard thanked the panel for its time and effort and apologized for the delay in clarifying the procedural issues involved the day's PMA process.

Dr. Tracy adjourned the Open Session at 5:02 p.m.

I certify that I attended the Open Session of the Circulatory Systems Devices Panel Meeting on April 23, 2001, and that this summary accurately reflects what transpired.


Megan Moynahan
Executive Secretary

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


Cynthia M. Tracy, M.D.
Chairperson

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