

SUMMARY MINUTES

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OF THE

CIRCULATORY SYSTEM DEVICES

ADVISORY PANEL MEETING

OPEN SESSION

SEPTEMBER 11, 2000

**Gaithersburg Marriott Washingtonian
Washingtonian Boulevard
Gaithersburg, MD**

CIRCULATORY SYSTEM DEVICES ADVISORY PANEL MEETING**September 11, 2000****ATTENDEES****ACTING CHAIRPERSON**

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

EXECUTIVE SECRETARY

Megan Moynahan, M.S.
Food and Drug Administration

VOTING MEMBERS

Michael D. Crittenden, M.D.
Harvard University

Julie Freischlag, M.D.
UCLA School of Medicine

CONSULTANTS (with Temporary Voting Status)

Kent R. Bailey, Ph.D.
Mayo Clinic

Melvin L. Griem, M.D.
University of Chicago

Geoffrey Ibbott, M.D.
University of Kentucky Medical Center

Mitchell Krucoff, M.D.
Duke University Medical Center

Kenneth E. Najarian, M.D.

University of Vermont College of Medicine
Tony W. Simmons, M.D.
Wake Forest University

J. Frank Wilson, M.D.
Medical College of Wisconsin

Guest

Robert L. Ayres
U.S. Nuclear Regulatory Commission

FOOD AND DRUG ADMINISTRATION

James E. Dillard III
Donna-Bea Tillman, Ph.D.
Bram Zuckerman, M.D.
Chris M. Sloan
Kimberly B. Peters
Henry T. Heaton II

OPEN SESSION—SEPTEMBER 11, 2000

Cynthia M. Tracy, M.D., Acting Panel Chairperson, called the Open Session to order at 10:05 a.m. **Executive Secretary Megan Moynahan** read the conflict of interest statement, noting that a waiver allowing full participation had been granted to Dr. Mitchell Krucoff, who had declared an interest in a firm potentially affected by the day's deliberations. Other matters concerning Drs. Krucoff, Tracy, Freischlag, Wilson, and Najarian were also 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 and noted that Consumer Representative Robert Dacy was unable to attend for health reasons. Ms. Moynahan read appointments to temporary voting status for Drs. Bailey, Griem, Ibbott, Krucoff, Najarian, Simmons, and Wilson and an appointment to serve as acting chairperson for Dr. Tracy.

OPEN PUBLIC HEARING

There were no requests to address the panel.

**PMA P000018 FOR NOVOSTE CORPORATION'S BETA-CATH INTRAVASCULAR
BRACHYTHERAPY SYSTEM****Sponsor Presentation**

Mr. Andrew Green, director of regulatory affairs for Novoste, gave the sponsor's overview. He discussed the history of the premarket approval application (PMA), noting that the device was specifically designed for intravascular brachytherapy in the catheterization laboratory

and had been tested in a large-scale, multi-center, masked, randomized trial of device versus placebo used to treat in-stent restenosis of native coronary arteries 2.7 mm to 4.0 mm in diameter. Sponsors sought to demonstrate 1) efficacy through improved clinical and angiographic outcomes, 2) safety through reduced major adverse coronary events (MACE) and no increased risk of thrombosis, and 3) ease of use through short treatment times and minimal exposure, allowing clinicians to remain with the patient throughout treatment.

Dr. Burton Speiser, director of radiation oncology at St. Luke's Regional Medical center and St. Joseph's Hospital, discussed the device and the procedure. He pointed out that radiation has a long history of use for proliferative diseases, both through external use and through brachytherapy. Dr. Speiser explained the selection rationale for the procedure and for the use of Strontium 90 (Sr -90) in it. He listed advantageous features of Sr-90 such as its dose rate, long half-life, and limited dose penetration, and he presented data on depth dose curves to nontarget areas and radiation exposure to patient and cath lab personnel. After listing the four components of the integrated system, Dr. Speiser listed system features and safety evaluation information to date. Dr. Speiser explained that the system team consists of a radiation oncologist, an interventional cardiologist, a medical physicist, and the cath lab staff. He also discussed in detail the five steps of the procedure: system preparation, dose and treatment time prescription, delivery catheter placement, and system removal.

Dr. Jeffrey J. Popma, principal investigator for the Stents and Radiation Therapy or START trial and director of interventional cardiology at Brigham and Women's Hospital, presented an overview of in-stent restenosis and clinical results of the pivotal trial. He reviewed statistics on in-stent restenosis and existing treatment options such as stent within a stent, atherectomy, and excimer laser. Dr. Popma stated that analysis of in-stent restenosis patterns shows that recurrence rates vary and are higher with bigger lesions and that aggressive debulking treatments have not solved the problem.

Dr. Popma explained that the START trial was a prospective, 50-center, triple-masked, randomized clinical trial enrolling 476 patients with in-stent restenosis to assess the safety and effectiveness of intracoronary beta radiation using a Strontium-90 source train versus placebo following successful coronary intervention. Dr. Popma defined the primary and secondary efficacy endpoints (8-month target vessel failure or TVF and 8 month angiographic restenosis, in-stent MLD and late loss) and the safety endpoints (8-month MACE and aneurysm formation). He listed the major inclusion and exclusion criteria and the method of dose prescription. As Dr. Popma explained, the protocol involving adjunctive antiplatelet therapy (APT) was changed from initially being at the physician's discretion to a recommended minimum of 90 days with new stents, based on recommendation of the Beta-Cath Data Safety Monitoring Board for the Beta-Cath System feasibility trial patients. Data at eight months showed a significant reduction in all outcome parameters such as TVF, MACE, target vessel revascularization or TVR, target lesion

revascularization or TLR, angiographic restenosis, and late loss, with no increased risk of thrombosis and no aneurysm formation.

Dr. Popma also looked at statistics on device performance in terms of device success and minor device malfunctions (MDMs). Successful treatment occurred in 98.1% of patients enrolled, with successful cases with MDMs in 18.7% of those treated. The majority of reported MDMs involved a source transit time of more than five seconds or source/ marker drift. It was suggested that causes might be suboptimal connection or operation of components and inadequate pressure on the syringe.

In response to the experiences of the START trial, device modifications to the system were submitted to the FDA, an in-depth training program incorporated trial experiences, and the user's manual was modified to include detailed instructions on component connections, pressure tests and monitoring, and the manual removal procedure. Dr. Popma briefly reviewed aspects of the training program, which includes regional and on-site training and 3-5 proctored clinical procedures. For long-term safety, Dr. Popma presented statistics from the U.S. feasibility study (the Beta Energy Restenosis Trial or BERT) that showed a rate of 69% in looking at four-year freedom from MACE.

Dr. Richard E. Kuntz, chief of the clinical biometrics division of Brigham & Women's Hospital, reviewed specific clinical topics such as the clinical impact of minor device malfunctions. An analysis of MDMs showed that 87.2% were reported as source drift and source

transit time of more than five seconds, with the remaining MDMs categorized as non-radiation related. The clinical impact of MDMs demonstrated no statistical difference in safety and efficacy as measured by MACE rates to 240 days and percentage of restenosis rates. The sponsors also proposed minor modifications to reduce the occurrence of source drift and source transit. Dr. Kuntz also looked at an edge analysis, from which he concluded that the difference in restenosis rates between the analysis and stent segments was due in part to the effectiveness of the treatment of Sr-90 and the masking of the progression of disease in the analysis segment.

Dr. Popma concluded the sponsor presentation by restating the medical need to treat in-stent restenosis for a difficult and growing population when there are no approved minimally invasive alternatives. The START trial showed that all prespecified hypotheses were achieved with statistical significance in reduction of TVF by 31%, reduction in MACE by 31%, reduction in TVR by 34% and reduction in TLR by 42%. Angiographic conclusions showed that restenosis was reduced in stent segments by 66% and analysis segment by 36%. Safety conclusions showed no difference in death, myocardial infarction (MI), late thrombosis, total occlusions, and aneurysms in Sr-90 versus placebo. He concluded that statistically significant differences in all safety and efficacy endpoints demonstrate that the Beta-Cath System is a viable treatment for in-stent restenosis, and that the safety and efficacy outcomes support a favorable risk-benefit ratio.

Questions to the Sponsors for Clarification

There were no initial questions from the panel following the sponsor presentation.

FDA Presentation

Kimberly Peters, lead FDA reviewer for the PMA, introduced the FDA summary. She listed the members of the FDA review team from various offices and described the device and its components. Ms. Peters noted that both the Alpha III and Alpha IV transfer device models were used in clinical evaluation, although only the Alpha IV rev. 2 device was the subject of the PMA. The main difference between models is the LED pressure indicators. She also noted that both 30 and 40 mm delivery catheters and source trains were used in clinical evaluation, although only the 30 mm delivery catheter and source train are the subject of the PMA. Nonclinical evaluation included five parts; of these the FDA is working with the sponsor on in vitro testing and source dosimetry as covered in the labeling. Biocompatibility testing showed the device to be nontoxic and found electrical, battery, and EMC testing to be in compliance with standards. Animal testing showed no difference in restenosis rates between device and control. Clinical investigations were a U.S. feasibility investigation called the Beta Energy Restenosis Trial (BERT) on 83 subjects, the Beta Radiation in Europe Trial or BRIE, which was a nonrandomized study on 150 patients, and the Stents and Radiation Therapy Trial (START), which was a randomized pivotal study.

Dr. Bram Zuckerman, medical officer of DCRD, presented the FDA clinical evaluation, which focused on the START pivotal trial. He described the trial as well designed and read the inclusion criteria. Dr. Zuckerman explained that a superiority hypothesis with the

conservative endpoint of TVF at 8 months was chosen, with TVF defined as a composite of death, MI, and TVR, with angiographic and ultrasound data as supporting data. Dr. Zuckerman presented statistics on device and procedure success, showing that device failure occurred in 9 cases in which either the catheter or source was not successfully delivered. He noted, however, that device or procedure success as defined by sponsors did not necessarily capture the variables of initial device failure with subsequent success or minor device malfunctions with suboptimal performance. Dr. Zuckerman showed 8-month safety results that indicated no difference between device and placebo in incidence of death, MI, stent thrombosis, total occlusion, or aneurysm. A minority were restented, however, and this population may be at greater risk for long-term safety problems. Device-related malfunctions were also observed. The 8-month effectiveness results showed that the primary endpoint of TVF and selected clinical and angiographic endpoints were all reduced by beta radiation treatment.

Ms. Peters read the FDA questions to the panel for discussion.

Panel Reviews

Dr. Tony Simmons gave the first review, in which he complimented both sponsors and FDA for the clarity of their presentations. He listed several questions for the sponsors, including why the presented data showed better clinical outcomes than those in the panel pack. It was suggested that this discrepancy might be the result of relative versus absolute difference in outcomes. He also expressed concern about the high rate of device failures, despite their lack of

clinical impact, noting that it might rise even higher in the hands of less experienced practitioners. Dr. Simmons stressed the importance of training in general and especially of the radiological oncologist in the catheter laboratory. He asked for more information about the recommendation of 90 days' antiplatelet therapy, which did not seem based on data. Noting that new stents were discouraged but 20% of patients received them nonetheless, he asked whether any one group received more stents and whether diabetic patients represented a distinctive subset in terms of restenosis. Sponsors replied to both questions that no differential effects were noted. Dr. Simmons also asked about the risk of radiation effects in terms of scar carcinomas, cancer incidence, and so forth, and raised labeling issues involving whether protocol and exclusion criteria should be built into the warnings and contraindications.

Dr. Kent Bailey agreed that the study was well performed and reported and listed a number of questions in his panel review. The first involved pooling drift and long transit time in the analysis of MDMs. He thought drift a more important issue that should have been analyzed separately and suggested that looking at the edge effect in cases of drift might have been useful. He also asked whether drift differences were random differences or might be related to patient differences. Dr. Bailey asked whether the results of the START trial were consistent enough with the BERT results to justify using the BERT recommendation on length of antiplatelet therapy. He also asked whether the fact that the treatment effect is more pronounced with longer lesions should be mentioned in the labeling in terms of the risk/benefit ratio for users to determine

whether shorter lesions would benefit less from this treatment. Dr. Bailey also asked for clarification on the heterogeneity between sites.

Sponsors replied that pooling drift and transit time was an issue of power, and that edge effect was not analyzed in drift cases. Patient analyses provided no indicators of drift. Sponsors said that patient differences in the BERT and START trials prevented further information on the recommended length of antiplatelet therapy. They stated that lesion length is associated with a higher risk of restenosis, but found it is hard to identify the break point on the value of using radiation with shorter lesions. Analysis of heterogeneity between sites produced no major issues.

In general panel discussion, panel members asked a number of questions of the sponsors. Some related to the dose range actually used in studies and a proposed upcoming change to medical regulations in which the licensee would be solely responsible for calibrating the brachytherapy source dose rate. Other issues involved the rationale for the recommended source transit time, the role of the radiation oncologist versus the interventional cardiologist, and the worrisome lack of animal data that the device works and about the mechanism through which it works. Other questions included the role of debulking techniques in large vessels, use of reprobng, learning curves on the device and effect on performance, and whether stents inside stents should be contraindicated.

FDA representative James Dillard reminded the panel that consideration of the PMA should be based on data in the PMA or published literature only, not data outside the PMA.

Panel Discussion of FDA Questions

1) Please discuss your recommendations for the antiplatelet therapy for patients who received a new stent, and for patients who do not receive a new stent.

The panel agreed that for patients receiving a new stent, the labeling recommendation for a 90-day use of antiplatelet drug therapy seems reasonable. Patients not receiving a new stent should be managed per the routine medical approach of the center doing the procedure.

2) Please discuss the clinical importance of the device failure and malfunction events in the evaluation of the safety and effectiveness of the Beta-Cath system.

The panel concluded that minor drift is not a major problem. Other engineering issues, however, should be monitored and must be addressed in relation to training, redesign, and so forth. The panel wanted augmented information showing that the incidence of device failure and malfunction events is decreasing over time and that training and modifications are sufficient to address the problem. Members of the panel expressed a concern over delivery, including the technical adequacy of the introduction method and the withdrawal of an active radioactive source. They asked for the most accurate analysis possible of new clinical data.

3) Please discuss whether you believe the probable clinical benefit of the radiation treatment outweighs the probable risks of death, myocardial infarction, late total occlusion, and late stent thrombosis posed by the device in the intended patient population.

The panel agreed that the clinical benefit of the treatment outweighs the probable risk, but wanted information on the shorter 30 mm device and more follow-up on the mechanics and effect of the delivery system on site irritation and the late effects of radiation in beta intervention.

4a) Please comment on the indications for use section as to whether it identifies the appropriate patient population for treatment with the device.

The Indications statement should read, "The Beta-Cath System is indicated for in-stent restenosis of native coronary arteries for patients who have undergone successful PCI for discrete lesions (treatable with a 20 mm balloon) with a reference vessel diameter ranging from 2.7 mm to 4.0 mm."

4b) Please comment on the contraindications section as to whether it identifies all conditions under which the device should not be used because the risk of use clearly outweighs any possible benefit.

The panel urged that all patient populations not studied should be listed somewhere, such as those with certain rates of ejection fraction, thrombotic lesions, stent sandwiches, vein grafts, or diffuse proliferative lesions extending beyond stent margins, and so forth. The section on special considerations should include women of childbearing potential because of unintentional

radiation exposure to the fetus. Number two under special considerations should be removed.

There should be an additional consideration or precaution about acute infarct vessels. After a discussion about whether to add morphology to “lesions that preclude revascularization,” it was agreed to leave the original.

4c) Please discuss comment on the warnings and precautions sections as to whether it identifies all potential hazards regarding device use.

The panel thought that all information should be collected in one place and that a message to the user on the importance of the whole team being assembled and training together should be stressed here.

4d) Please discuss whether any improvements could be made to the labeling to help minimize the occurrence of device failures and malfunction as discussed under question 2.

The statement about the importance of assembling and training the whole team approach should be placed here, as should comments about proper use and technique with the introducer.

4e) Please comment on the remainder of the device labeling as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events.

The panel initially suggested describing the optimal bailout procedure, but there was a divergence of views about whether to mandate the bailout procedure or leave this to operator choice. It was suggested that the phrase “and guide wire” should be removed. Lesion length and

efficacy data should be presented here. It is key that the labeling state where safety and efficacy were demonstrated and what the inclusion and exclusion criteria were.

4f) Does the panel have any other recommendations regarding the labeling of the device?

The panel stated that the device should not be used for primary treatment of lesions. The panel also added a recommendation that a multispecialty team for the procedures must be maintained. Other recommendations were that more dosimetry and efficacy information and radiation dose options should be given, and it should be noted that the dose should be along the long axis of the source. Recommended procedure for facility staff to calibrate the source strength should be added. The panel recommended that position, treatment time, and exit time should be emphasized as important, but labeling should not extrapolate beyond the data.

5a) Please discuss any improvements that could be made to the training program to help minimize the occurrence of device failures and malfunctions as discussed under question 2.

The panel stressed that proficiency should be ensured with the entire team receiving first-hand training through mock procedures. Training should be required until proficiency is demonstrated, with success being monitored through MDM rates and so forth. Retraining should be done whenever team members change.

Mr. Dillard noted the limits to FDA's regulatory authority, but underscored his understanding that the panel was recommending demonstration of proficiency for all team members, proficiency criteria, and company backing and oversight during training. Training

should be individualized rather than a cookbook approach. The sponsors stressed their intention to be with medical centers and operators as needed.

5b) Please identify any other important elements that should be contained in a physicians' training program for this device.

Documentation that training was received, through certification, was the only panel suggestion.

6) Based on the clinical data provided in the panel pack, do you believe that additional clinical follow-up data or postmarket studies are necessary to evaluate the chronic effects of intravascular radiation administration? If so, how long should patients be followed, and what endpoints and adverse events should be measured?

The panel recommended definition of safety and efficacy endpoints to look at device malfunctions for the new cohort and follow-up of the old cohort for clinical outcome for a minimum of 24 months, with four years preferable, although it was noted that it is difficult to distinguish device effect on a particular lesion as time goes by. It was suggested that reasonable benchmarks be dovetailed in as a part of the training program.

Open Public Hearing

There were no requests to address the panel.

FDA and Sponsor Closing Remarks

Neither the FDA nor the sponsor representatives had closing remarks.

Final Recommendations and Vote

Ms. Moynahan read the voting instructions and options. A motion to recommend the PMA as approvable with conditions was made and seconded. The conditions were as follows:

- 1) There should be postmarketing surveillance with five-year follow-up of the current population of START patients and observation and data gathering on any new patient population for new and previously unsuspected problems or previously identified device malfunctions. This condition passed unanimously (9-0).
- 2) Data on only the 30 mm device group should be reanalyzed to see if safety and efficacy are still proven without the 40 mm device data. This condition passed unanimously (9-0).
- 3) Completion of mandatory training should be documented. Training should include mock and real training to establish proficiency and should be conducted each time a new team member is added. This condition passed unanimously (9-0).
- 4) The wording on indications, warnings, and precautions should be changed as discussed above and the data reanalysis should be included in a format analogous to Table 1. This condition passed unanimously (9-0).

The panel also encouraged the sponsor to cooperate fully with the FDA on all bench testing.

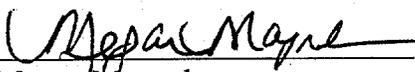
The motion to recommend the PMA as approvable with the above conditions passed unanimously. Members of the panel stated that they voted for approval with conditions

because the data support a demonstration of safety and efficacy, with the reasonable conditions noted to address human and device factors. Sponsors were also encouraged to look at device malfunction and dose curve data closely as the information is gathered.

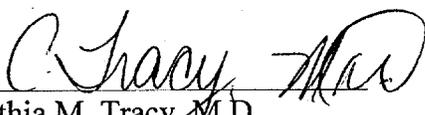
Both sponsor and FDA representatives thanked the panel for their time and careful review of the PMA.

Acting Chairperson Dr. Tracy adjourned the Open Session at 5:15 p.m.

I certify that I attended the Open Session of the Circulatory Systems Devices Panel Meeting on September 11, 2000, 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.
Acting Chairperson

Executive Summary prepared by

Aileen M. Moodie
9821 Hollow Glen Pl.
Silver Spring, MD 20910
301-587-9722