

FOOD AND DRUG ADMINISTRATION

MEDICAL DEVICES ADVISORY COMMITTEE

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CIRCULATORY SYSTEM DEVICES PANEL

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MEETING

+ + + + +

MONDAY

JUNE 19, 2000

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The Panel met at 10:00 a.m. in Salons A,B and C of the Gaithersburg Hilton, 620 Perry Parkway, Gaithersburg, Maryland, Dr. Anne B. Curtis, Chairperson, presiding.

PRESENT:

ANNE B. CURTIS, M.D.	Chairperson
KENT R. BAILEY, PhD	Temporary Voting Member
ROBERT L. AYRES, PhD	Guest
MICHAEL D. CRITTENDEN, M.D.	Voting Member
ROBERT DACEY	Consumer Representative
MICHAEL J. DOMANSKI, M.D.	Temporary Voting Member
MELVIN L. GRIEM, M.D.	Temporary Voting Member
RENEE S. HARTZ, M.D.	Voting Member
GARY JARVIS	Industrial Representative
MINESH P. MEHTA, M.D.	Temporary Voting Status
KENNETH E. NAJARIAN, M.D.	Temporary Voting Status
ALFRED F. PARISI, M.D.	Temporary Voting Status
TONY W. SIMMONS, M.D.	Voting Member
CYNTHIA M. TRACY, M.D.	Temporary Voting Status
J. FRANK WILSON, M.D.	** Temporary Voting Status
MEGAN MOYNAHAN	Executive Secretary

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## P-R-O-C-E-E-D-I-N-G-S

(10:00 a.m.)

CHAIRPERSON CURTIS: I'd like to call this meeting of the Circulatory System Devices Panel to order.

The first order of business is going to be the reading of the conflict of interest statement by Megan Moynahan.

MS. MOYNAHAN: Good morning. My name is Megan Moynahan. I'm the panel Executive Secretary of the Circulatory Systems Devices Panel.

The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of a impropriety.

To determine if any conflict existed, the agency reviewed the submitted agenda for this meeting and all financial interests reported by the committee participants. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employer's financial interests. However, the

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1 agency has determined that participation of certain  
2 members and consultants, the need for whose services  
3 outweighs the potential conflict of interest involved,  
4 is in the best interest of the government.

5 Therefore, waivers have been granted for  
6 Doctors Renee Hartz and Alfred Parisi for their  
7 interest in firms that could potentially be affected  
8 by the panel's recommendations. Copies of these  
9 waivers may be obtained from the agency's Freedom of  
10 Information Office, Room 12A-15 of the Parklawn  
11 Building.

12 We would like to note for the record that  
13 the agency also took into consideration other matters  
14 regarding Dr. Anne Curtis, Minesh Mehta and Kenneth  
15 Najarian. Each of these panelists reported interests  
16 in firms at issue, but in matters that are unrelated  
17 to today's agenda. The agency has determined,  
18 therefore, that they may participate fully in all  
19 discussions.

20 In the event that the discussions involve  
21 any other products or firms not already on the agenda  
22 for which an FDA participant has a financial interest,

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1 the participant should excuse him or herself from such  
2 involvement, and the exclusion will be noted for the  
3 record.

4 With respect to all other participants, we  
5 ask in the interest of fairness that all persons  
6 making statements or presentations disclose any  
7 current or previous financial involvement with any  
8 firm whose products they may wish to comment upon.

9 CHAIRPERSON CURTIS: The next thing I'd  
10 like to do is to have the panel members introduce  
11 themselves. I'm Anne Curtis. I'm a cardiac  
12 electrophysiologist from the University of Florida.

13 DR. SIMMONS: Tony Simmons. I'm a cardiac  
14 electrophysiologist, Wake Forest University.

15 DR. CRITTENDEN: Michael Crittenden. I'm  
16 a heart surgeon from the West Roxbury VA, Harvard  
17 University.

18 DR. NAJARIAN: Kenneth Najarian,  
19 interventional radiologist at the University of  
20 Vermont.

21 DR. WILSON: \*\* Frank Wilson, radiation  
22 oncology, Medical College of Wisconsin.

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1 DR. TRACY: I'm Cynthia Tracy. I'm an  
2 electrophysiologist at Georgetown University Hospital.

3 DR. BAILEY: Kent Bailey, biostatistician,  
4 Mayo Clinic.

5 MR. DACEY: Robert Dacey, consumer  
6 representative from Longmont, Colorado.

7 MR. DILLARD: Jim Dillard. I'm the  
8 Director of the Division of Cardiovascular Respiratory  
9 Devices, Food and Drug Administration.

10 DR. AYRES: Robert Ayres, staff member of  
11 the U.S. Nuclear Regulatory Commission.

12 MR. JARVIS: Gary Jarvis industry  
13 representative to the panel.

14 DR. GRIEM: Mel Griem, emeritus  
15 professor, University of Chicago, radiologist.

16 DR. DOMANSKI: Mike Domanski. I'm a  
17 cardiologist at the National Heart, Lung and Blood  
18 Institute.

19 DR. MEHTA: Minesh Mehta, radiation  
20 oncologist, University of Wisconsin.

21 DR. PARISI: I'm Al Parisi. I'm a  
22 cardiologist at Brown University.

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DR. HARTZ: Renee Hartz, cardiac surgeon,  
Tulane University.

MS. MOYNAHAN: Also for the purpose of  
this PMA application today, I'd like to read into the  
record the appointments of temporary voting status.

Pursuant to the authority granted under  
the Medical Devices Advisory Committee charter dated  
October 27, 1990, as amended April 18, 1999, I appoint  
the following people as voting members of the  
Circulatory System Devices Panel for this meeting on  
June 19, 2000: Melvin Griem; Minesh Mehta; Alfred  
Parisi; Cynthia Tracy; Kent Bailey; Michael Domanski;  
Kenneth Najarian; Frank Wilson.

For the record, these people are special  
government employees and are consultants to the panel  
under the Medical Devices Advisory Committee. They  
have undergone the customary conflict of interest  
review and have reviewed the material to be considered  
at this meeting.

The memo is dated June 8, 2000 and signed  
by David Feigal, Director, Center for Devices and  
Radiological Health.

1 CHAIRPERSON CURTIS: We are scheduled next  
2 for an open public hearing, but as far as I know, no  
3 one has previously requested time now. Is there  
4 anyone among the public who would like to speak now?  
5 There will be another opportunity later on for  
6 comments from the public.

7 If not, then what I'd like to do is move  
8 on to the presentation by the Cordis Corporation on  
9 PMA P990036, the Cordis Checkmate system. In each  
10 case, if you could introduce yourself and your  
11 financial interest in the product.

12 DR. DONOHOE: My name is Dennis Donohoe.  
13 I'm the Vice President of Clinical Research for  
14 Cordis.

15 Madam Chairperson, panel members, panel  
16 consultants and representatives of the FDA, it is our  
17 pleasure to come before this panel to present a review  
18 of the clinical trials conducted in support of the  
19 Cordis radiation Checkmate system.

20 It is once again an opportunity for Cordis  
21 to introduce a novel technology, including an  
22 intravascular therapy which we believe, represents as

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1 an significant advance in patient management as did  
2 the introduction of the stent.

3 At the start of the formal presentation,  
4 I'd like to take a few minutes to provide some brief  
5 background information on this program which we  
6 believe that panel members may find beneficial before  
7 presenting the clinical trial results.

8 Cordis chose to study radiation therapy in  
9 patients with in-stent restenosis, because these  
10 patients and physicians have no good effective therapy  
11 available to them in managing this chronic disease.

12 There have been a number of other  
13 interventions and therapies that have been tested and  
14 published over the past few years, all of which have  
15 failed to show the desired level of efficacy that both  
16 patients and physicians are looking for.

17 Additionally, there are a large number of  
18 patients in the United States with in-stent  
19 restenosis, and this number is going on a yearly  
20 basis, secondary to the increased use of  
21 interventional procedures in treating coronary artery  
22 disease, as well as the increase in percent of cases

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1 using new stents to treat de novo lesions.

2 Form the patient's perspective, this is a  
3 debilitating disease resulting in increased frequency  
4 and recurrent admissions to the hospital,  
5 interventions, adjustments in medical therapy, and  
6 operative procedures, all on the part of the  
7 physicians in order to try and relieve the patients of  
8 the persistent restenosis process, this process being  
9 one of intimal hyperplasia resulting in overgrowth of  
10 tissue through the stent, causing recurrent stenosis  
11 and occlusion.

12 Brachytherapy has been used for about 100  
13 years in the treatment of a variety of malignancies.  
14 As a result, there is a sizeable body of knowledge  
15 available on both the safe handling and storage of  
16 radioactive sources as well as clinical response of  
17 tissue to implants.

18 Within the past ten to 20 years, this  
19 therapy has been extended to the treatment of benign  
20 hyperproliferative lesions, including pterygiums and  
21 keloids, which have demonstrated good effect and no  
22 long term safety problems. It seems logical then to

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1 apply this therapy to another benign  
2 hyperproliferative lesion. That is in-stent  
3 restenosis.

4 Iridium 192 was used as the source in the  
5 clinical studies, because it is a gamma-emitter which  
6 provides the desired dose distribution for in-stent  
7 restenosis. It is an NRC registered source for the  
8 past 40 years, and two years ago was registered for  
9 intravascular use.

10 It provides a satisfactory safety margin  
11 with an average dwell time of 20 minutes, minimizing  
12 the chance of accidental overdose. The presence of  
13 calcification and metallic stents within the arterial  
14 wall have no significant effect on the dose  
15 distribution, and there is extensive experience by the  
16 radiation oncologists and physicists in the use of  
17 gamma radiation.

18 The picture at the top of this slide shows  
19 the ribbon that was used in the clinical trials. As  
20 you can see from the picture and a little more clearly  
21 from the diagram underneath, the ribbon is composed of  
22 a series of seeds. Each seed contains a maximum of 33

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1 millicuries of iridium 192 surrounded by stainless  
2 steel. These seeds are then covered with a nylon  
3 polymer which securely holds the seeds in place and  
4 allows flexibility of the ribbon.

5 As you can see at the bottom of the slide,  
6 there are different ribbon lengths, and they are  
7 varied by adding different numbers of seeds to the  
8 ribbon. This allows flexibility for the physician in  
9 choosing the right seed length or ribbon length for  
10 the lesion to be treated.

11 One other point on this slide: The lesion  
12 -- or the length of the ribbon chosen was to be  
13 matched to the lesion length. However, the ribbon  
14 length should extend three to five millimeters beyond  
15 the length of the treatment, so the edges of the  
16 stents were treated. Next slide, please.

17 There are two other key components to the  
18 Cordis radiation system. On the left is a picture of  
19 the delivery catheter. This allows for rapid  
20 exchange. It is 3.5 French system and 1.2 millimeters  
21 in diameter and is a closed-end catheter into which  
22 the source ribbon is delivered.

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1                   On the right is a very simple storage and  
2 delivery device, lead lined, allowing ports for simple  
3 manual delivery and retrieval of the source ribbon by  
4 the radiation oncologist. Next slide.

5                   The radiation procedure itself is very  
6 straightforward. Following the performance of a  
7 routine angioplasty procedure in which the  
8 interventionalist achieves the best results possible,  
9 an IVUS assessment of the lesion is performed.

10                   Following this, the delivery catheter is  
11 inserted with a dummy ribbon. The dummy ribbon  
12 resembles the active source ribbon in all respects  
13 except for the lack of activity. Once this is done  
14 and is placed across the lesion, both the cardiologist  
15 and the radiation oncologist assess to make sure the  
16 ribbon is placed in the right position and the  
17 appropriate length ribbon is chosen for the length of  
18 the lesion to be treated.

19                   The radiation oncologist with the  
20 assistance of the physicist calculate the appropriate  
21 dwell time based on the IVUS determined distance to  
22 the external elastic membrane as well as the measured

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1 activity of the ribbon on that day.

2           Once this is completed, the dummy ribbon  
3 is removed, and the active source is manually  
4 delivered by the oncologist for the calculated dwell  
5 time and removed manually back into the storage  
6 device.

7           This, obviously, is truly a team approach.  
8 The radiation oncologist is responsible for the safe  
9 storage and transport of the device, as well as the  
10 manual delivery and retrieval of the source ribbon.  
11 The medical physicist assists the oncologist in  
12 calculating the dwell time and measuring the source of  
13 the ribbon. The interventional cardiologist is  
14 responsible for management of the patient and all  
15 other technical aspects of the procedure.

16           The radiation safety officer assures  
17 proper shunting is in place and measures the level of  
18 radiation in the cath lab during the procedure. Next  
19 slide.

20           This PMA was submitted in June of 1999.  
21 It was granted expedited review status by the FDA,  
22 given that this patient population has no good

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1 alternative therapies available.

2 The PMA consists of three randomized,  
3 double-blind, placebo controlled trials which, we  
4 believe, show overwhelming efficacy as well as  
5 durability of treatment.

6 Given that these clinical studies involve  
7 the novel use of an old therapy, Cordis conducted a  
8 thorough analysis of the clinical data to assess any  
9 potential safety issues involved with the use of  
10 radiation. A single safety issue was identified,  
11 involving the late total occlusion rate and late  
12 thrombosis, which were higher compared to the placebo  
13 group.

14 The analysis involved probably the largest  
15 single dataset involving over 550 patients who had  
16 been treated with iridium 192, and the data have  
17 pointed to two factors that contributed to this, the  
18 use of a new stent in conjunction with radiation  
19 therapy and short duration antiplatelet therapy.

20 The risk/benefit: As you know, for each  
21 case the physician assess the risk and benefit of any  
22 therapy for every patient they treat. We believe the

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1 benefit of this therapy has been demonstrated by the  
2 overwhelming efficacy in a difficult disease process  
3 as well as in a patient population that has no good  
4 alternative therapies available to them.

5 The risk of late thrombosis has been  
6 identified, and the analysis has indicated two factors  
7 that clearly are manageable and controllable by the  
8 physician. That is avoiding the placement of new  
9 stents and providing extended antiplatelet therapy.

10 As a result, we believe the potential  
11 clinical benefit outweighs the manageable risk.

12 I would now like to introduce the next two  
13 speakers in the remaining part of our agenda. Dr.  
14 David Holmes will present a review of the primary  
15 safety and efficacy endpoints across all three  
16 randomized studies, and Dr. Richard Kuntz will present  
17 a more detailed discussion of late total occlusion and  
18 late thrombosis. Finally, Dr. Holmes will make some  
19 closing remarks.

20 DR. HOLMES: It's great to be here to talk  
21 about this important technology and this important  
22 group of patients. I'm the Director of the Cardiac

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1 Catheterization Laboratory and Professor of Medicine  
2 at the Mayo Clinic. Next slide.

3 CHAIRPERSON CURTIS: Could you state what  
4 your financial interest is here?

5 DR. HOLMES: I have received an honorarium  
6 for this morning's meeting and travel expenses. I do  
7 not have any other financial interest either in terms  
8 of stock or options or consultancies or anything in  
9 this important technology.

10 CHAIRPERSON CURTIS: Thank you.

11 DR. HOLMES: Stents have truly been  
12 breakthrough technology in the treatment of  
13 cardiovascular disease, and they have revolutionized  
14 the field of modern cardiovascular care. We know that  
15 in 1999 the data would suggest that there were 750,000  
16 interventions performed in the United States, and 75  
17 percent of those interventions included a stent. At  
18 least, in our institution in Rochester about 90  
19 percent of the cases involve a stent. So there are a  
20 large number of stents that have been placed.

21 We know, though that stents, despite the  
22 fact that they have improved restenosis, have not made

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1 it completely go away. So there are a group of  
2 patients in whom we see with recurrent in-stent  
3 restenosis. It's about 20 percent of the overall  
4 population of stented patients.

5 It's anticipated that that frequency will  
6 probably increase as we extend and expand the  
7 indications for stent implantation to smaller vessels  
8 and more diffuse disease and higher risk subsets.

9 As we think about the numbers then,  
10 750,000 dilatations, 75 percent of which involve a  
11 stent and 20 percent in-stent restenosis, the math  
12 would indicate that more than 100,000 patients will be  
13 seen with in-stent restenosis annually in the United  
14 States, and it's this patient population that we're  
15 dealing with. It's this patient population that we  
16 have to deal with repeatedly because of recurrent  
17 events.

18 We also know not only about the frequency,  
19 but we know about the mechanism of restenosis, and  
20 that is different in contrast to conventional balloon  
21 angioplasty. It is excessive neointima hyperplasia.  
22 On this slide we can see what that neointima

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1 hyperplasia looks like.

2           This happens to be from a human LAD  
3 specimen. Here we can see the atherosclerotic plaque.  
4 Here we can see the stent tines and metal here, and we  
5 can see within that lumen there is the development of  
6 exuberant new tissue, neointima hyperplasia, that has  
7 resulted in stenosis in this particular patient, can  
8 result in an occlusion and increase in morbidity and  
9 even mortality in this patient subset. Next slide.

10           Although this is perhaps a little unusual,  
11 I'd like to start out with a case, because it  
12 illustrates the issues of this group of patients.  
13 It's a 42-year-old man who was doing everything right,  
14 thin, running, everything under control with the  
15 exception of the fact that he developed angina. Then  
16 he was found to have critical left main coronary  
17 disease. That was in 1992.

18           So in 1992 in the fall of that year he  
19 underwent coronary bypass graft surgery, as would be  
20 the traditional approach, and he had a left internal  
21 mammary to the LAD, and he had a vein graft to the  
22 circumflex. He did well for three years until 1995

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1 when he developed recurrent angina.

2 At the time of angiography he was found to  
3 have a patent LIMA. He had, however, an occluded  
4 circumflex graft. So then he was ischemic in the  
5 lateral wall. He had a stent implanted in the ostial  
6 circumflex in June of 1995.

7 He initially had improvement in his  
8 symptoms. However, three months later he had the  
9 first of his in-stent restenoses, and he was treated  
10 with conventional dilatation. That lasted for a month  
11 until October of 1995 when he had his second in-stent  
12 restenosis, and this is what it looked like.

13 Here we have the left main, severe  
14 stenosis and then an ostial circumflex stenosis. It  
15 was treated now with not only conventional angioplasty  
16 but with excimer laser coronary angioplasty, and we  
17 initially got a nice result in this now 45-year-old  
18 patient. Next slide.

19 However, in January of that year, just a  
20 few months later, he had his third in-stent  
21 restenosis. He had again excimer laser coronary  
22 angioplasty and a new stent placed. That did well for

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1 six months, and then he had his fourth in-stent  
2 restenosis treated with conventional angioplasty and  
3 another stent.

4 You can see with each occasion prior to  
5 the intervention, he had severe stenoses there, and  
6 usually he gets a very excellent result, whether it be  
7 from excimer laser or conventional dilatation. The  
8 problem is it's not durable. It doesn't last.

9 So in February of 1997 he had his fifth  
10 episode of in-stent restenosis, now treated with  
11 rotational atherectomy and dilatation, and was  
12 enrolled in one of the trials to see whether we could  
13 improve on the outcome in this patient that had  
14 already been back see you on five different occasions  
15 for in-stent restenosis. Next slide.

16 So the issues in this patient are he has  
17 already had one surgical procedure. It's a good  
18 surgical procedure. The LIMA was excellent. The  
19 problem is that he has recurrent angina from recurrent  
20 in-stent restenosis, despite medical therapy, and he  
21 has had five interventions, including stent  
22 implantation, rotational atherectomy, laser and

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1 conventional dilatation.

2 This is one end of the spectrum, somebody  
3 who has already been treated with surgery. The other  
4 end of the spectrum is a patient with single vessel  
5 disease involving the distal right coronary or the  
6 distal circumflex in whom the LAD is normal; and in  
7 that patient, when they have recurrent angina  
8 following stent implantation, we are reluctant to send  
9 the patient to surgery, because the LAD is normal, and  
10 a LIMA wouldn't reach.

11 So the other end of the spectrum are that  
12 group of patients who have not yet had surgery, who  
13 are not sick enough for surgery yet, because their LAD  
14 is normal, and yet they have recurrent angina.

15 You need to realize that this is a group  
16 of patients that is large. When I go back to  
17 Rochester, Minnesota, tomorrow, the nurse coordinator  
18 is going to want to find out how things went, because  
19 the nurse coordinator has 50 patients on a list with  
20 in-stent restenosis. Then I have to say how things  
21 are going, who are we going to select for therapy,  
22 what are we going to tell the local physician at home,

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1       how are we going to prioritize these 50 patients that  
2       have in-stent restenosis and recurrent symptoms that  
3       need to be treated.     Next slide.

4                 We know things about factors associated  
5       with in-stent restenosis.     We know that vessel  
6       diameter is important.     We know that lesion length is  
7       important.     The longer the lesion, the more potential  
8       for in-stent restenosis.     We know that the patients  
9       with diabetes melitis have more restenosis, and those  
10       patients with LAD location of the stenosis have more  
11       problems with recurrent in-stent restenosis.

12                We know that in the past, like we did in  
13       this 42-year-old man, we've tried conventional  
14       dilatation and rotational atherectomy.     We've tried  
15       laser and restenting singly or in combination.

16                The problem is that there is a recurrent  
17       rate in these patients of about 50 percent.     It  
18       depends to a certain extent on what that restenosis  
19       looks like.     If it is diffuse in-stent restenosis, the  
20       chance of recurrence is 80 percent, and that's a major  
21       issue for the patients with recurrent diffuse in-stent  
22       restenosis like this patient presented with.     Next

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1 slide.

2 This just looks at some of the data. We  
3 talked about the overview of what might result in  
4 increased restenosis. This looks at the influence of  
5 lesion length on restenosis rates. Here we have the  
6 lesion length in millimeters from ten to 35, and here  
7 we have the frequency of restenosis.

8 As we can see, as we go from shorter  
9 lesions to longer lesions, we can approach or even  
10 exceed 50 percent recurrent restenosis rates in those  
11 lesions that are 35 millimeters or longer. So as we  
12 deal with more diffuse disease, we're going to see  
13 more restenosis, undoubtedly. Next slide.

14 That's the background. Let's talk then  
15 about these three randomized, placebo-controlled,  
16 double-blind trials conducted with Iridium 192, the  
17 radiation system we're talking about today.

18 I think the important thing as we review  
19 these clinical trials are that there was an  
20 independent data safety monitoring committee. There  
21 was a superb angiographic core laboratory. Clinical  
22 events were adjudicated for all the studies by the

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1 same people. So we have common definitions and common  
2 approaches and common analyses, so that we can make  
3 some summary conclusions. Next slide.

4 This is the evolution of information about  
5 the technology. Started with the SCRIPPS trial, a  
6 single site, small number of patients, initiated in  
7 1995, moved on to a larger study, still a single site  
8 study, the WRIST trial initiated in 1997; and then the  
9 pivotal study, the GAMMA I multi-center, more  
10 patients, 250 patients, initiated at the end of 1997.

11 So this is the evolution of the evidence that we're  
12 going to present and talk about. Next slide.

13 This just looks at some of the design of  
14 these three trials. They were all randomized, as  
15 we've talked about. The inclusion criteria typically  
16 included in-stent restenosis, and that's the group  
17 that we're going to focus on.

18 The source was identical in all of those.  
19 As we look at the patient population: In GAMMA I, 98  
20 percent were native vessels. In the other two trials,  
21 75 or 80 percent were native vessels. We're going to  
22 talk and focus on native vessel disease and in-stent

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1 restenosis in native vessels rather than vein graft  
2 disease which is quite a bit different. Next slide.

3 These are more of the issues about design.  
4 Crossover was allowed in SCRIPPS I and WRIST. It was  
5 not allowed in GAMMA, and that has some important  
6 issues that we will need to consider.

7 The dosimetry varied. It was IVUS based  
8 in GAMMA and SCRIPPS, and it was fixed in WRIST, but  
9 the dose range schedule, as Rick is going to talk  
10 about, overlapped between all three studies.

11 The antiplatelet therapy evolved over the  
12 course of this time from 1995 to 1997 when GAMMA was  
13 started from two weeks of antiplatelet therapy with  
14 aspirin and diclopadin out to then finally eight weeks  
15 in the GAMMA I trial, as we began to learn something  
16 about the issue of subacute closure and potential for  
17 late thrombosis. Next slide.

18 This just looks at some of the clinical  
19 variables which identified this patient group. We can  
20 see that diabetes is very frequent. If you were to  
21 look at most interventional<sup>\*\*</sup> practices in the United  
22 States, only about 20 percent of the patients

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1       undergoing a percutaneous intervention are diabetic  
2       patients. This is an enriched group, because anywhere  
3       between 30 and 40 percent have diabetes. LAD at about  
4       a third. These patients were significantly limited by  
5       their angina pectoris.

6               One of the most striking parts of this  
7       slide is the information on prior procedures, and look  
8       at the range. Up to six prior procedures have been  
9       performed in the patients in the SCRIPPS trial. In  
10       the GAMMA I trial there was one patient that had had  
11       12 recurrent restenoses events that needed to be  
12       treated.

13               You can see that the average was 1.6 to  
14       1.9, but a large number of patients had had very  
15       frequent need for repeat procedures. Next slide.

16               This looks at some of the angiographic  
17       variables. Lesion length varied. The SCRIPPS trial  
18       was the shortest of these in terms of lesion length,  
19       but look at the range of these lesions.

20               There were very long lesions, out to 50 or  
21       60 millimeters; and as we remember the graph on the  
22       relationship between lesion length and subsequent

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1 restenosis, this identifies a group of patients that  
2 would have very high recurrent restenosis events.

3 In WRIST you can see that the lesion  
4 length was 20 millimeters, and very similar in GAMMA.  
5 The reference vessel diameter: Remember, the smaller  
6 the reference vessel, the more potential for  
7 restenosis. These were very similar across the board,  
8 2.7 to 2.8. But there were some very small lesions  
9 that were treated, very small vessels that were  
10 treated in 1.5 millimeter vessels. Next slide.

11 What's the data in this group of patients?  
12 This is the data. As we look at the data, we will  
13 look at different ranges and different definitions of  
14 restenosis. Here we have in caricature at the top.  
15 We can see the in-stent segments. This is bracketed  
16 by the segment here. That allowed and included the  
17 ribbon placement for the seeds, and then on either  
18 side of that there was a five millimeter segment  
19 defined as the edge or the margin.

20 So as we look at in-stent restenosis in  
21 SCRIPPS I and WRIST, we can see that in the smaller  
22 trial, the SCRIPPS trial, there was a decrease. No

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1 question about that. The numbers were small, but it  
2 decreased the in-stent restenosis by 50 percent in the  
3 radiation group.

4 The striking thing that was in the WRIST  
5 trial there was even greater decrease, and we can see  
6 that in this trial with higher risk patients radiation  
7 resulted in 65 percent reduction in in-stent  
8 restenosis. The improvement was maintained in both of  
9 those, even though there were higher risk patients  
10 with longer lesions in the GAMMA trial and more  
11 diabetes in the GAMMA trial.

12 If you would look at the placebo group of  
13 patients, we can see that the restenosis rate is very,  
14 very high. It's 57 percent in this group of patients  
15 treated with placebo alone. Next slide.

16 How about the in-lesion segment? You'll  
17 remember that includes in-stent restenosis as well as  
18 the ribbon area, as well as the marginal edge of that.  
19 Looking again at SCRIPPS and at WRIST, we can see that  
20 the directionality is the same, and the efficacy is  
21 maintained in both SCRIPPS<sup>\*\*</sup> and WRIST, because the in-  
22 lesion restenosis rate in the radiation group is very,

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1 very similar, 21 and 22 percent.

2 Look again at that group of patients  
3 treated with the placebo in whom the recurrent in-  
4 lesion segment restenosis rate is 61 percent. Next  
5 slide.

6 That's the angiographic part of it from  
7 the patient standpoint. There are more important  
8 things sometimes.

9 Major adverse cardiac events in SCRIPPS  
10 and WRIST included mortality, myocardial infarction  
11 and a need for recurrent procedures. This is the data  
12 for SCRIPPS at 12 months and WRIST at six months. The  
13 power scheme is the same, placebo and radiation.

14 You can see that the efficacy is  
15 maintained, even though this group of patients in  
16 WRIST were at higher risk of recurrent major adverse  
17 cardiac event, and you can see a dramatic reduction,  
18  $P=.001$ , a 57 percent reduction in MACE events.

19 There was the same directionality. The  
20 numbers were small. No question about that in the  
21 SCRIPPS trial, but the directionality is the same, and  
22 the final result was very similar between the

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1 radiation limbs in both of these trials. Next slide.

2 How about the pivotal trial? We've talked  
3 about the preliminary data, the warm-up data. How  
4 about GAMMA I looking at in-stent and in-lesion  
5 restenosis rates at six months. Remember, this was  
6 the multi-center trial with 252 patients in it.

7 Looking at in-stent restenosis and in-lesion  
8 restenosis, there was a dramatic reduction in the  
9 radiation group of 57 percent in-stent restenosis and  
10 42 percent in-lesion restenosis.

11 People have said that perhaps this is a  
12 group of patients in whom they did much worse than the  
13 control group in another series. You need to realize  
14 that there was a randomized trial of 300 patients  
15 presented at the American College of Cardiology that  
16 randomized patients with in-stent restenosis through  
17 either rotational atherectomy or balloon dilatation.  
18 The recurrent restenosis rates in that group of  
19 randomized patients was between 52 and 65 percent.  
20 That's the sort of information that we have.

21 This is a group<sup>\*\*</sup> of patients that, if we do  
22 not use radiation, have a very high event rate in

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1 terms of recurrent restenosis.

2 We can see that there is some edge effect,  
3 some margin effect. It is seen in both the patients  
4 treated with placebo as well as in the radiation  
5 group. At the edges of the treatment, there seems to  
6 be some increase in stenosis, and Rick is going to  
7 talk about that during his part of this.

8 It is seen both in the placebo group as  
9 well as in the radiation group, a little bit more in  
10 the radiation group, but still at the very end of the  
11 day, in-lesion MACE and restenosis rates are  
12 dramatically decreased in the radiation treated  
13 patients. Next slide.

14 This is an important slide, because it  
15 relates to those patients who fail radiation, and  
16 clearly there will be some who fail radiation. This  
17 looked at the six-month follow-up lesion length in the  
18 placebo group and the radiation group.

19 Here we have the baseline lesion length.  
20 It was similar between the placebo and the radiation  
21 group. When restenosis occurs following radiation, it  
22 tends to be shorter, eight millimeters as compared to

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1 12 millimeters.

2 The important thing about that is that  
3 shorter lesions can be treated more successfully the  
4 second time around or the third time around. So  
5 you're moving in the right direction with this group  
6 of patients treated with radiation, even if they get  
7 a recurrence. Next slide.

8 How about MACE events in GAMMA, looking at  
9 MACE at nine months, looking at target lesion  
10 revascularization at nine months and target vessel  
11 revascularization at nine months. There is  
12 concordance across the board with a dramatic reduction  
13 in that group of patients who were randomized to  
14 receive radiation, irrespective of whether we define  
15 it with MACE or those individual components, target  
16 lesion revascularization or target vessel  
17 revascularization. Next slide.

18 let's look then at some subsets of the  
19 GAMMA trial. We talked about the importance of lesion  
20 length on in-lesion restenosis. Let's look at the  
21 group of patients that we would expect would be at  
22 highest risk for restenosis. That would be the

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1 patients with greater than 25 millimeter length of  
2 lesions.

3 Look at the placebo group. Eighty percent  
4 of these long lesions have recurrent restenosis. in  
5 the group of patients treated with radiation it's only  
6 30 percent. It's a 50 percent reduction. It's not  
7 perfect, but it's a 50 percent reduction in this group  
8 of patients at perhaps highest risk for in-stent  
9 recurrent restenosis. Next slide.

10 The second group we talked about were the  
11 diabetic patients. Looking at those patients with  
12 diabetes on the right, we can see that the placebo  
13 group has a 76 percent incidence of recurrent  
14 stenosis, and the radiation group is cut by, again, 50  
15 percent. So even in the highest risk patients, there  
16 is a dramatic reduction in events when they are  
17 treated with radiation. Next slide.

18 It has been said that new medicines and  
19 new methods of cure always work miracles for a while.  
20 Let's talk then about durability. What are the issues  
21 about durability? \*\*

22 This looks at the risk data, freedom from

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1 major adverse cardiac events at two years. You need  
2 to remember that in the risk trial crossover was  
3 allowed, and 65 percent of the patients initially  
4 treated with placebo crossed over within the first few  
5 months, and that accounts for this flat line of the  
6 graph in the placebo group of patients.

7 We can see that, looking at the radiation  
8 treated group of patients, there is some decrease in  
9 event free survival from nine months out to two years,  
10 but still at the end of two years there's a dramatic  
11 improvement in freedom from major adverse cardiac  
12 events in the group of patients treated with  
13 radiation, in contrast to the group of patients  
14 treated with placebo. So it is durable.

15 There is a slight decrease in it, but it  
16 lasts out to two years in terms of that improvement.  
17 Next slide.

18 Looking at GAMMA I, that was the risk  
19 data. GAMMA I, you will remember, did not allow  
20 crossover. This looks at the MACE-free survival at  
21 two years. We can see again the radiation group is on  
22 the top, and it stays on the top throughout.

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1           They have improved event-free survival out  
2 to two years, 60 percent as compared to 47 and 48  
3 percent. There is some decrement in both of these.  
4 No question about that. It is a progressive and  
5 inexorable disease, but still at the end of two years  
6 the patients do better if they've had the chance to be  
7 treated with radiation. Next slide.

8           What could we then say about efficacy,  
9 the first part of the equation? We could say that  
10 there has been concordant efficacy in all three  
11 trials, angiographic and clinical. They all show  
12 dramatic improvement in outcomes.

13           It's effective across a wide range of  
14 patient populations, the patients with diabetes, the  
15 patients with longer lesions. We can say that. The  
16 third thing is that it last. Durability of the  
17 efficacy is seen in the three-year SCRIPPS I data, the  
18 two-year WRIST data, and the two-year GAMMA I data.  
19 Next slide.

20           That's the efficacy side of the equation.  
21 Let's talk about the flip<sup>\*\*</sup> side, some of the risks.  
22 We've talked about the benefit. Let's talk about

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1 mortality. Let's talk about myocardial infarction.  
2 Let's talk about long term safety, because those are  
3 important issues as we deal with the specific patient  
4 in front of us with recurrent in-stent restenosis.  
5 Next slide.

6 We've talked about the fact that there has  
7 been a difference in mortality, and you know that.  
8 That's in your packet. This just looks at the summary  
9 of all deaths, the intention to treat analysis.

10 The SCRIPPS three-year data, the WRIST  
11 two-year data is seen in the middle, and they are the  
12 very same. There is no statistically significant  
13 difference, and they are very close, and we're not  
14 going to talk about those, because the very pivotal  
15 trial is the GAMMA I trial, and we're going to talk  
16 about that.

17 As you look at the mortality, there is a  
18 difference. It's not statistically significant, but  
19 clearly, as you look at it, there is a difference. So  
20 we need to explore that difference in the mortality of  
21 2.5 percent versus 6.1 percent in the radiation group.  
22 So we're going to look at these events in close

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1 detail. Next slide.

2 This is the summary of deaths. There was  
3 one non-cardiac death in the radiation group, a  
4 suicide. We're not going to talk further about that.  
5 There was one post-procedural -- immediately post-  
6 procedural death in the radiation group. It was a  
7 guidewire perforation. We're not going to talk about  
8 that, because that could have occurred with either  
9 limb.

10 We are going to talk about, however, the  
11 nonprocedural cardiac deaths, because you will  
12 remember there were six in the radiation group and  
13 only three in the placebo group, and we will go  
14 through each of these mortalities in turn to give you  
15 a feel for that. Next slide.

16 These were the first two. At day 153 in  
17 this patient, he had dilatation for target lesion  
18 restenosis. It was not thrombosis. At day 256 had  
19 target restenosis and was found to have severe 3  
20 vessel disease.

21 The physician<sup>\*\*</sup> said we should cross over.  
22 We should send him to surgery. So he was scheduled

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1 for surgery for 3 vessel disease. Six days later  
2 while awaiting surgery, had Q-wave infarction and  
3 shock, leading to death. This is now almost a year  
4 out from his treatment.

5 The second patient, at three months  
6 admitted with unstable angina, no myocardial  
7 infarction, and this is an important patient for us to  
8 remember, because this patient will come up again.

9 The angiogram documented target lesion  
10 restenosis with thrombus. He underwent successful  
11 dilatation, although at that time there was evidence  
12 for distal embolization of the thrombus.

13 Four days later he had a ventricular  
14 fibrillation arrest and died. That's a group -- a  
15 specific patient in whom there could be a relative  
16 influence of the radiation treatment. So we need to  
17 remember this patient 118/15. Next slide.

18 The next two: At day 173 had dilatation  
19 for target lesion restenosis, not thrombosis. At day  
20 291 had on-Q wave infarction and was found to have  
21 diffuse disease but no target lesion restenosis or  
22 thrombosis. Unfortunately, at the time of angiography

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1 everything went wrong that could go wrong, shock,  
2 heart failure, renal failure, leading to death on day  
3 293.

4 Fourth patient, day 135 had dilatation for  
5 target lesion restenosis, not thrombosis. Then at a  
6 little bit more than two years had sudden death at  
7 home. Next slide.

8 The final two deaths in the radiation  
9 group: One at day 67 had a Q wave infarction, was  
10 found to have an occluded vessel, presumably due to  
11 late thrombosis. They thought it was successfully  
12 treated with dilatation. At day 265 had coronary  
13 bypass graft surgery. This was a patient that had had  
14 congestive heart failure in the past, and at day 690 -  
15 - 690 days following the index procedure died of  
16 congestive heart failure.

17 The final patient: At day 181 had  
18 dilatation for target lesion restenosis, not  
19 thrombosis. Day 311 came to hospital with shortness  
20 of breath and was taken to the radiographic department  
21 and had a chest x-ray, and during that time arrested,  
22 was found to have pulmonary edema, no myocardial

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1 infarction.

2 Those were the deaths in the radiation  
3 group, the six deaths. How about the three deaths in  
4 the non-radiation, the placebo group? Next slide.

5 This is the data at six months.  
6 Angiogram, he had no restenosis, 618 days death of  
7 unknown cause. Couldn't get anymore data. Tried like  
8 crazy. Couldn't.

9 Second patient: AT day 78 had coronary  
10 surgery for target lesion restenosis. At day 175 had  
11 dilatation. At day 485 things are still going poorly,  
12 had TMR, complicated by ventricular arrhythmia and  
13 death.

14 The final patient is at three months had  
15 target lesion restenosis, not thrombosis, treated with  
16 coronary surgery, and post-operatively had  
17 ventricular tachycardia, ventricular fibrillation,  
18 arrested and died.

19 The important part of these messages are  
20 that this is a group of patients that have congestive  
21 heart failure. This is a group of patients that have  
22 problems in the future related to their disease

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1 process, whether they are treated with conventional  
2 dilatation or coronary surgery.

3 We need to prevent restenosis, because the  
4 treatment of these patients for restenosis some of the  
5 time led to problems down the road when restenosis was  
6 recurrent. Next slide.

7 The next group of clinical safety issues  
8 relate to late thrombosis. The definition of late  
9 thrombosis is important. We defined it as myocardial  
10 infarction attributable to the target vessel with  
11 angiographic documentation, with the site reported or  
12 by QCA, of thrombus or total occlusion at the target  
13 site more than 30 days from the index procedure in the  
14 absence of any pattering around in the vessel, the  
15 target vessel. Next slide.

16 This is the data on those deaths possibly  
17 associated with late thrombosis. There was one  
18 placebo patient and one radiation treated patient that  
19 we had insufficient information, despite the fact that  
20 we tried to get that, to definitely exclude the  
21 possibility of an association with late thrombosis.

22 That single patient that we've already

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1 talked about the death in the radiation group was  
2 possibly associated with late thrombosis. You  
3 remember, that was the patient who was found to have  
4 target lesion restenosis and thrombus, underwent  
5 successful dilatation, and arrested four days later  
6 and died. That's a group -- That's that single  
7 patient in whom the death is possibly or probably  
8 related with late thrombosis. Next slide.

9 How about myocardial infarctions? We've  
10 talked about death and late thrombosis. This is the  
11 summary of all patients with myocardial infarctions,  
12 different lengths of follow-up, three years and two  
13 years.

14 We're going to concentrate on the GAMMA,  
15 because even though it was not statistically  
16 significantly different, there clearly is a trend in  
17 that direction, 6.6 percent in contrast to 13.7  
18 percent in the radiation group. Next slide.

19 What is the relationship between  
20 myocardial infarction and late thrombosis? That's  
21 seen here, and we'll concentrate again on the GAMMA  
22 trial. We can see that late thrombosis is

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1 substantially more frequent in the group of patients  
2 in the radiation who developed myocardial infarction.

3 There was only a single patient in the  
4 placebo group in contrast to seven patients, still  
5 small numbers, but seven patients in the radiation  
6 group. Let's look at those seven patients. Next  
7 slide.

8 This is the data on those seven patients.  
9 There are a couple of important pieces of information  
10 on this slide in GAMMA I. Looking at the days to  
11 event, they range from 67 out to 270 days.

12 An important point is look at the duration  
13 of antiplatelet therapy. In every single case the  
14 antiplatelet therapy had been discontinued prior to  
15 the event. That's the first important piece of  
16 information.

17 We can see the distribution of myocardial  
18 infarction. It was typically a non-Q wave myocardial  
19 infarction. Perhaps the most important piece of data  
20 on this slide is that in each of these seven patients  
21 a new stent had been placed at the time of the  
22 radiation procedure.

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1                   So the pieces of information here are that  
2                   the antiplatelet therapy had been stopped, and a new  
3                   stent had been placed. Next slide.

4                   Let's look then at myocardial infarction  
5                   and that impact of late thrombosis. There is a  
6                   difference. It's not statistically significantly  
7                   different in myocardial infarction with late  
8                   thrombosis, but clearly it's increased in those  
9                   patients that have new stents placed, in those  
10                  patients in whom there is a shorter duration of  
11                  antiplatelet therapy, and Rick is going to talk about  
12                  that.

13                 Looking at the frequency of myocardial  
14                 infarction without thrombosis -- so this would be a  
15                 myocardial infarction in another segment of the vessel  
16                 or potentially even in another vessel -- there is no  
17                 statistically significant difference between those  
18                 patients in the placebo group and the radiation group.  
19                 It appears to be a late thrombosis thing, and that's  
20                 a group of patients that we can identify and work with  
21                 and treat. Next slide.       \*\*

22                 The final consists of information dealing

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1 with the long term. We've talked about major adverse  
2 cardiac events at two years and at one year. How  
3 about the longer term?

4 This is data from the angiographic follow-  
5 up from SCRIPPS I, looking at the three-year  
6 angiographic follow-up and radiation treated patients.  
7 There aren't any aneurysms, no pseudo-aneurysms.  
8 There aren't any perforations. This isn't something  
9 that's waiting to happen. It hasn't happened in the  
10 longer term follow-up of these patients treated with  
11 radiation therapy. Next slide.

12 We've talked about some safety issues for  
13 individual patients. What's the conglomerate of  
14 safety issues? What's the overall picture of safety?  
15 In over 1,000 patients treated to date, there have not  
16 been any device failures. The ribbons were delivered  
17 100 percent of the time. That's the first piece of  
18 information.

19 The second is that there have not been any  
20 NRC reportable events, and the third is that no  
21 procedures were aborted. We did not need to use the  
22 bailout box or the bailout pig in any of these more

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1 than 1,000 patients treated. Next slide.

2 So what then could we say about some of  
3 these safety issues? We've talked about the efficacy  
4 issues. The efficacy is very real. It is concordant  
5 across all three studies.

6 What could we say about the safety  
7 summary? There was one death in the radiation group,  
8 possibly associated with late thrombosis. I think  
9 that's real, true, true, and related.

10 I think that there is an overall higher  
11 rate of infarction in the radiation group because of  
12 the occurrence of late thrombosis, and indeed Rick is  
13 going to talk about that.

14 Myocardial infarctions unrelated to late  
15 thrombosis occur at comparable rates. So if we can  
16 get over the problem -- If we can solve the problem of  
17 late thrombosis, then we have a technology that looks  
18 like it is truly going to be a major improvement for  
19 this very high risk group of patients to improve their  
20 outcome. Next slide.

21 With that, we'll talk about then some of  
22 these late thrombosis issues, and Rick is going to do

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1 that.

2 DR. KUNTZ: Good morning. My name is Rick  
3 Kuntz. I'm a cardiologist at Brigham's and Women's  
4 Hospital. I'm also the Chief of the Clinical  
5 Biometrics Division at the Brigham's and Women's  
6 Hospital. I also am the Director of Academic CRL at  
7 Harvard that conducted this trial.

8 I have no financial disclosures to talk  
9 about. I have no consulting arrangement with Cordis.  
10 I have no equity in their company or any other medical  
11 device or medical pharmaceutical company, and I'm not  
12 being paid for my presentation today. Next slide.

13 CHAIRPERSON CURTIS: They paid your travel  
14 expenses?

15 DR. KUNTZ: Yes, they've covered the  
16 airline flight.

17 Now I'm going to focus this portion of the  
18 presentation on the analysis of the late occlusions  
19 and a subset of late thrombosis. So far we have  
20 talked about the results of this trial with typical  
21 endpoints that were proposed and pre-specified in the  
22 IDE. That is, we looked at the comparison of major

1 efforts, cardiac event rates, and restenosis broken  
2 down by angiographic measures and by clinical  
3 measures.

4 All of the typical pre-specified endpoints  
5 of this trial were positive. We did recognize that  
6 there was a component of major event cardiac event  
7 rate that, although in the conglomerate was  
8 significantly different than placebo, was higher for  
9 the radiation group; and that is the occurrence of  
10 occlusions and thrombosis.

11 So we did post hoc analysis to understand  
12 this phenomenon and go forward. As is typical with  
13 most observations of new epiphenomena in this issue of  
14 late thrombosis, new epiphenomenon, one has to follow  
15 a typical procedure, and that is to understand the  
16 issues, to try to reduce the phenomena down to its  
17 most irreducible components, and then to try to  
18 analyze and see if there is a solution  
19 biostatistically and clinically.

20 There's an example of that. Early on when  
21 coronary stents were initially introduced in 1990, the  
22 aim of coronary stents was to reduce the rate of

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1 restenosis. When re-narrowings, which was how we  
2 measure restenosis, were compared between stented  
3 groups versus angioplasty groups, there were no  
4 differences. However, when we broke those down --  
5 this was around 1990 -- into the occurrence of  
6 thrombus versus neointimal hyperplasia, it was  
7 discovered that there was a high rate of thrombus  
8 related events compared to neointimal events.

9 It was only after that breakdown that one  
10 could then focus on removing the thrombus portion by  
11 adding antiplatelet therapy that stents became  
12 effective. This same process occurred in this  
13 analysis.

14 That is, we evaluated the occurrence of  
15 more occlusions and tried to break them down into  
16 their irreducible pathophysiological components and  
17 characteristics, so that we could make better  
18 inference and do better analysis. I'll review those  
19 definitions.

20 We then looked at those definitions under  
21 the GAMMA I trial. Then we looked at those  
22 definitions under the pooled group, and then made

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1 conclusions.

2 So when we looked at how to define this,  
3 we started with the most basic observation, and that  
4 is a hundred percent occlusion at the angiogram, which  
5 all these patients had, and used that as the basis for  
6 comparison.

7 We then broke them into their clinical  
8 presentations as late thrombosis or as occlusions that  
9 were not associated with thrombosis.

10 Now initially, late occlusions were the  
11 observation, but they are made up of two dissimilar  
12 endpoints. That is, there is a late thrombus portion  
13 which is due to clot, and there is a late restenosis  
14 portion which is due to neointima. Next slide,  
15 please.

16 So if we expand these definitions of late  
17 total occlusion, these two different definitions  
18 emerge. One, we called late thrombosis, and again  
19 this process necessitates some changes in concepts and  
20 changes in terms that we were going through both with  
21 this group and other radiation groups that we were  
22 consulted and contracted to work with over the course

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1 of the last year or so.

2 The good thing about this company was they  
3 allowed us to make these definitions and discover this  
4 on our own and come up with these terms. So the  
5 dynamic changes that have occurred in the last two  
6 years or so is actually an external process by the  
7 investigators and the academic groups in analyzing  
8 this and other trials.

9 So far, we've decided that late total  
10 occlusions are made up of an acute clinical process,  
11 usually associated with acute myocardial infarction  
12 which is called late thrombosis to distinguish it from  
13 early thrombosis seen in previous stent trials.

14 Most thrombosis that occur with stent  
15 trials occur in the first seven to 14 days. We  
16 observed that there was a thrombosis that occurred  
17 beyond 30 days and, therefore, the word late  
18 thrombosis was used.

19 We defined that in the clinical events  
20 adjudication committee, which has experience in over  
21 7,000 events adjudicated in other stent trials --  
22 determined this on their own, that it would be defined

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1 as the presence of an MI with angiographic  
2 documentation of thrombus or total occlusion of a  
3 target vessel 31 days or greater from the index  
4 procedure.

5 We then wanted to look at the remainder of  
6 patients who had occlusions at angiographic follow-up  
7 that were not associated with an acute clinical event,  
8 and we called that total silent occlusion, silent  
9 referring to a non-acute clinical event.

10 Those were associated with angiographic  
11 occlusions at the target site, generally a compulsory  
12 angiographic follow-up at six months. Next slide.

13 If we want to break down how these two  
14 definition can be positioned with respect to the  
15 pathophysiology, I think we start to see that we are  
16 obtaining and converging to two irreducible events:  
17 One, the late thrombosis, which we think is due to  
18 fresh thrombus formations, and probably due to total  
19 inhibition of neointima.

20 So that, in the case of a freshly placed  
21 stent, the stent is exposed to the blood stream. The  
22 radiation therapy has inhibited neointimal coverage of

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1 that stent longer than it normally does, longer than  
2 the normal two-week period to possibly three or four  
3 months, and the patient is vulnerable to clot  
4 formation, especially if they use the standard  
5 antiplatelet therapy regimen of two to four weeks  
6 which we use for stents, which occurred in this study.

7 We then have the other pathophysiological  
8 underlying mechanism for occlusion, the so called  
9 total silent occlusion, which is the complete opposite  
10 of thrombus. This is actually excessive neointimal  
11 formation, not lack of, and is due to essentially  
12 excessive restenosis leading to occlusion, which we  
13 see at a rate of about one to two percent in all stent  
14 studies and slightly higher in patients with in-stent  
15 restenosis at the three to four percent range. Next  
16 slide, please.

17 In order to try to make sure that we  
18 compared apples to apples, the company gave us data  
19 from SCRIPPS and WRIST that we obtained from both the  
20 investigators at the Washington Hospital Center and  
21 SCRIPPS clinic, in addition to GAMMA I trials, and the  
22 exact same clinical events adjudication committee

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1 evaluated these events, the same definitions, blinded  
2 to their distribution of study and treatment  
3 assignment. Next slide.

4 So let's look at the GAMMA I trial under  
5 this definition. The incidence of late total  
6 occlusions that occurred in this study was 13.5  
7 percent versus 5.8 percent.

8 Now, again, this is a component of the  
9 major adverse cardiac event rate of which the  
10 conglomerate was better for radiation therapy compared  
11 to placebo, statistically better, but we break it down  
12 by this component which, I think, is proper to do.

13 We see that actually this component was  
14 higher for radiation therapy compared to that. We  
15 tried to understand, based on the two mechanisms  
16 causing occlusions, what was the factor that was  
17 causing this difference.

18 It became apparent that it was the  
19 thrombosis issue and less likely to be total silent  
20 occlusion issue. Again, it was more likely to be the  
21 thrombus appearance on usually a newly placed stent,  
22 compared to the excessive neointima hyperplasia which

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1 we normally see in a definition of total occlusion.

2 So at this point we're starting to see  
3 some discriminatory capability of trying to figure out  
4 where the problem is when one observes the phenomenon  
5 of increased total occlusions for radiation therapy  
6 compared to placebo. Next slide, please.

7 In order to formally evaluate whether the  
8 presence or absence of those components are associated  
9 with one or two of these assignments, we did multi-  
10 variable analysis of the GAMMA I study, looking for  
11 determinants of late thrombosis and late silent  
12 occlusions.

13 We assessed multiple parameters, including  
14 the typical usual suspect, lesion length, minimal  
15 luminal diameter after procedure, presence of a new  
16 stent which was used in a sizable minority in some  
17 cases and a majority in other cases in other trials,  
18 the treatment assignment, the dose, and reference  
19 vessel diameter.

20 In the GAMMA I study, we didn't find any  
21 significant predictors that met statistical  
22 significance, because of the infrequency of the late

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1 thrombosis event rates and late occlusion event rates.

2 Next slide.

3           So in order to take that one step further  
4 to confirm our observations by the subset analysis  
5 using multivariable modeling, we decided to combine  
6 the other studies into a pooled dataset so that we  
7 could perform more effective statistical analysis.

8           So the motivation for pooling was to  
9 increase statistical power for this rare event of  
10 total occlusions. Again to review, the trials  
11 independently were powerful enough to show the  
12 difference in efficacy of restenosis, but because the  
13 occurrence of these late thromboses were much less  
14 frequent, we required pooling in order to understand  
15 that. Next slide.

16           Now the justification for pooling, we  
17 feel, is proper in this analysis. In all cases there  
18 were equivalent inclusion/exclusion criteria. The  
19 treatments were very, very similar. The same source  
20 and the dose ranges are highly overlapping, which I'll  
21 show you, and the classical FDA requirements for  
22 pooling justification were performed, looking at

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1 typical issues of treatment and site interaction and  
2 treatment and trial interaction.

3 We found that there were no significant or  
4 direction terms to not justify pooling in this study.  
5 Next slide.

6 This is an illustration of the  
7 distribution of reference diameters among the three  
8 trials using non-parametric box plots in which we see  
9 the median and mean, the 25 and 75 percent of trial  
10 distribution, the lists or the outliers, and you can  
11 see the fairly high level of overlap to justify these  
12 as being quite similar vessels among the three trials.

13 Next slide.

14 In the radiation dosing we see also the  
15 wide distribution of dosing within the trial which  
16 basically has wider distribution than the medians  
17 between the trials, suggesting that there is a fair  
18 amount of overlap of these trials to suggest that this  
19 is poolable.

20 Now there is a distribution of these two  
21 trials, because they were <sup>\*\*</sup>generated by measures of the  
22 reference vessel. In the risk trial there was a fixed

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1 dose given for all patients. But you can see that the  
2 within-variability is larger than the between-  
3 variability of the studies. Again, I think  
4 justification for pooling is present. Next slide.

5 Now one of the next steps to understand  
6 this problem of late thrombosis which explains the  
7 difference in late occlusions was to understand -- and  
8 its relationship with radiation assignment, was to  
9 understand what might be causing that.

10 One of the observations that everyone had  
11 was the possibility that the placement of a new stent  
12 exposed the patient to the risk of thrombosis. So we  
13 broke the patients into the next dimension.

14 We found that, basically, there was a  
15 fairly nice distribution of looking at new stent  
16 placement versus no new stent placement for placebo  
17 and radiation in the pooled groups. Next slide.

18 Their totals are summarized here, just to  
19 show that we had a fairly nice distribution of  
20 patients with stents that were freshly placed and with  
21 no new stents -- that is, dilatations were performed  
22 without new stents -- between both the radiation and

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1 the placebo assignment. Next slide.

2 When we looked at the incidence of late  
3 thrombosis by that schema, what we see -- Here are the  
4 counts for all of the studies. If we look at the  
5 totals here, we see a tendency for a clustering of a  
6 late thrombosis to occur in the radiation group with  
7 new stents.

8 We see a background incidence in the other  
9 groups of late thrombosis. Now again this is a  
10 clinical and angiographic definition determined by a  
11 blinded clinical events adjudication committee that  
12 normally occurs in the order of one percent in most  
13 stent studies.

14 So in cases where the placebo was used  
15 with no radiation, we get the typical one percent-ish  
16 rate that we normally see in stent studies. In the  
17 radiation group we see that same rate when no new  
18 stent is used.

19 So it appears by this analysis that the  
20 problem of late thrombosis is confined to patients who  
21 receive radiation and new stents. Now we also have to  
22 remind you that during this study there was no

1 extended antiplatelet therapy for any of these  
2 patients. So these were cases of new stents placed  
3 without extended antiplatelet therapy.

4 So in the cases where no new stents were  
5 used, you see the same background use even without  
6 extended antiplatelet therapy. Next slide.

7 This is the graphical illustration showing  
8 that clustering, suggesting that we may have hit a hot  
9 spot here of understanding where the problem of late  
10 thrombosis occurs when we break patients down by use  
11 of new stents versus no new stents. Next slide.

12 Now if we look at the overall pooled data,  
13 we can see that -- Pointing back to the occurrence of  
14 our initial trauma of late total occlusion, we see the  
15 same distribution of higher rates of occlusion  
16 associated with radiation therapy compared to placebo.  
17 But when we look at those distributions with no new  
18 stents used, we see the same not statistically  
19 different distribution, which we think doesn't  
20 represent thrombosis but rather represents excessive  
21 neointimal hyperplasia as is seen in most studies of  
22 in-stent restenosis. Next slide.

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1           Now with a satisfactory and substantial  
2 sample size, we can do the multivariable analysis on  
3 late thrombosis. In fact, when we look at the  
4 dependent variable, which would be late thrombosis or  
5 the total silent occlusion, we can determine different  
6 predictors which basically help to confirm our  
7 underlying pathophysiological concepts.

8           In the dependent variable of late  
9 thrombosis, a multivariable model would suggest that  
10 the predictor is the use of radiation with a new stent  
11 and longer lesion lengths, which makes sense because  
12 they would be longer stents.

13           In the analysis of the total occlusions,  
14 we determined that's the pre-procedure of reference  
15 vessel diameter which determines restenosis. The  
16 smaller the vessel, the more likely that total silent  
17 occlusions occur.

18           If we go back with our pathophysiological  
19 concepts, that makes sense. We think the late  
20 thrombosis is a thrombotic event. This is a component  
21 of total occlusion, and we see that it's associated  
22 with radiation and new stent use.

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1           If we go back to our concept of what we  
2 thought total silent occlusion was, which was  
3 excessive neointima hyperplasia, we see the fact that  
4 its predictor is a typical restenosis predictor. That  
5 is, a small vessel size, which is typical in all stent  
6 studies. Next slide, please.

7           Now if we look at the efficacy of cases  
8 that didn't receive a new stent, it's important to  
9 evaluate patients under that paradigm, because it's  
10 clear that this story is leading to the recommendation  
11 that patients receive no new stents with radiation  
12 therapy in order to avoid this problem of late  
13 thrombosis.

14           So how did the patients do who received no  
15 new stents? We can see that the pooled data suggests  
16 that all three definitions that we use for restenosis,  
17 the angiographic definitions of in-stent and in-lesion  
18 and the clinical definition of major adverse cardiac  
19 event rate, and again we could extend this to target  
20 lesion, target vessel and so on, were significantly  
21 efficacious differences between placebo and radiation.

22           That is, the subset of patients who

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1 received no stents still had tremendous benefit from  
2 radiation therapy without the problem of late  
3 thrombosis observed in this analysis, very similar to  
4 the overall efficacy data demonstrated earlier by Dr.  
5 Holmes. Next slide.

6 So the prevention of late stent thrombosis  
7 and late thrombosis, which actually is stent  
8 thrombosis, is based on the pooled data. Pooled data  
9 from the three trials identified the fact that it is  
10 associated with late thrombosis and allowed the  
11 hypothesis to be generated that late thrombosis would  
12 be prevented with the avoidance of new stents in  
13 conjunction with radiation therapy.

14 The efficacy of the anti-restenosis effect  
15 of radiation therapy is preserved when no new stent is  
16 used. So we expect this to be just as efficacious if  
17 we tell patients -- if we told physicians not to use  
18 new stents. Next slide.

19 Now that's the examination of the data so  
20 far. One of the concepts regarding the prevention of  
21 restenosis was also to extend antiplatelet therapy.  
22 After all, that makes sense, and it worked initially

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1 with stents to prevent stent thrombosis in the acute  
2 era. Why shouldn't it work to prevent it in the late  
3 era?

4 So this could not be evaluated  
5 retrospectively in the three studies, because all  
6 patients received just a short term therapy. We don't  
7 have long term therapy to compare. So we used this  
8 concept and looked at the prospective occurrence of  
9 late thrombosis in which antiplatelet therapy was  
10 extended in two ongoing trials, the SCRIPPS III  
11 registry and the WRIST Plus registry. Next slide.

12 These trials were initiated a year ago,  
13 and they are registries at the SCRIPPS clinic and at  
14 the Washington Hospital Center and have close to over  
15 -- or slightly over 500 patients enrolling at this  
16 point. There were three sites involved, actually, in  
17 these studies.

18 Now the distribution of vessels was mainly  
19 native, some vein grafts, and the use of new stents is  
20 much different than the use of new stents in the  
21 pooled data. Instead of it being 50 or 60 percent,  
22 it's down to 25 percent.

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1           So we're starting to see analyses -- or  
2 behavior of trials where we would suggest, based on  
3 this data -- that is, the use of infrequent --  
4 infrequent use of stents, and the prolonged use of  
5 antiplatelet therapy for six months in all studies.  
6 Next slide.

7           What we have here is the follow-up density  
8 so far. We can see here that at 180 days follow-up,  
9 we have 140 patients or more who have 180 days or more  
10 of follow-up. We have not observed a single late  
11 thrombosis rate in these 500 patients to date, and we  
12 have a fairly decent density of follow-up at 180 days,  
13 because we observed the major hazard associated with  
14 late thrombosis from the three pooled trials was  
15 within the six-month period.

16           So, so far we think we've covered this  
17 pretty well with this density curve and have not  
18 observed a single event.

19           What's the upper confidence interval based  
20 on the follow-up so far? It's defined over here. So  
21 that we can see that, if we were to use the ongoing  
22 sample as we stand today and determine the probability

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1 of a late thrombosis when we observe zero, we can see  
2 that the rates are between one and two percent. So  
3 that the 180 days would be zero percent observation of  
4 sample is most associated with a 2.1 percent upper  
5 bound 95 percent confidence interval. Next slide,  
6 please.

7 If we want to graphically look at that in  
8 a different way, we can show in fact this continuous  
9 distribution function curve of the follow-up. That  
10 is, this shows the number of days of follow-up ranked  
11 over here. So we have a CDF curve, and we have  
12 plotted here the upper bounds of the 95 percent  
13 confidence interval for a zero percent rate.

14 We can see that in the period of six  
15 months follow-up where we observe this hazard of late  
16 thrombosis, we have extremely low 95 percent upper  
17 confidence bounds, suggesting the problem has been  
18 rectified, and a fairly decent density of follow-up so  
19 far, to suggest that what we observed in the  
20 retrospective analysis is, in fact, being confirmed in  
21 this prospective dataset. Next slide, please.

22 So what have we learned? One is that late

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1 thrombosis is predictable. It's definitely associated  
2 with the use of new stents. All cases of late  
3 thrombosis have new stents. And it's very likely due  
4 to lack of antiplatelet coverage, which is being  
5 confirmed by the prospective analysis I just showed  
6 you. Next slide, please.

7 So conclusions: The rate of late  
8 thrombosis for radiation without the new stent  
9 placement is comparable to that of placebo.

10 Late thrombosis is largely confined to  
11 patients who received a new stent at the time of  
12 radiation therapy.

13 Finally, extended antiplatelet therapy  
14 prevents late thrombosis, as we've seen so far, in  
15 this cohort of 500 patients who have been followed out  
16 well beyond a year, and a good density beyond six  
17 months. Next slide, please.

18 I'll hand it over to Dr. Holmes for  
19 concluding comments.

20 DR. HOLMES: Next slide. We have reviewed  
21 a lot of data, and I guess we need to then come to  
22 some conclusions, at least from our standpoint, on how

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1 we address this issue of new technology in this  
2 patient group.

3 I think it's fair to say that in-stent  
4 restenosis is a major clinical need. We talked about  
5 the fact that more than 100,000 patients each year  
6 with in-stent restenosis in the United States. That's  
7 the first thing.

8 The second thing is that we don't really  
9 have any other alternative therapies. Many of these  
10 patients have already had bypass graft surgery or many  
11 of these patients are not very good candidates for  
12 bypass graft surgery by virtue of their anatomy.

13 When we talk about other therapies that  
14 could be used -- for instance, conventional dilatation  
15 or rotational atherectomy -- the randomized trials  
16 that are current randomized trials would indicate that  
17 in these patients in whom we do not give them  
18 radiation, that their chance of recurrent restenosis  
19 is 50 to 60 or 70 percent, even in the best of hands  
20 and the best of trials.

21 The second part of this is that this PMA  
22 is supported by three randomized, double-blind, well

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1 controlled trials that looked at the data, that  
2 carefully studied the data and evaluated the pros and  
3 cons of this to document the results. Next slide.

4 What could we say then about the efficacy?  
5 What are the conclusions that we could make? There's  
6 really a marked and concordant efficacy demonstrated  
7 in all three trials, irrespective of whether we use  
8 angiographic endpoints or major adverse cardiac event  
9 endpoints or need for recurrent procedure endpoints.  
10 They have been concordant.

11 It is of interest that the efficacy is on  
12 the range of a magnitude decrease in events of 50  
13 percent in those patients treated with radiation.  
14 That is far greater than the 30 percent reduction in  
15 events upon which stents were improved initially. An  
16 interesting concept to look at that in historical  
17 perspective.

18 That efficacy has been demonstrated in  
19 high risk patients, the diabetic patients, the  
20 patients with longer lesions. It's been maintained  
21 either with or without a new stent use, and it lasts.  
22 There aren't long term issues, because the durability

1 has been demonstrated over two to three-year follow-up  
2 both clinically and angiographically with follow-up.

3 Next slide.

4 We could say from the system standpoint --  
5 So we've talked about efficacy from the patient  
6 standpoint. We could say from the system standpoint  
7 that this system has been demonstrated to be safe and  
8 easy to use in more than 1,000 procedures that have  
9 been performed without the need for bailout and  
10 without any NRC reportable event. And we can say that  
11 the long term safety with this system has been that at  
12 three-year angiographic follow-up there isn't any  
13 radiation injury to the vessels. That's the safety  
14 side of the equation. Next slide.

15 We do know that there have been some other  
16 safety issues. We know that, and Rick has really  
17 eloquently talked about the late thrombosis. It was  
18 an unanticipated event. We didn't realize that that  
19 was going to happen. It did happen, and it's been  
20 studied, and it evolved.

21 It was discovered through that initial  
22 incredible adjudication process during follow-up, and

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1 has resulted in creating and modifying the  
2 definitions, as Rick has talked about, to better  
3 understand the event, and then has resulted in the  
4 analysis that we've just seen on the late thrombosis  
5 event, to look at factors associated with it. How are  
6 we going to solve it? Next slide.

7 We know that we have seen that the late  
8 thrombosis occurs with new stent and radiation  
9 treatment. We can do something about that. The  
10 interventional cardiologist can do something about  
11 that. They can avoid the use of new stent.

12 It occurs with a short course, a short  
13 duration of antiplatelet therapy, and we can also do  
14 something about that, because we can use longer and  
15 extended platelet therapy, the antiplatelet therapy;  
16 and that has been done in other trials, and it is very  
17 safe.

18 This information, this hypothesis about  
19 preventing late thrombosis has been validated by the  
20 recent trials which continue, the SCRIPPS III trial  
21 and the WRIST Plus trial. Next slide.

22 What then could we say in conclusion?

1 What will I say as I begin to go back to begin to see  
2 this 50 patients on the waiting list with in-stent  
3 restenosis that has been recurrent?

4 As we think about those patients, as we  
5 think about training physicians, I think it's  
6 important to manage the risks. We talked about some  
7 of the risks. Label warning is going to be incredibly  
8 important. A physician training program and post-  
9 market surveillance is going to require incredible  
10 effort on the basis of the sponsor and other agencies,  
11 so that we make sure that we manage the risk.

12 As I talk about and to those 50 patients,  
13 how do we put the risk/benefit ratio in balance? We  
14 can say that there are risks to anything, at least as  
15 we deal with coronary artery disease, but by changing  
16 the procedure, by extending the antiplatelet therapy,  
17 we can manage that.

18 The most important thing is that in this  
19 group of patients with recalcifant lesions and  
20 recalcifant clinical problems we now have technology  
21 that works. It is effective across the board. It  
22 decreases target lesion revascularization. It

1 decreases angiographic restenosis.. It decreases the  
2 need for other procedures. It works in this highest  
3 risk group of patients.

4 So in the very end of the day, we come  
5 back to that patient who is now 50. Next slide.

6 How is he doing at the age of 50? Is 50  
7 a good year? It's a pretty good year for him. You  
8 remember that in 1997, early in 1997, at the time of  
9 his fifth recurrent restenosis, he was enrolled and  
10 received gamma radiation as part of his therapy.

11 When he came back in six months for his  
12 follow-up angiogram that Rick has talked about, it was  
13 perfectly clean. The stents, you can't even see them,  
14 because the angiographic contrast goes all the way out  
15 to them. There isn't any neointimal hyperplasia. ■  
16 most important thing is that since August of 1997,  
17 although he's been back to see you, he's been back to  
18 tell you he's doing a great job. He's now running  
19 again. He's not had any angina. He's not had any  
20 recurrence, and he's not needed to see you for any  
21 other angiogram. So this is technology that works in  
22 this highest risk group of patients.

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1 Thank you.

2 CHAIRPERSON CURTIS: Okay. We'll move on  
3 now to the FDA presentation.

4 DR. STUHMULLER: I'm going to sit at the  
5 table for my presentation. I'm John Stuhlmuller. I'm  
6 a cardiologist with FDA and the lead reviewer and the  
7 clinical reviewer for this file. I'm going to provide  
8 the FDA summary.

9 The FDA summary will identify the FDA  
10 review team and provide a brief overview of the  
11 nonclinical and clinical data.

12 The multi-disciplinary FDA review team has  
13 members from the Office of Device Evaluation, Kim  
14 Peters, Ramiah Subramanian, and myself; the Office of  
15 Science and Technology, Tom Heaton; the Office of  
16 Surveillance and Biometrics, Gary Kamer; and the  
17 Office of Compliance, Marian Linde.

18 The nonclinical evaluation consisted of  
19 four categories of testing: in vitro;  
20 biocompatibility; in vivo; animal testing and source  
21 dosimetry.

22 The in vitro testing evaluated the

1 mechanical integrity and function of the Cordis  
2 Checkmate catheter, dummy ribbon, and source ribbon.  
3 The sponsor has satisfactorily addressed FDA's major  
4 concerns, and only minor clarification issues are  
5 outstanding.

6 The Cordis Checkmate catheter is the only  
7 patient contacting component, while compatibility  
8 testing was completed in accordance with ISO Standard  
9 10993 and demonstrated the catheter is nontoxic and  
10 non-hemolytic. As noted in the FDA summary, the  
11 limitations to the animal testing completed by Dr.  
12 Waxman under IDEG 960234 included small numbers of  
13 observations, incomplete information on healing after  
14 acute radiation injury and chronic radiation effects.

15 Animal testing completed by the sponsor  
16 was limited to an acute handling and tracking study.  
17 The sponsor has adequately addressed FDA's main  
18 concerns regarding source dosimetry.

19 FDA has requested several revisions in the  
20 labeling to provide additional dose rate information  
21 and seed activity in SI units. The sponsor has agreed  
22 in principle to the requested changes.

1           Now I'll move on to the clinical  
2 evaluation. The sponsor has provided clinical data  
3 for five different clinical studies, SCRIPPS I, GAMMA  
4 I, WRIST, SCRIPPS III, and WRIST Plus. In addition,  
5 information on a retrospective pooled analysis  
6 containing various information from SCRIPPS I, GAMMA  
7 I, and WRIST has been provided.

8           FDA considers the SCRIPPS I study to be  
9 the feasibility study and the GAMMA I study to be the  
10 pivotal study for evaluation of safety and  
11 effectiveness.

12           The SCRIPPS I study was a feasibility  
13 study that enrolled 60 patients using a stratified  
14 randomization in subgroups based on lesion length less  
15 than 15 and greater than 15 millimeters, the type of  
16 restenosis (in-stent versus after angioplasty) and  
17 type of vessel (native versus saphenous vein graft).  
18 An IVUS based dose prescription was used.

19           Clinical and angiographic follow-up were  
20 completed at four to six months post-procedure. Two  
21 cases of stent thrombosis occurred at 17 and 39 days  
22 post-procedure. Stent thrombosis was confirmed via

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1 surgical pathology in the patient who experienced  
2 stent thrombosis at day 39.

3 Based on the "late occurrence" of stent  
4 thrombosis at 39 days after the index procedure, the  
5 post-procedure anticoagulation regiment was extended  
6 from 14 days to eight weeks.

7 Two of the outstanding issues regarding  
8 the SCRIPPS I study are the following: First, the  
9 sponsor has not provided information indicating that  
10 patient data can be pooled across the eight patient  
11 subgroups enrolled in the study.

12 Second, a footnote to the table for the  
13 1,080 day angiographic follow-up data indicates that  
14 the results for angiographic follow-up for patients at  
15 180 and 1,080 days have been combined. FDA interprets  
16 this to be a pooled analysis.

17 The sponsor has not provided any  
18 information indicating that the 180 and 1,080 day  
19 angiograms can be pooled and that valid conclusions  
20 can be reached from this pooled analysis.

21 Further, there are differences in the  
22 three-year angiographic follow-up reported in the

1 medical literature and the TMA dataset. Consequently,  
2 FDA is unable to evaluate recent discussion in the  
3 medical literature regarding differences in the six-  
4 month and three-year angiographic follow-up.

5 The GAMMA I study is the pivotal study for  
6 evaluation of safety and effectiveness. The study  
7 enrolled 252 patients with native coronary artery in-  
8 stent restenosis with three different lesion lengths,  
9 less than 15, 15, 15-30 and 30-45 millimeters in  
10 length.

11 The sponsor agreed to limit patient  
12 enrollment to native coronary artery lesions based on  
13 FDA concerns regarding poolability of data for native  
14 coronary and saphenous vein graft lesions.

15 Angiographic follow-up was completed at  
16 six months. Clinical follow-up was completed a nine  
17 months. FDA discussed generally recognized  
18 limitations of this study design during review of this  
19 investigational plan.

20 FDA believed that clinical follow-up  
21 should have preceded angiographic follow-up at nine  
22 months. The sponsor declined to have clinical follow-

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1 up precede angiographic follow-up at nine months.

2 FDA also asked the sponsor to consider  
3 stratified randomization based on the type of  
4 interventional treatment, based on concerns regarding  
5 an unexpected treatment interaction. The sponsor  
6 declined to stratify randomization based on  
7 interventional treatment.

8 An IVUS based dose prescription was also  
9 used in this study. Post-procedure anticoagulation  
10 duration was eight weeks, based on the documented  
11 stent thrombosis in patient 57 at 39 days after the  
12 index procedure in the SCRIPPS I study.

13 The primary endpoint for the GAMMA I study  
14 was a composite clinical endpoint consisting of death,  
15 myocardial infarction, and target lesion  
16 revascularization at nine months.

17 The FDA review team noted during review of  
18 the panel pack that the definitions used for  
19 myocardial infarction and target lesion  
20 revascularization were modified in the GAMMA I report  
21 from those submitted in the GAMMA I protocol.

22 In addition, based on information provided

1 to FDA in response to the FDA letter dated December  
2 22, 1999, FDA inferred that clinical follow-up  
3 preceded angiographic follow-up at six months. As a  
4 result, FDA would like panel input regarding whether  
5 any conclusions can be made regarding a nine-month  
6 clinical outcome.

7 The definition for myocardial infarction  
8 in the GAMMA I protocol required at least two of the  
9 following: Clinical symptoms; EKG changes; and enzyme  
10 changes. The definition in the GAMMA I report appears  
11 to only include EKG and enzyme changes.

12 FDA's concern is that the definition used  
13 in the GAMMA I report appears to increase the  
14 specificity of the diagnosis and could underestimate  
15 the incidence of myocardial infarction. As a result,  
16 FDA would like panel input regarding whether  
17 modification of the definition for myocardial  
18 infarction affects evaluation of patient outcome.

19 Target lesion revascularization has been  
20 characterized as clinically driven and non-clinically  
21 driven in the GAMMA I report. Clinically driven TLR  
22 is defined in the following ways:

1 First, positive functional study in the  
2 distribution of the target vessel; second, ischemic  
3 symptoms at rest in the distribution of the target  
4 vessel; third, ischemic symptoms with an in-lesion  
5 diameter stenosis greater than 50 percent by  
6 quantitative coronary angiography (QCA); fourth, no  
7 ischemic symptoms with an in-lesion diameter stenosis  
8 greater than 70 percent by QCA.

9 Nonclinically driven TLR was defined in  
10 the following ways: Non-emergent revascularization  
11 for a diameter stenosis less than 50 percent by QCA;  
12 non-emergent TLR for a diameter stenosis less than 70  
13 percent by QCA without either a positive functional  
14 study or angina.

15 FDA's concerns include the following:  
16 First, asymptomatic patients who meet QCA criteria for  
17 restenosis are counted as clinically driven TLR.  
18 Thus, patients who are treated based on the oculo-  
19 stenotic reflex could be considered clinically  
20 driven.

21 Second, no criteria are provided for what  
22 constitutes a positive functional study. Without

1 criteria for what constitutes a positive functional  
2 study, FDA is concerned that symptomatic patients who  
3 fail to meet QCA criteria could be considered  
4 nonclinically driven.

5 As a result, FDA would like panel input  
6 regarding whether these concerns affect evaluation of  
7 patient outcome.

8 Composite clinical endpoints is a group of  
9 individual clinical endpoints that together form a  
10 single clinical endpoint in a clinical trial. Three  
11 factors contribute to the use of composite clinical  
12 endpoints.

13 First, from a statistical perspective,  
14 composite clinical endpoints generally have higher  
15 event rates. Therefore, they commonly result in a  
16 smaller sample size needed to detect a treatment  
17 difference.

18 Second, use of a composite clinical  
19 endpoint allows for the evaluation of one or more  
20 nonfatal clinical endpoints relevant to the  
21 pathophysiology of the <sup>\*\*</sup>disease being treated, in  
22 addition to mortality. However, two caveats must be

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1 considered when using nonclinical -- excuse me,  
2 nonfatal clinical endpoints.

3 First, the occurrence of nonfatal  
4 endpoints is associated with an adverse prognosis; and  
5 second, failure to present approved and nonfatal  
6 endpoints improve mortality.

7 Third, use of the composite clinical  
8 endpoint allows a broader view of the net clinical  
9 benefit of the treatment being evaluated.

10 The major adverse cardiac event rate,  
11 known as MACE, typically incorporates death,  
12 myocardial infarction, and target lesion  
13 revascularization. Evaluation of myocardial  
14 infarction and target lesion revascularization is  
15 nonfatal clinical endpoints addressed two caveats  
16 regarding the use of nonfatal clinical endpoints.

17 First, the occurrence of myocardial  
18 infarctions in clinical symptoms requiring target  
19 lesion revascularization are associated with an  
20 adverse prognosis.

21 Second, therapy directed at preventing  
22 myocardial infarction and target lesion

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1 revascularization improved mortality.

2 Finally, the MACE rate is commonly used in  
3 evaluation of investigational devices.

4 Limitations to the use of composite  
5 clinical endpoints include the following: First, the  
6 total sample size can be under-powered to allow  
7 statistical evaluation of the individual study  
8 endpoints that contribute to the composite clinical  
9 endpoint.

10 Second, uniform weighting of the  
11 individual clinical endpoints does not take into  
12 account differences in prognosis of patient outcome  
13 for each individual clinical endpoint.

14 Third, statistical significance can be  
15 achieved for the composite clinical endpoint with non-  
16 uniform or discordant changes in individual clinical  
17 event rates.

18 At this point I'd like to make some  
19 comments regarding safety and effectiveness based on  
20 the GAMMA I study.

21 Regarding evaluation of effectiveness with  
22 the GAMMA I study, a statistically significant

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1 reduction in MACE was demonstrated for the treatment  
2 arm compared to the placebo, 28.2 percent versus 43.8  
3 percent, as reported in the non-hierarchical analysis  
4 of complications in Table 11 on page 5-320 in the  
5 panel pack.

6 This reduction in MACE was principally  
7 driven by the lower TLR rate in the treatment, 24.4  
8 percent versus 42.1 percent in the control arm. There  
9 was a higher rate of death at 3.1 percent in the  
10 treatment arm versus 0.8 percent in the control arm,  
11 and myocardial infarction occurred in 12.2 percent of  
12 the treatment arm versus 6.6 percent of the control  
13 arm.

14 In terms of the evaluation of safety,  
15 FDA's concerns are related to differences in event  
16 rates for death, myocardial infarction, late total  
17 occlusion, late stent thrombosis, and edge effect.

18 FDA would like panel input regarding how  
19 to evaluate the differences in these event rates in  
20 the context of the overall risk/benefit evaluation of  
21 this product.

22 Late total occlusion was observed at a

1 higher rate in the treatment arm versus the control  
2 arm. The sponsor has provided multiple definitions.  
3 Further, late total occlusion has been characterized  
4 as symptomatic and asymptomatic, as discussed by the  
5 sponsor.

6 FDA's concerns regarding late total  
7 occlusion include the following: First, establishing  
8 a definition, capturing appropriate clinical events,  
9 and adequately differentiating late total occlusion  
10 from late stent thrombosis.

11 Stent thrombosis was identified as a  
12 potential adverse event based on previous clinical  
13 evaluation of coronary artery stents. The general  
14 definition of stent thrombosis based on the presence  
15 of intraluminal thrombus was provided in the original  
16 investigational plan.

17 Stent thrombosis is generally  
18 characterized as acute, subacute and late, based on  
19 the time of occurrence after the index procedure.  
20 "Late stent thrombosis has been characterized as  
21 thrombosis occurring 30 days or later after the index  
22 procedure."

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1           The sponsor has provided multiple  
2 definitions for late stent thrombosis. FDA's concerns  
3 regarding late stent thrombosis include the following:  
4 Establishing a definition; capturing appropriate  
5 clinical events; identification and evaluation of risk  
6 factors.

7           Limitations to the sponsor's definitions  
8 are highlighted by information provided on Patient 57  
9 enrolled in the SCRIPPS 1 study. This patient  
10 underwent re-stent and for in-stent saphenous vein  
11 graft stenosis and was randomized to the active  
12 treatment arm.

13           Thirty-nine days after the index  
14 procedure, this patient developed clinical symptoms,  
15 an elevated CPK, and reported total occlusion of the  
16 vein graft. The patient underwent repeat bypass  
17 surgery.

18           Surgical pathology demonstrated stent  
19 thrombosis. Surgical pathology is generally  
20 considered to be a "gold standard," and consequently,  
21 this patient was excluded.

22           Intercoronary radiation may stimulate

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1 neointimal hyperplasia at the lesion edge. This  
2 phenomenon has been termed the edge effect. Edge  
3 effect is defined in the GAMMA I report as the in-  
4 lesion restenosis rate minus the in-stent restenosis  
5 rate. Edge effect was present in 10.8 percent of  
6 patients in the treatment arm and 4.8 percent in the  
7 control arm.

8 In summary, the evaluation of safety again  
9 incorporates the differences in death, myocardial  
10 infarction, late total occlusion, late stent  
11 thrombosis and edge effect, as outlined on this slide.

12 In summary, FDA would like panel input  
13 regarding how to evaluate differences in clinical  
14 benefit based on the composite MACE rate, which is  
15 primarily due to differences in TLR versus the  
16 increase in death, myocardial infarction, late total  
17 occlusion, late stent thrombosis and edge effect, as  
18 shown on this slide.

19 At this time I'd like to go over the panel  
20 questions.

21 Question 1: <sup>\*\*</sup> d The composite clinical  
22 endpoint consisting of death, Q-wave and non-Q-wave

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1 myocardial infarction and target lesion  
2 revascularization at 270 days post-procedure was the  
3 primary endpoint for the GAMMA I study. This  
4 composite endpoint of major cardiac event rates is  
5 commonly referred to as MACE.

6 The definitions for myocardial infarction  
7 and target lesion revascularization in the GAMMA I  
8 report are provided on pages 5-298 and 5-299. Please  
9 discuss whether you believe these definitions are  
10 adequate to assess the clinical performance of the  
11 device.

12 Question 2: In the GAMMA I study,  
13 patients were scheduled to complete angiographic  
14 follow-up at six months and clinical follow-up at nine  
15 months. FDA infers from information provided by the  
16 sponsor on page 5-733 that all patients completed  
17 clinical follow-up preceding angiographic follow-up at  
18 six months.

19 Please discuss whether you believe any  
20 conclusions can be reached regarding patient outcome  
21 at nine months, since it appears that patients  
22 completed both angiographic and clinical follow-up at

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1 six months.

2 Question 3: Late total occlusion was  
3 observed a higher rate in the treatment arm of the  
4 GAMMA I study. Late total occlusions were comprised  
5 of late stent thrombosis leading to myocardial  
6 infarction or asymptomatic total occlusions.

7 Although stent thrombosis has previously  
8 been recognized as an acute adverse event occurring at  
9 less than 30 days post-stent implantation, the GAMMA  
10 I study showed that the incidence of late stent  
11 thrombosis at greater than 30 days was higher in the  
12 treatment arm compared to the placebo arm. Please  
13 references page 5-0094 through 5-0096 of the panel  
14 pack for thrombosis/occlusion definitions and results  
15 as you address the following questions:

16 Please discuss which definitions of late  
17 stent thrombosis and occlusion are adequate to assess  
18 the clinical performance of the device.

19 Please discuss whether the definitions  
20 employed by the sponsor are clinically meaningful and  
21 whether they adequately differentiate late stent  
22 thrombosis from late total occlusion.

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1                   Question 4: Intracoronary radiation may  
2 stimulate neointimal hyperplasia at the lesion edge.  
3 This phenomenon has been termed edge effect. Edge  
4 effect in the GAMMA I report was defined as in-lesion  
5 restenosis rate minus in-stent restenosis rate.

6                   Information on edge effect is located on  
7 pages 5-0727 through 5-0732 and 5-0773 through 5-0822  
8 of the panel pack.

9                   Please discuss the adequacy of the  
10 sponsor's definition and methodology used to quantify  
11 edge effect.

12                   Question 5: The sponsor provided a  
13 retrospective analysis in November 1999 that contained  
14 pooled data for patients from SCRIPPS I, GAMMA I and  
15 WRIST with native coronary artery in-stent restenosis  
16 who did not receive an additional stent.

17                   The sponsor has proposed the hypothesis  
18 that additional stenting is a risk factor for late  
19 stent thrombosis and should be avoided. Preliminary  
20 information from the SCRIPPS II and WRIST Plus studies  
21 has been provided regarding the effect of extended  
22 antiplatelet therapy on late stent thrombosis rate in

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1 patients treated with intravascular radiation with and  
2 without placement of an additional stent. The sponsor  
3 has proposed the following boxed warning in the  
4 labeling based on the above analyses:

5 Warning: Placement of a new stent during  
6 the radiation procedure has been associated with a  
7 higher rate of late thrombosis in comparison to the  
8 placebo arm. Every attempt should be made to avoid  
9 new stent placement in the irradiated area. However,  
10 if placement of a new stent was necessary, it is  
11 recommended that the patient be placed on antiplatelet  
12 therapy for 12 months.

13 Please discuss whether the study data and  
14 analyses provided support the information contained in  
15 this warning.

16 Please comment on whether any other  
17 information should be included in the labeling  
18 regarding late thrombosis.

19 Question 6: A statistically significant  
20 reduction in MACE was demonstrated for the treatment  
21 arm compared to the placebo (28.2 percent versus 43.8  
22 percent, respectively) as reported in the non-

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1 hierarchical analysis of complications in Table 11 on  
2 page 5-320 of the panel pack.

3 This reduction in MACE was principally  
4 driven by the lower TLR rate in the treatment arm  
5 (24.4 percent versus 42.1 percent) with a higher  
6 incidence of death (3.1 percent versus 0.8 percent)  
7 and a higher rate of myocardial infarction (12.2  
8 percent versus 6.6 percent).

9 Also, as discussed earlier, other  
10 secondary safety measures such as late total  
11 occlusion, late stent thrombosis, and edge effect  
12 occurred at a higher rate in the radiation treatment  
13 arm compared to the control arm.

14 Please discuss whether you believe the  
15 probable clinical benefit of the radiation treatment  
16 (i.e., reduction in TLR) outweighs the probable risks  
17 of death, MI, late total occlusion, late stent  
18 thrombosis, and edge effect posed by the device in the  
19 intended patient population.

20 Question 7: One aspect of the  
21 premarketing evaluation of a new product is the review  
22 of its labeling. The labeling must indicate which

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1 patients are appropriate for treatment, identify the  
2 product's potential adverse events, and explain how  
3 the product should be used to maximize benefits and  
4 minimize adverse effects. Please address the  
5 following questions regarding the product labeling:

6 Please comment on the Indications for Use  
7 section as to whether it identifies the appropriate  
8 patient population for treatment with the device.

9 Please comment on the Contraindications  
10 section as to whether it identifies all conditions  
11 under which the device should not be used because the  
12 risk of use clearly outweighs any possible benefit.

13 Please comment on the Warnings and  
14 Precautions sections as to whether it identifies all  
15 potential hazards regarding the device use.

16 Please comment on the remainder of the  
17 product labeling as to whether it adequately describes  
18 how the product should be used to maximize benefits  
19 and minimize adverse events (for example, late stent  
20 thrombosis, late total occlusion and edge effects).

21 Does the <sup>\*\*</sup> panel have any other  
22 recommendations regarding the labeling of the device?

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1                   Question 8: Use of the Cordis CHECKMATE  
2 System during the investigational studies required the  
3 collaboration of a cardiologist, radiation oncologist,  
4 and radiation physicist.

5                   Please discuss what important elements  
6 should be contained in a physicians' training program  
7 for this product.

8                   Finally, the last question: Published  
9 literature on radiation-induced heart disease is  
10 primarily related to late effects on normal tissue in  
11 which the heart is irradiated as part of the treatment  
12 of intrathoracic neoplasms. There is generally a long  
13 latent period between the index treatment and the  
14 development of coronary artery disease.

15                   Based on the literature, do you believe  
16 that additional clinical follow-up is necessary to  
17 evaluate the chronic effects of intravascular  
18 radiation administration? If so, how long should  
19 patients be followed, and what endpoints and adverse  
20 events should be measured?

21                   CHAIRPERSON CURTIS: Thank you. I think  
22 we have a little time before the scheduled lunch

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1 break. So we could start the open committee  
2 discussion. I think Dr. Domanski, you are the lead  
3 reviewer?

4 DR. DOMANSKI: Let me begin by saying it's  
5 certainly a carefully prepared presentation by the  
6 company, by a real eminent scholar in the area, and I  
7 would certainly - - I thank you for a clear  
8 presentation.

9 I guess I have a number of questions that  
10 I'm going to try to use to sort of set the stage for  
11 the discussion of this. The problem that's being  
12 addressed, trying to prevent in-stent restenosis, is  
13 a major problem for which there are not currently --  
14 or at least prior to the radiation, there certainly  
15 haven't been the sort of effective treatments that we  
16 really needed, and the radiation on the face of it,  
17 from preliminary data or at least from the data here  
18 as well, suggests that this might be a solution or  
19 part of the solution.

20 I guess the things that strike me as being  
21 central issues, because we're talking here about  
22 effectiveness and about safety, is what we're trying

1 to be effective for. It seems to me that -- and I'm  
2 going to ask for correction from the -- You know, I'm  
3 going to ask this as a question ultimately. But it  
4 seems to me that the issue is, first of all, whether  
5 or not this device prevents or reduces the need for  
6 target lesion revascularization. That's sort of the  
7 effectiveness. Then is it really safe?

8 The things that -- I guess there are  
9 several things that I'm concerned about and would like  
10 to see addressed. You know, the first thing and  
11 perhaps a central issue is that, while one seems to  
12 reduce target lesion revascularization -- the primary  
13 endpoint was MACE -- if you look at that whole  
14 endpoint, more people die and have an MI, and that's  
15 a bad outcome.

16 I mean, it's unpleasant to come back to  
17 the cath lab, but a target lesion revascularization  
18 strikes me as less important than having an MI or  
19 dying. So that, while it's nice to think that I'm not  
20 coming back to the lab, if I thought I had a higher  
21 chance of either death or MI, I wouldn't be very  
22 enthusiastic myself as a patient about having this

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1 procedure done.

2 So it seems to me that the first question  
3 that I'd like to ask you is to tell me how you can  
4 convince me as a patient or as a physician that you  
5 really have a procedure -- you know, we really  
6 understand how to reduce death plus MI.

7 Now the point, of course, has been made  
8 that it's related to stents. But I'm concerned about  
9 a number of things. I'm concerned about poolability  
10 of these data. I mean, the data that were pooled to  
11 do that were done over a long period of time.

12 If you just take the admittedly small  
13 number of patients and do a multivariate analysis on  
14 the pivotal trial, stenting doesn't really -- you  
15 know, stenting doesn't drop out as an independent risk  
16 factor.

17 So convince us, one, that pooling is  
18 reasonable across this group of patients, and that  
19 you're really safe. Who will take that?

20 DR. KUNTZ: I'll respond to that. I guess  
21 the crux of this whole <sup>\*\*</sup>meeting is the questions that  
22 you posed.

1 Just to review, the major adverse cardiac  
2 event rates are made up of diverse outcomes which are  
3 typical for intervention trials. That is, they look  
4 at bad things that can happen to patients, death,  
5 heart attacks, and the need to have the procedure  
6 repeated again, looking at success.

7 Failure to find is the need for the  
8 procedure again. We call that target lesion  
9 revascularization and have focused on that  
10 specifically. In this trial I think that all the  
11 trials showed significant differences in the target  
12 lesion revascularization rate independently and  
13 pooled.

14 The issues of death, I think, when I look  
15 at the data there is no difference in death, that this  
16 is a chance event in the slightly higher estimate for  
17 the GAMMA study for radiation versus placebo. There  
18 was no statistical difference there, and the rates of  
19 death in the other two trials, SCRIPPS and the WRIST  
20 trial, were also low.

21 So I think that<sup>\*\*</sup>, when we look overall, I  
22 don't think that there is any instance of increased