

1 things we learned was how people used it, and that's kind of
2 where we've gotten with the training now, taking those
3 experiences with that and how can we make that what is
4 actually a very well calibrated and accurate gauge and make
5 it something that the user can use most beneficially in the
6 treatment here.

7 The other piece of that would be, just to segue
8 into the question you asked Dr. Speiser, would be with
9 regard to the source transit time. I think--this is the
10 second time we've covered this. I think the first time I
11 forgot to mention that when we prospectively designed the
12 trial to try to figure out--you know, one of the objectives
13 of the trial was to determine device--you know, what the
14 device could do and how it would be used, and that was built
15 into the protocol, and you can see that in the protocol as
16 one of the objectives.

17 So we developed on the case report forms multiple
18 pages to collect some of these pieces of information. The
19 best information we had without clinical data was that on
20 the bench source transit could be accomplished in five
21 seconds. So we put one of the items on the case report form
22 as being, you know, was source transit greater than five
23 seconds. And in most cases it was a check box with very
24 little information to be added or able to be added. So we
25 incorporated that. And as I said, now having had the

1 clinical experience, having had the feedback in cases where
2 it was reported how long it actually took send or deliver,
3 given the time to evaluate the clinical situation, and
4 having the feedback from actually specifically asking the
5 oncologists and physicists in the trial what is clinically
6 acceptable with regard to how long is this taking, given the
7 anatomy where this would be located, the fact it's in a
8 guide catheter, et cetera, and that's where we came with the
9 source transit recommendation of 15 seconds, which does kind
10 of put things a little more in perspective when you look at
11 the minor device malfunctions in that about fifty--I believe
12 54 was the number of my device malfunctions, with source
13 transit greater than 5 seconds. You know, if you apply what
14 would be the clinical reality and the practicality in the
15 cath lab of doing this procedure to that of 15 seconds, you
16 actually see a great reduction in the number of those
17 reports.

18 Dr. Speiser?

19 DR. SPEISER: I'd like to reiterate that the 5
20 seconds was chosen before the clinicians were involved, and
21 it was based on an engineering bench testing. What we've
22 done with the radiation oncologists and physicists in the
23 study is look at different parameters and decide that 15
24 seconds would be achievable in the real world clinically,
25 and that it was a safe dose for transit. So that the

1 transit itself being more than 5 seconds I do not see as
2 causing a problem to the patient.

3 The drift was a bigger problem, because if the
4 drift truly means that the source is outside of the target
5 area, then we'll have a diminished effect. We've done some
6 bench testing recently to show that the gold marker, which
7 is very dense, moves a long time before any of the sources
8 move. So that while I can't say whether the sources moved
9 or not because they're very difficult to see on fluoroscopy,
10 we still have to assume that if the gold moves, that
11 eventually the sources will move, and if the sources move,
12 we'd have a decreased benefit to the patient.

13 However, I don't really see with the very slight
14 movement an increased deleterious effect for those treatment
15 times, just the opposite, a decrease of the beneficial
16 effect.

17 DR. CRITTENDEN: Now, when I went over the
18 protocol, I didn't realize this--and this is my fault--that
19 the radiation oncologist actually injects the source train
20 after the cardiologist places the delivery catheter at the
21 appropriate spot?

22 DR. SPEISER: That's correct.

23 DR. CRITTENDEN: I realize that the radiation
24 oncologist brings a lot of expertise to this that is
25 absolutely necessary in the cath lab. But it seems to me,

1 just on face value, if I want someone injecting something in
2 my coronary artery. I'd prefer a cardiologist to do it. Why
3 do we need--and I'm not trying to be funny. I just--why do
4 we need someone who, by your admission, hasn't been the cath
5 lab in years now injecting a catheter, which the
6 interventional cardiologist does--I mean, they can do that
7 not literally--but you know what I'm saying.

8 DR. SPEISER: Yes. The catheter is placed by the
9 interventionalist, not the radiation oncologist. The
10 radiation oncologist sends the sources within a closed
11 system. So there's no effect on the coronary system. The
12 primary role of the radiation oncologist is not mechanically
13 to do it, but for the other attributes of making sure the
14 device is prepared correctly, the dose as well as any
15 problems that might come up. So that right now at the
16 present time it's an NRC-mandated rule that this amount of
17 radiation be handled by somebody who is licensed through NRC
18 or through an agreement state to handle the radiation.

19 DR. CRITTENDEN: And that includes--because if I
20 understand that correctly, you're squeezing the syringe and
21 you're pushing the source train--

22 DR. SPEISER: That's correct.

23 DR. CRITTENDEN: And then aspirating it. But the
24 NRC--

25 DR. SPEISER: Well, it's not really--it's a

1 hydraulic system, but it works that way where I'm putting
2 pressure on the syringe to move hydraulically the sources up
3 to position, keep that in position, and then with the change
4 of the valve, the same syringe will return my sources back
5 into the device.

6 MR. GREEN: I think the key--one of the key--the
7 two things here--there's actually two points to be made.
8 One is that there's a regulatory requirement. Within the
9 facility, the radiation oncologist is the authorized user or
10 the person licensed to actually not only handle but actually
11 treat with or apply the treatment of radiation, the second
12 piece being the cardiologist is actually controlling the
13 delivery catheter, if you will, the patient contact portion
14 for the coronary anatomy and that the oncologist is
15 delivering the therapy, as they are licensed to do.

16 It's also important to point out that the team
17 approach that comes from the oncologist, the cardiologist,
18 and the physicist I think puts the right emphasis on both
19 the dynamic cardiac responsibilities and care that need to
20 be taken for the patient as well as the radiation safety,
21 and then the radiation protection type issues that the
22 medical physicist and the oncologist bring from their arena
23 I think is very important.

24 DR. POPMA: To put this in perspective, usually in
25 a case, as you've probably seen in the cath lab, there's a

1 first operator position and a second operator position. The
2 cardiologist is always in the first operator position. And
3 my responsibility as part of the case is to make sure the
4 catheter position is, in fact, appropriate through the whole
5 period of time. The second operator position is actually
6 the radiation oncologist who's injecting the source train.
7 So it's not that--the catheter position is clearly our
8 responsibility.

9 MR. GREEN: Just one subtle note. When you send
10 the source train, you apply a positive pressure on the
11 syringe. In order to return the source train, you still
12 apply a positive pressure. There's a fluid control valve.
13 You simply change direction and apply a positive pressure
14 again and it comes back. So it's continuous.

15 DR. CRITTENDEN: The next question is for Dr.
16 Popma. In this trial, there were a few cases of late
17 thrombosis, at least out to 8 months, but historically there
18 has been a question of whether brachytherapy leads to late
19 thrombosis. There is data that has come from the Washington
20 Hospital Center and it was just kind of a meta analysis of
21 some of their trials that suggested that late thrombosis was
22 related to new stent placement.

23 So, with that preamble, why do you think the rate
24 was so low in this study? Is this from a reduced radiation
25 dose? In the trials before, they had higher radiation doses

1 and different sources; some of it was gamma radiation as
2 well. So does this represent a difference between beta and
3 gamma radiation? Or is it due to this adjunctive platelet
4 therapy?

5 Then, finally, is the sponsor going to make a
6 claim in this regard vis-a-vis late thrombosis?

7 DR. POPMA: I am academically aware of the data
8 from the Washington Hospital Center suggesting that there
9 are cases of late subacute stent thrombosis that have been
10 associated with other forms of therapy. It's very difficult
11 to make comparisons, and I don't feel comfortable making a
12 comparison of gamma and beta about incidence of late
13 subacute stent thrombosis rate because in this trial we
14 didn't use very many stents. And I think that the reason
15 that this was such a safe trial, which it was, and we didn't
16 really observe much in the way of stent thrombosis, is that
17 we only used stents in 100 patients, and only approximately
18 50 of those got radiation therapy.

19 Having said that, we don't think it's a very
20 frequent event. We have this one case that we have been,
21 you know, in due diligence, I think, reporting, but that was
22 outside the 8-month time frame. Other than that, we saw no
23 occurrences within there.

24 Personally, I was a little surprised about how
25 many patients did not receive extended antiplatelet therapy.

1 It was my impression that the clinical investigators,
2 knowing the data that had been coming out, would have put
3 patients on their own on extended antiplatelet therapy, but
4 in this trial they did not. And you saw the vast majority
5 of the patients had relative short antiplatelet therapy
6 durations.

7 That just comes back to one thing, and I think
8 that that is we didn't use stents very often. And we used
9 them specifically for bail-out indications. It wasn't
10 always perfect. Sometimes they were cosmetic, but the
11 majority of time they were for bail-out indications. And I
12 think for us as operators that is a very important lesson.
13 When you're treating in-stent restenosis, it's important
14 that you try to get the best you can mechanically without
15 adding a new stent. It means sometimes debulking devices,
16 sometimes balloon angioplasty, being patient with it, but
17 then avoiding using a new stent if possible.

18 I think following those rules we should anticipate
19 that we're going to have continually lower subacute stent
20 thrombosis rates. I do think it's premature to make any
21 comparisons between one isotope versus another isotope.

22 DR. CRITTENDEN: The next question is for Dr.
23 Speiser. I realize that emergency coronary bypass was rare,
24 but what recommendations would you make for surgeons or
25 other OR personnel if we had to do an emergent case on

1 someone who just had this therapy? Not worry about it?
2 Should we worry about it? I know it's an extreme example,
3 but it's been talked about kind of at the water cooler at
4 conventions. If you had to remove a stent, how should it be
5 disposed of?

6 DR. SPEISER: The stents in this case are not
7 radioactive, so the minute that I withdraw the device, there
8 is no radiation in the patient. So to answer the question,
9 you do not have to take any precautions vis-a-vis the
10 radiation.

11 DR. CRITTENDEN: That's all I have.

12 DR. IBBOTT: Thank you. I'm Geoff Ibbott. I'm a
13 medical physicist, and I have a couple of questions about
14 radiation safety issues and dosimetry.

15 My first question is: In the description of the
16 device, the device is described as having a quartz chamber
17 where the sources are housed which attenuates the beta
18 radiation from the sources. But in the labeling there are
19 warnings about avoiding holding the device with your hand
20 over the quartz chamber because of the risk of exposure.
21 And so I'm wondering what the exposure rate or dose rate at
22 the surface of that quartz chamber is and what the exposure
23 might be to an individual.

24 MR. GREEN: You are correct that there is a quartz
25 in the device that does provide the shielding for the beta

1 radiation from the source train. There's a slight rem
2 strong component. There is a stainless steel capsule to the
3 source.

4 I think Dr. Lobdel, if he could come back, I think
5 he could answer the question, just provide to you what the
6 numbers in the instructions for use mean and what the
7 component that you're seeing and he's talking about there
8 is.

9 DR. LOBDEL: Again, John Lobdel, employee of
10 Novoste. We don't know what the dose rate is at the surface
11 of the quartz. That has never been measured. The quartz is
12 sufficient to stop all of the beta. Obviously, there's a
13 rem strong output. We have not quantitated that. We do
14 know what the dose rate is on various surfaces of the
15 device. Specifically over the lens you could see roughly
16 100 mRAD per hour at contact with the lens. Again, that's
17 due to the rem. But there is no reason for the operator to
18 open up the device. It is sealed and our instructions
19 clearly say don't open up the device.

20 DR. IBBOTT: Perhaps I misunderstood the
21 description of the device. So the lens that you mentioned
22 is the surface that the operator would be in contact with.

23 DR. LOBDEL: Right.

24 MR. GREEN: Just for orientation, yes. The
25 transfer device--the quartz is actually enclosed inside the

1 device, and when you look through the device--if you refer
2 to your picture, we can find it in the panel pack. When you
3 look through a lens, a magnifying lens so you can see in the
4 device, the quartz chamber is actually below that lens
5 internal to the device. So measurements that are in the
6 instructions for use would be described at different
7 surfaces on the outside of the transfer device, the part
8 that you could actually come in contact with. As Dr. Lobdel
9 said, the quartz--the viewing lens is on top. Of course, we
10 (?) device on the bottom.

11 DR. IBBOTT: Yes, I see. Okay. Thank you.

12 I'd like to follow up on Dr. Ayers' questions
13 about the doses to the target site. Presumably there were
14 variations from one patient to another treated with the
15 device because of differences perhaps in the timing of the
16 source placement and in the drift of the sources that's
17 already been mentioned. Have you estimated the range of
18 doses that were received by the target lesions over the
19 course of the number of treatments you delivered?

20 MR. GREEN: There's really two pieces, I think, to
21 answer the question you asked. One is how you handle
22 variations in the trial. Another is how do you try to look
23 at that more, I'd say, mechanistically or from trying to see
24 what was going on.

25 We had a randomized trial, so what we tried to do,

1 of course, in the randomized trial was look at what would be
2 the realistic occurrences in actual use. So use, you know,
3 visual estimate of reference vessel diameter to choose your
4 dose, the catheters are placed after the standard treatments
5 that you would expect, debulking, et cetera. So that you
6 would get the expected type of outcomes you would expect to
7 see in the real clinical application, and then we look to
8 see how did those--were those effective were those safe when
9 we did that.

10 Now, the second part to that is to actually look
11 at the individual patients in as many cases as we could to
12 see what was happening. I think we--we did an IVUS--
13 retrospective IVUS dosimetry was done by Dr. Crocker and Dr.
14 Fox at Emory University on 28 IVUS patients that we did have
15 come back, and Dr. Crocker could touch on what was found in
16 that first part of variations.

17 DR. CROCKER: The maximum surface dose based on
18 that retrospective IVUS dosimetric analysis was 75 Gray.
19 That, of course, is, you know, a high dose, but I think you
20 need to keep in mind that that is a dose that's received by
21 an extremely small volume, an extremely small portion of the
22 vessel wall and the dose, you know, falls off rapidly from
23 that point.

24 When considering tolerance doses, I think you also
25 need to keep in mind that this is a dose--or that the

1 volumes that we're treating are about 1/30,000th of what one
2 might normally treat with external radiation treatment.

3 So, yes, there were high doses received on the
4 luminal surface of the vessel. Those doses do fall off
5 fairly rapidly. The average dose received to the vessel
6 wall is much lower than that, and we haven't see any adverse
7 effects from these localized high doses in either the START
8 or in the BERT trial.

9 I guess I should also mention that, you know, the
10 vessel is supported by a stent in this situation as well.

11 ACTING CHAIRPERSON TRACY: Could I just ask you to
12 state your name? This is being recorded, so just remember
13 to state your name.

14 DR. CROCKER: I'm sorry. Ian Crocker, Emory
15 University.

16 DR. IBBOTT: Dr. Crocker, before you go, I guess
17 I'm understanding that the variations in the dose due to
18 positioning of the catheter within the vessel and the
19 dimensions of the vessel are much more important in
20 determining the final dose to the target lesion than any
21 variations in the length of time that the sources are in
22 position. Those variations--

23 DR. CROCKER: Yeah, I think that--

24 DR. IBBOTT: --are much smaller.

25 DR. CROCKER: You know, there is a substantial

1 variation in the thickness of the vessel wall, which is then
2 reflected in a heterogeneity of dose, and that is a much
3 greater determinant of the heterogeneity of dose than, as
4 you say, the estimate of the vessel size that we used in
5 order to determine the dose prescription in this study.

6 DR. IBBOTT: Thank you.

7 You have mentioned the minor device malfunctions,
8 and I wondered if there was a correlation between the
9 frequency of these malfunctions and the institution
10 performing--participating in the study, if you looked at the
11 incidence of those malfunctions from one institution to
12 another.

13 MR. GREEN: One of the things that makes this a
14 very interesting analysis to look at is that when you start
15 to go into it, we were running, of course, two other trials
16 at the same time. We had the Beta-cath system trial, and we
17 had the START trial, and we had the START 4020 trial. So
18 there were more than one trial going on at the site. So to
19 begin with, it kind of made it difficult to look at a site's
20 experience based on that. Was this the first patient they
21 had treated in this trial and all trials, et cetera?
22 Another piece would be that we would train--you could train
23 multiple--we could train multiple teams of users at a site,
24 so collection of the information was not always made on the
25 user; therefore, we couldn't determine if it was the users

1 at first.

2 So what we do know is that there was a difference
3 in the reporting at some sites, i.e., when you look at the
4 data there was some, if you will, clumping of reports. In
5 some cases, there was more reports from one institution
6 than, say, the other, many of the others.

7 DR. IBBOTT: Then that makes me wonder if there
8 was a--if this is a training issue, if you see that as an
9 indication of inadequacy of the training at some
10 institutions as compared to others.

11 MR. GREEN: I think that in all cases that we can-
12 -you know, we can look at these, and we believe that the
13 training is very important here. And we learned with a new
14 technology and a new device here, we've learned a lot of
15 things about the device. And I think that that is the most
16 important thing from the interaction with the company,
17 figuring out what we need the companies to do with the sites
18 and we can put that in the training program. And I do
19 believe that that would make a difference.

20 Again, we said as you look at things like manual
21 removal or the bail-out procedure, as sites became more
22 experienced and did more treatments, those numbers--the
23 rates went down of those incidents, and it was clear that
24 the training and learning curve was a portion of that.

25 DR. SPEISER: I definitely feel that training is

1 important, and there was variation from institution to
2 institution. I think at this point training will include
3 physicians involved in the procedure, which will be a major
4 advantage for the future.

5 MR. GREEN: I guess one other thing to point out
6 would be that it's also possible--I mean, we have to show
7 both sides of that angle. It's also possible to--some sites
8 were--if you could be overtrained in the reporting of
9 incidents, and maybe they--they were doing exactly what we
10 wanted, trying to give the feedback to our design
11 development system, and they did a very good job of that.

12 DR. IBBOTT: One last question, and this may be
13 something I missed in your package or my own naivete, but
14 I'm wondering why you assigned a maximum usage of six months
15 or 250 treatments to the device.

16 MR. GREEN: It's quite simply based on the data,
17 the bench data and the testing data that we have to support
18 the number of uses of the device. We both collected
19 information from the clinical trials on the number of uses
20 and time of use of the devices, and we've also done
21 reliability and other engineering tests that have been
22 submitted to the agency. And that is what that testing
23 supports, and that really implies a safety margin above what
24 could actually be done. That's what we recommend.

25 DR. IBBOTT: Thank you.

1 ACTING CHAIRPERSON TRACY: Thanks. I just have
2 one brief question and one comment to make.

3 What exactly is the recommendation for
4 antiplatelet therapy in patients who did not receive a
5 stent, a new stent?

6 MR. GREEN: In the instructions for use, we
7 basically made a recommendation that reflects what we did in
8 the clinical trial. Patients received--we recommended that
9 patients be treated after a successful result. If they did
10 receive a new stent, they got a minimum of 90 days. We did
11 not make a recommendation in the clinical trials for
12 patients without new stents. And those patients, as you
13 saw, received what reflected probably the clinical practice
14 of about 14 to 30 days.

15 ACTING CHAIRPERSON TRACY: So you're not making a
16 specific recommendation on that.

17 MR. GREEN: We're not. We are not making a
18 recommendation.

19 ACTING CHAIRPERSON TRACY: There's a discordance
20 between what you have in the labeling and what you have in
21 your training recommendations in terms of the frequency of
22 fluoroscopic evaluation to prevent drift. One says 15
23 seconds and one says 15 to 30 seconds. I would just
24 encourage you to make sure that there aren't other
25 discrepancies like that.

1 MR. GREEN: Thank you.

2 DR. FREISCHLAG: Julie Freischlag. I read your
3 animal study summary that's in the booklet, and I guess I
4 was impressed that it doesn't seem to be working in animals.
5 Usually with our studies we find perhaps it may work in an
6 animal model and not in humans. It seems that perhaps there
7 isn't any animal proof that it worked, but it looks like it
8 works in humans. Can you explain that?

9 MR. GREEN: Yes. Actually, we looked at--the
10 progression through the FDA process was actually earlier on,
11 which was not reviewed in the memo provided by Dr.
12 Subramanian. There were five additional studies--two 2-week
13 studies, two 4-weeks studies, and a 6-month study--looking
14 at the device safety and performance and the reduction of
15 proliferation. That was provided in the PMA. It was not
16 reviewed in the memo.

17 Those studies were the studies that provided the
18 safety device performance and the initial information on
19 whether there seemed to be feasibility of radiation
20 including proliferative tissues to go into clinical studies,
21 and that's what we did.

22 In conjunction or in parallel with the clinical
23 studies we ran, the studies we've done now, the model there
24 did not show concurrence with what we've seen in the BERT
25 data out to four years and the START data. It did, however,

1 provide similar information on device safety, device
2 performance, and the initial feasibility of doing the study.

3 DR. FREISCHLAG: So you think--if you look at why
4 you think the radiation works, why is it preventing intimal
5 hyperplasia in the stent, it sounds a little bit better than
6 on the edge of the stent, what do you think the reason is
7 that this works at all? Most of us haven't been able to
8 figure out even what causes intimal hyperplasia. It looks
9 like you may be able to prevent it in the stent. What is it
10 doing to those cells in the human model that perhaps it
11 didn't do in the animal?

12 MR. GREEN: I think I'm going to have to defer
13 that question probably to one of our cardiologists, Dr.
14 King, if he could step up and provide some insight on some
15 of the more biological issues.

16 DR. KING: I'm Spencer King from Emory University
17 and Atlanta Cardiovascular Research Institute. As a
18 developer of the technology, I have a licensing agreement
19 with the sponsor and also research support.

20 The information in the packet seems to indicate
21 that it didn't work in animals, but, in fact, the reason
22 that we went into patient trials had to do with animal
23 research. For the last 15 years, we've been using the pig
24 model, tried to look at not restenosis model but a model of
25 vascular injury. You blow a balloon up, you damage the pig

1 coronary artery, and you get a healing response. It's not
2 restenosis, of course, because the pig never had stenosis in
3 the first place.

4 All our work was short term, two-week to a month
5 work, with radiation, and it had been the same with other
6 things, lipid-lowering agents and a lot of things over the
7 past 15 years.

8 What we saw in the animal lab, with the work of
9 Dr. Waxman and Dr. Robinson in our lab, was that the animal
10 proliferation was dramatically inhibited in that model, two
11 weeks, at four weeks, and we had some six-month data at
12 Emory that was not included in the packet. That encouraged
13 us to apply to FDA for the feasibility trial, and that's
14 what got us to that level.

15 I would emphasize that this model--we don't know
16 from radiation or other therapies what the long-term pig
17 effect in growing young pigs is in terms of modifying a
18 healing response after vascular injury. So the model I
19 think was a good model to look at acute proliferation,
20 migration of cells. We know things about the effect on
21 measures such as bromodeoxyuridine measures to show that
22 cell proliferation is being reduced and that sort of thing
23 acutely. And that led us into the clinical trials.

24 But in terms of the pig having a sustained long-
25 term benefit, the pig model, particularly with stenting, is

1 a very difficult model. A lot of thrombosis, we've had a
2 lot of deaths with pig models using all kinds of agents.
3 And so I don't know why or even if we should expect that it
4 has this good long-term effect in the pig.

5 DR. FREISCHLAG: If you were to hypothesize how
6 this works, you think it is because it decreases
7 proliferation of the smooth muscle cells? Do you think
8 anything else might be involved besides that?

9 DR. KING: Yes, well, we think that in terms of
10 the lesion that develops in the pig model, that is,
11 cellular, that those cells are inhibited. We've seen that
12 with, as I say, the proliferation part with BrDu staining.
13 There's work on apoptosis that may be a part of this formula
14 as well. There's extracellular matrix elaboration that may
15 be modified.

16 There's also a modification of the vessel
17 contracture, we believe, that occurs, not as well
18 demonstrated in the pig as in the patient with IVUS
19 examination, but we think it affects not only the smooth
20 muscle cells but also fibroblast and periadventitial
21 scarring that occurs with contracture of vessels. So we
22 think all these mechanisms are operative in what we're
23 seeing.

24 Now, with the stent model, the contracture part is
25 less active because the stent is holding everything open.

1 So in the stent model it's almost all animal proliferation
2 and extracellular matrix elaboration.

3 DR. FREISCHLAG: Did you ever treat normal vessels
4 that hadn't been dilated or injured with the radiation?

5 DR. KING: Yes. Normal vessels have been treated,
6 and that's been reported, and there's been little observable
7 effect in normal vessels.

8 DR. FREISCHLAG: Did you check for apoptosis in
9 normal vessels?

10 DR. KING: I might have to defer to my colleague.
11 I don't know if Ron is still here. Ron, did you do
12 apoptosis in the--I can't remember in the normal vessels if
13 you looked at that?

14 ACTING CHAIRPERSON TRACY: Can you come up to the
15 microphone and introduce yourself? And also state whether
16 you have any relation with the company.

17 DR. WAXMAN: I'm Ron Waxman. I'm from the
18 Washington Hospital Center. I do have an interest in the
19 device, and I'm entitled to royalties through Emory, an
20 agreement, but I'm not(?) serving a consultant to the
21 company.

22 We have performed studies in which we have seen
23 apoptosis in normal vessels and injured vessels as a result
24 of the radiation. There were different time points as
25 compared to the placebo, but definitely apoptosis is one of

1 the mechanisms. There is also clearly a reduction of acting
2 as smooth muscle cells--staining to smooth muscle cells,
3 (?) staining. So we have seen a reduction of the smooth
4 muscle cell population, and I think literally what we're
5 doing with the radiation is we're killing the cells.

6 Now, as opposed to the models, at two weeks and
7 four weeks it's very suggestive that you reduce the amount
8 of new intima formation within the stent. When it comes to
9 six months, there is actually no studies except one that we
10 have performed before with gamma radiation that in others
11 that showed that you do have a benefit on the long term.
12 But in terms of the answer to the apoptosis, it's probably
13 part of the mechanisms, but we don't know to what extent
14 it's explained the entire phenomenon.

15 DR. FREISCHLAG: One more follow-up. Have you
16 followed normal vessels treated with the radiation longer
17 than two weeks?

18 DR. WAXMAN: We have performed the examinations,
19 and there were others that reported on that. If you take a
20 source in a normal artery without injury, you do see some
21 effects, deleterious effects on this artery. Now, it
22 depends on the dose. This is only coming from animal data,
23 and it was shown on the rabbit and in the pig.

24 However, in our human data from gamma radiation,
25 when we looked by ultrasound on the areas that were exposed

1 to radiation and were not injured, we have not seen any
2 deleterious effect at six months with intravascular
3 ultrasound on these segments. Again, these are segments
4 that were not injured and were treated with radiation.

5 So there could be some differences between the
6 animal models and the human, which we appreciate, and we can
7 summarize in this respect that the animal data does show
8 some effects. The human data so far on arteries that were
9 not exposed to injury does not show any deleterious effects.
10 It comes from our lab in the Washington Hospital Center, and
11 also from the Toric (ph) Center there was a paper that was
12 published and a paper that's about to be published.

13 DR. FREISCHLAG: I had another question concerning
14 the edge effect, and perhaps this is best to Dr. Kuntz since
15 he talked to us about that.

16 Is 5 millimeters enough to look at on either side
17 to see whether or not your edge effect may actually be
18 further away from your treated site?

19 DR. KUNTZ: Right. Rick Kuntz, cardiologist in
20 Boston. There are a variety of ways to look at the edge
21 effect. The first analysis--these are very labor-intensive
22 analyses to be done, and maybe if Dr. Lansky can talk about
23 the more technical aspects of this, it would be helpful as
24 well. But as an opening statement, we chose this analysis
25 or, more precisely, Dr. Lansky chose this analysis because

1 the biggest concern about edge effect was the point of the
2 end of the source; that is, if there was any theoretical
3 problem associated with the radiation therapy on normal
4 vessel, or on a vessel causing so-called edge effects, that
5 is, effects not targeted outside the target lesion, that is,
6 effects not anticipated outside the target area, it would be
7 at the area where the patient was exposed to injury and
8 potentially exposed to reductions in radiation therapy. So
9 because of that, the edge of the source was the center of
10 the analysis, and we went 5 millimeters on each side to
11 bracket a 10-millimeter segment.

12 Now, since the source is 30 millimeters long in
13 the majority of these cases and the stents are on average
14 between 15 and 20 millimeters in length, that 10-millimeter
15 bracket covered almost everything up to the edge of the
16 stent in the majority of cases. But there was possibly a
17 few millimeters on each side of the stent that wasn't
18 included in this analysis that was still outside the stent.
19 And that would require a second analysis to go forward.

20 I feel pretty confident that the analysis, because
21 of its broad range in this 30-millimeter train for 20-
22 millimeter lesions, was pretty comprehensive in looking at
23 the edge effect as it was done up front. But there are
24 multiple different ways to look at edge effect, each of
25 which will require different labor-intensive analysis to go

1 forward.

2 So I would say that as an initial look
3 specifically at edge analysis, which has never been done in
4 any other study yet, that this was a very good first pass
5 and probably covered most of the territory which we could
6 see the problem of theoretical edge effect if, in fact, it
7 did occur. And I do want to leave the podium open for Dr.
8 Lansky if she wants to make any further comments.

9 DR. FREISCHLAG: Was there any effect in other
10 vessels that may be in close proximity to the treated vessel
11 with effects that may be related to the use of the device?

12 DR. KUNTZ: That's a very interesting question,
13 and we have not specifically looked at that question, at
14 least I haven't specifically. I do know that there are
15 indicators indirectly that suggest that there was no
16 untoward effect. That is, we do have information about the
17 frequency of repeat revascularization in other vessels that
18 looks very similar to other trials that we've done without
19 radiation therapy. But we haven't done a specific analysis
20 looking at the incidence of new events at other vessels in
21 the adjacent area.

22 I think theoretically it might be tough to imagine
23 that vessels that may be separated by 4 or 5 centimeters
24 might be affected by beta radiation in the heart. But at
25 first blush, looking at the distribution of

1 revascularizations, we didn't see anything that looked like
2 there was an increased frequency of new lesions or
3 restenosis at the other vessels. But I can't say that we
4 specifically looked at that question.

5 DR. SPEISER: Can I make a comment on that?
6 Burton Speiser, radiation oncologist. Along the source axis
7 linearly, 5 millimeters away within the vessel, the dose
8 falls down to about 1 percent. So it's a very low dose. At
9 a right angle, the dose falls down well below 1 percent at
10 10 millimeters, so that any of the vessels close by will get
11 a very low dose.

12 DR. FREISCHLAG: Dr. Speiser, you mentioned when
13 you spoke that the radiation effects in vessels you felt
14 from this device would be seen at 6 to 24 months, is the
15 range I think I heard you say, and you followed these
16 patients for 8 months. Can you hypothesize what might
17 happen to these vessels up to 24 months, or have you seen
18 any vessel treated with your device at 24 months after it's
19 been treated?

20 DR. SPEISER: The only information is from the
21 BERT study where there's 4-year follow-up. Is there
22 adequate anatomical material? No. But I stand by the
23 statement that most radiation effects usually have a time
24 course of 6 to 24 months after delivery when we see that.
25 The higher the dose, the sooner we see the effect. And what

1 type of effects? It would be decreased proliferation so
2 that if you gave a very high dose of radiation well above
3 what we're giving, you would completely stop all healing and
4 lead to other problems such as aneurysmal formation.
5 Another effect, which would be less likely, would be usually
6 destruction of the endothelial lining can lead to a problem,
7 but the endothelial lining is already destroyed during the
8 process. So that the other possibility would be fibrosis in
9 the future.

10 However, because of the small area, radiation also
11 has an effect that's volume related, so that the smaller the
12 volume or length of artery, the less the effect for the same
13 dose.

14 DR. FREISCHLAG: Is the vasovasorum preserved with
15 treatment of these vessels when you've looked at them after
16 treatment with your device?

17 DR. SPEISER: Well, the vasovasorum are usually in
18 the wall of the major arteries, and those would be affected
19 if we were to treat them. For the most part, we're in much
20 smaller vessels, usually about 2.7 millimeters, so that it's
21 less of a concern. And those vessels have an intermediate
22 sensitivity between the very small and the larger vessels.
23 But specifically I know the effects of the vasovasorum, but
24 not with this device.

25 DR. FREISCHLAG: And my last question has to do

1 with the 20 percent of patients in each group which got that
2 stent. Did you look at those cohorts separately compared to
3 head to head? Because couldn't they--the reason they got
4 better was the stent and it had nothing to do with the
5 device or anything else we did to those patients. And was
6 the stent the reason that those patients at separate cohorts
7 in both groups did better? And did you compare those two 20
8 percent head to head even though I know it's only 100
9 patients, but was that the group that did better in both
10 groups, and, therefore, we really should be just putting
11 more stents in and not doing something new?

12 DR. KUNTZ: Right. That's a very good question,
13 and we did do the analysis, and what we found was that
14 treatment effect was diminished in patients who received
15 stents, that is, the cohort who received stents, the
16 difference provided by radiation therapy was diminished
17 compared to patients who did not receive stents.

18 However, the ultimate restenosis rate for both
19 groups was intermediary between the actual treatment effect
20 on patients who didn't receive stents and the placebo arm.
21 So that, on average, we may say--and I'll just use this as
22 an arbitrary example. It's not the real numbers. Say, for
23 example, we had a 15-percent restenosis rate with active
24 patients treated without stents. We may have had a 25-
25 percent treatment rate on average between the group that

1 received stents, a little bit better for radiation compared
2 to political, and a 40-percent restenosis rate for patients
3 who didn't receive stents and had placebo.

4 So the answer is that when stents were placed, the
5 radiation therapy was diminished, the effect was diminished;
6 however, the performance of antirestenosis effect observed
7 for both the radiation arm and the placebo arm were not a
8 substitute for the largest effect seen in patients who
9 didn't receive stents overall. So stenting was better than
10 placebo, but not as good as radiation therapy for patients
11 who did not receive stents.

12 DR. FREISCHLAG: Okay. Thanks.

13 ACTING CHAIRPERSON TRACY: Dr. Krucoff?

14 DR. KRUCOFF: Mitch Krucoff from Duke. I also
15 want to thank everybody for the clarity of presentations and
16 what's obviously a strong fundamentally designed clinical
17 trial to look at the safety and efficacy of their device
18 approaching a very tough and complicated clinical problem.

19 I do have some questions, and a couple relate to
20 pieces of data that you guys showed that, at least to my
21 eyes, were not in the panel pack. And, Jeff, if you could
22 go back to them, they were on classifications, which you
23 mentioned. We have seen data elsewhere as affecting
24 significantly what we would expect from a procedural
25 outcome.

1 I didn't see anything in the START data that
2 actually characterized the patients on inflow, the patients
3 enrolled in the study, relative to the nature or the class
4 of in-stent restenosis. Were these all truly in-stent
5 restenosis or were these all classifications from diffuse
6 restenosis and in between?

7 DR. POPMA: There are some lesion characteristics
8 that we know for comparative purposes. The average lesion
9 length was 16 millimeters, which is longer than we typically
10 see for a focal *de novo* lesion.

11 I think that your point is well taken, and I
12 wouldn't want the introductory slides that we have to
13 confuse the picture at all. I think the summary statement
14 that we're trying to make about showing the Mayron data was
15 that there is some heterogeneity with respect to outcome
16 based on what the pattern morphology was. Because this was
17 a randomized trial, there was equal distribution of the
18 complexity of the lesions in both groups. The investigators
19 at the clinical site were blinded as to whether the patient
20 was going to receive radiation therapy or not. So it would
21 be very unlikely, and we have not seen any of the data
22 analysis so far, that there was a misreputation of more
23 complex lesions in one group and less complex lesions in the
24 other, because they were--the investigators were blinded at
25 the time of randomization.

1 One thing about these trials as you look at the
2 literature is that the restenosis rates in the literature
3 are fairly heterogeneous. Some trials will have very low
4 restenosis rates. Other trials will have very high
5 restenosis rates, which makes registry type comparisons
6 very, very different.

7 What was done in this trial was a randomized
8 clinical trial, randomly assigning the two different
9 complexities of the lesion subsets to treatment or to
10 placebo. And I think that's the real strength of doing a
11 blinded randomized clinical trial in this fashion because
12 the appropriate issues that you're raising about the fact
13 that morphology of the baseline lesion can affect result is
14 absolutely true, and may likely be the source of bias in a
15 trial that's not randomized and blinded.

16 So we know at least in our trial that the
17 restenosis rate in placebo was ranging between 41 and 45
18 percent in the placebo group, with equal distribution of
19 pre-procedural lesion morphology. And we know that the
20 treatment associated with that was significant resulting in
21 a 36- to 66-percent reduction.

22 DR. KRUCOFF: Okay. My question may be a little
23 different or you may have answered it, so let me just find
24 out. Lesion morphology, for instance, an 18-millimeter
25 lesion, slightly eccentric, inside of--that is the result of

1 having placed a 9-millimeter stent would be classified
2 differently than an 18-millimeter lesion that is in the
3 middle of a 30-millimeter previously placed stent.

4 So I guess what I'm asking is the lesion
5 complexity, as it was analyzed, at least in my appreciation,
6 was not the Mayron type of classifications relative to the
7 previously implanted stent.

8 DR. POPMA: Correct. That's correct.

9 DR. KRUCOFF: And I just wonder--and I think a
10 theme that we're going to come back to--because I'm
11 literally sitting here thinking about if I were to use this
12 device selecting patients for whom it was most appropriate,
13 what would go through my head?

14 DR. POPMA: Right.

15 DR. KRUCOFF: And one of the things that I think
16 we've talked about, as was mentioned earlier, with the
17 longer lesions possibly having a greater benefit, is where
18 is the real benefit relative to classifications that we know
19 are--

20 DR. POPMA: Right.

21 DR. KRUCOFF: So did you guys actually look at
22 whether the Mayron type classifications randomized equally?

23 DR. POPMA: I can let Rick answer that as well,
24 but oftentimes the initial stent length itself was
25 difficult, and I'm not aware that we did any analyses

1 looking at lesion length compared to the relative stent
2 length at the start. So your point is well taken. A lot of
3 the retrospective data that came from the Hospital Center
4 for that was when we had 15-millimeter stent available or a
5 20-millimeter stent available.

6 DR. KRUCOFF: Right.

7 DR. POPMA: But now with the tremendous
8 heterogeneity of stent lengths ranging from 9 to, you know,
9 34, absolutely there can be some relationship that may
10 require refinement of the classification system.

11 For the purposes of the study, which is a clinical
12 and angiographic study, we know that the complexity of the
13 lesions was the same, and there's no reason to think that
14 the stent length pre-procedurally wasn't the same in the two
15 groups, because that was not--that was also blinded to the
16 investigators.

17 So I think the bias was introduced, but I'll let
18 Rick comment about that.

19 DR. KUNTZ: Rick Kuntz. I just want to maybe
20 clarify that for you, Mitch. Following up on Jeff's comment
21 about the fact that there were longer stents available for
22 this study compared to when the analysis of Washington
23 Hospital Center was done, almost all these stents, if not
24 all these stents, contained a lesion; that is, there was a
25 requirement on entry. So these lesions tended to be within

1 the stents in almost all cases, and I think that's probably
2 true, Dr. Lansky.

3 The second is that we do know the distribution of
4 the lesion lengths. The average lesion length was 16
5 millimeters, but we do have a breakdown of other lesion
6 lengths by minimum amounts. For example, one-third of the
7 cases had lesion lengths of at least 20 millimeters long,
8 and when we averaged those patients, it actually was 25
9 millimeters. So we did have a fairly large cohort of
10 individuals that had long lesions in this study.

11 The other issue is that we do know that this study
12 verified the fact that the longer lesions made the placebo
13 group at risk of having higher restenosis. But we also know
14 from the interaction terms that the radiation therapy had
15 its biggest effect in the longest lesions. So your notion
16 that there's a cutoff by which radiation therapy is
17 effective is actually true. Where that cutoff exists is
18 hard to say, but most likely--and I don't know if this will
19 be reflected in the label or whatever. This is probably not
20 appropriate for short discrete lesions. It's probably more
21 appropriate for lesions that are moderate lengths and longer
22 based on the data we see so far.

23 DR. KRUCOFF: I guess part of my other concern is
24 whether we know or whether we can tell or whether you can
25 tell us from the data you have whether lesions that are

1 restenotic and extend beyond the margins of a previously
2 implanted stent would be effectively treated.

3 DR. POPMA: Right. I know that you know this, but
4 sometimes it's hard to see the stents, and even as an
5 investigator in the trial, I try to guess where the stent is
6 based on what I see angiographically. But sometimes it's
7 still difficult to do.

8 DR. KRUCOFF: Okay. Another, I think, new piece
9 of information, Rich, was the data from Dr. Lansky's QCA lab
10 on the edge effect, and that to me is very important, and
11 I'm not sure I really understood what you said.

12 What I think I heard you say was that when you
13 looked at the edges per se, the edge areas, the placebo-
14 treated group and the Sr-90 treated group were actually not
15 very different, and that some of that may be the result of
16 the healing of the inner segment being better as a relative
17 artifact or illusion. And yet the data--I guess my question
18 is: Are you saying that the analytic segment binary
19 restenosis rates that are reported in the panel pack are, in
20 fact, not hemodynamically significant restenoses?

21 DR. KUNTZ: No. I'm glad you brought that up,
22 Mitch. I think from my perspective as a cardiologist, the
23 analysis segment restenosis rate is the actual restenosis
24 rate that we should be quoting, because that's what the
25 patient cares about. The patient doesn't care whether their

1 narrowing is in the stent or somewhere else. So the
2 overall--this treatment effect was 36 percent. That's what
3 this trial shows. We showed that within the stent it was
4 profound, but that doesn't matter if it turns out there's a
5 lesion on the outside. So I don't think anybody is trying
6 to say that the actual treatment effect can be nullified
7 because the analysis segment is more.

8 I think what we found, though, is that after you
9 treat a segment, that is, what we call the analysis segment
10 or from--you know, wherever the radiation therapy and a
11 little bit outside that was, then almost all patients had an
12 opening that was less than 50-percent residual.

13 What Dr. Lansky found was that when we look just
14 at the edges, there was about a 12-percent rate of
15 narrowings that actually tripped the 50-percent threshold
16 that in and of themselves could be called a restenotic
17 lesion. Okay?

18 If you have a lot of failure in the middle of the
19 stent, you never get to see those 50-percent lesions show up
20 because they're always the second or third MLD, not the
21 first. If you have an effective therapy in the middle, all
22 of a sudden they become the minimum lumen diameter. So
23 that's why the radiation therapy has such a jump from stent
24 to analysis segment and the placebo had not much jump at
25 all.

1 That's the artifact as to why it looks like there
2 may be an edge effect, but, in fact, the edge narrowing
3 portion, which represented 10 to 12 percent of the cases,
4 was identical for both placebo and for active arm,
5 suggesting this is just the typical carrier restenosis
6 effect associated with dilating a stent on the outside.

7 DR. KRUCOFF: Okay. But we are on the same page
8 that ultimately the binary analytic segment or target vessel
9 restenosis rate is a real clinically meaningful--

10 DR. KUNTZ: And that more reflects the level of
11 degree of effect seen in the clinical restenosis rates of 30
12 and 40 percent as well.

13 DR. KRUCOFF: Okay. A couple of quick questions.
14 Is it the notion to go forward that the way to deal with the
15 touie borst clamping down too hard is to put in an arrow
16 sheath introducer? I haven't heard of any other either
17 existing or planned engineering designs that would--that
18 seemed to me to be a significant, if perhaps not a cause of
19 patient harm but a significant operator nightmare to clamp
20 down a little too hard on the touie and then not be able to
21 deliver or retrieve the train. Is the plan simply to go
22 forward with an arrow sheath introducer as an optional part
23 of the instructions for use?

24 MR. GREEN: That's the current plan for this
25 device as you go forward, the arrow sheath as well as the

1 training on not only the use of the arrow sheath but also on
2 the use of, you know, the touie borst, the catheter, the
3 entire system, as well as going through training on what
4 could occur in a clinical procedure and how to avoid that.

5 DR. KRUCOFF: Okay. And am I correct in reading
6 the routine use of the instrument involves over-the-wire
7 both insertion and retrieval, while the bail-out strategy
8 for the instrument includes removing the guide wire from the
9 coronary?

10 MR. GREEN: The manual removal procedure, the
11 bail-out procedure could be done over the wire or as an
12 entire catheter and guide wire.

13 DR. KRUCOFF: Now, as I read the instructions for
14 use, it's pretty clear that you say yank the whole thing.

15 MR. GREEN: Removing the catheter and the guide
16 wire at the same time would be the most expeditious way to
17 remove the entire system and limit the exposure to all
18 personnel and patient.

19 DR. KRUCOFF: And the reason for an expeditious
20 removal is an exposure issue rather than anything else?

21 MR. GREEN: Yes.

22 DR. KRUCOFF: I wonder about just ischemic
23 tolerance of this device. I don't see data reported to it.
24 Obviously your patients are pre-selected to already have a
25 fairly well dilated segment, so presumably that gives a much

1 more forgiving environment to cross a lesion. But dwelling
2 for 5 minutes in any coronary, as we know, is not always
3 well tolerated even with IVUS sometimes shorter passes.

4 Can you give either data or a flavor of what the
5 ischemic tolerance was or whether there was a non-exposure
6 reason to remove the device encountered during this trial?

7 MR. GREEN: This was actually a question asked to
8 us by the FDA, and we did provide it. It's provided in the
9 panel pack in the addendum to the START report, in the START
10 section on page 12, page 12 after the START clinical report.
11 It's called average dwell time and patient tolerance. It
12 provides the average--again, the average dwell time and
13 describes only one of the patients who was unable to
14 tolerate the dwell time necessary to deliver the dose.

15 DR. KRUCOFF: Thank you. And in the instructions
16 for use, it also talks about what to do in case of a breach
17 of the system. Either in the Beta-cath or START
18 experiences, I didn't see any description. Obviously that
19 wouldn't be a minor sort of event. Have you actually
20 encountered that in the human application?

21 MR. GREEN: No, we have not encountered that in
22 the human application or in animal application.

23 DR. KRUCOFF: Okay. I'm going to pass over my
24 questions about dosing, although I think they've already
25 been addressed, but hopefully in the future we'll continue

1 to learn about eccentricity and curvature and clearly I
2 think the dosimetry involved here are some of the real open-
3 ended--still issues, but I think they've been largely
4 addressed.

5 In the START study, I was very struck that 40
6 percent of the patients had rotational atherectomy applied
7 to debulk the stenosis, even though, as you showed in
8 European and other data, there's been the suggestion made
9 that this may be more a stimulator than a solution to in-
10 stent restenosis.

11 Can you share some of your thoughts about how you
12 think that falls out? Were there more detailed looks? I'm
13 sure you took more detailed looks at whether this was an
14 interactive factor. I didn't see it as a feature in either
15 the univariable or multivariable models.

16 DR. KUNTZ: Yes, Rick Kuntz. We did look at the
17 effect of different pre-treatments on outcomes, and we found
18 that there was no significant effect, which essentially
19 validated some of the other debulking studies in the past
20 and showed no significant differences if you used rotational
21 atherectomy versus not.

22 I can share my interventional cardiology kind of
23 qualitative feelings. I think Dr. Popma may want to chime
24 in as well.

25 I think the study, the ARTIST study, which is

1 actually the only good randomized study to look at the
2 effect of rotational atherectomy as a debulking agent, may
3 have had some limitations; that is, the burr sizes used were
4 small and the tolerance for an acceptable result is
5 different in Europe than what we do in America. So I still
6 feel in my own practice that there's a role for debulking,
7 especially in big beefy lesions in large vessels. And if we
8 can get a big burr in there, it's very helpful because it
9 just reduces the amount of plaque that we have to push
10 through the struts.

11 So I think that this data validates the fact that
12 rotational atherectomy was not detrimental, and I think for
13 selected individual cases, the discretion of the operator
14 who is versed and comfortable with rotational atherectomy I
15 think is still compatible with the use of this device.

16 Jeff, I don't know if you want to comment.

17 DR. POPMA: I was hoping that we'd have some data
18 comparing those that got rotational atherectomy with those
19 that didn't, because amongst the 50 investigators cited, it
20 becomes a little bit religious about whether you use it or
21 you don't use it. We didn't see that there was any
22 beneficial effect to rotational atherectomy and yet another
23 trial.

24 I agree with Rick that we still want to do
25 something for very diffuse lesions. That involves

1 debulking. But I have to say as a clinician scientist that
2 we sure haven't proven that so far.

3 We didn't see that there was an interactive effect
4 with rotational atherectomy and radiation. It appeared that
5 radiation worked in those patients who got rotational
6 atherectomy, and it also worked in those patients who didn't
7 get rotational atherectomy. I think that's the most we're
8 going to be able to say about debulking from the study.

9 DR. KRUCOFF: I'm sorry to hear that because, you
10 know, I think really and truly what you'd love to know is if
11 this had just been balloon with only provisional stenting,
12 whether beta radiation would be enough. And as everybody
13 knows, in the practice at this point the relative costs of
14 adding these technologies together--rotational atherectomy
15 with angioplasty, with beta radiation--is not a negligible
16 increment. So I guess maybe an unfair question, but if this
17 had just been a balloon angioplasty study, do you have any
18 basis for saying whether you think the effects we are seeing
19 would be the same or larger or--

20 DR. KUNTZ: Sure. We do have indirect evidence of
21 that. We did multivariate modeling to look at the
22 predictors of restenosis, and after adjustment for those
23 predictors we added the variable of rotational atherectomy.
24 It was not effective.

25 This study supports the fact that this works just

1 as well with balloon angioplasty as it does with rotational
2 atherectomy.

3 We also did interaction terms to look at any
4 interaction between the devices and the outcomes and found
5 none. So, actually this device is more supportive by the
6 fact that the plain old balloon angioplasty is probably just
7 fine and less supportive for the use of rotational
8 atherectomy, especially if it comes down to a cost issue.

9 DR. KRUCOFF: Okay. So you know my next question,
10 which is Reapro (ph). What was the instance of usage, and
11 did you examine it again? It isn't indicated in the
12 multivariate or univariate analyses, but did you look and
13 can you share with us what it looked like?

14 DR. KUNTZ: Yes, the Reapro was discouraged in
15 this study because when the study was started, there was a
16 feeling that--or at least a disseminated feeling that Reapro
17 reduced restenosis. So because of that we didn't want to
18 have a potential confounding effect of an unbalanced Reapro
19 effect explaining differences in restenosis.

20 So given the fact that in-stent restenosis is
21 generally associated with a low complication rate, anyway,
22 and that Reapro is used mainly to prevent complications and
23 the fact that Reapro may have had a potential to reduce
24 restenosis based on when this trial was designed, we tried
25 to discourage the active use of Reapro in the study. So

1 there was Reapro used, but the frequency was low enough that
2 it didn't allow us to do any meaningful analysis.

3 DR. KRUCOFF: What was the frequency? Twelve
4 percent, I think--right around 12 to 15 percent?

5 DR. KUNTZ: Right. Very low.

6 DR. KRUCOFF: Learning curves, you know, this I
7 think has been touched on several times, but it seems to me
8 despite this semi-disclaimer earlier that this was too
9 complicated to look at because people are in multiple trials
10 going on at the same time that actually it's probably n to
11 all that complicated to look at, and whether particularly
12 your minor device failures were in earlier phases of
13 operator experience or not would I think be a very
14 meaningful piece of information, particularly if you're
15 going to mandate training or some other kind of approval-
16 oriented condition.

17 So have you guys actually looked at how cases 1
18 through 5 and operators went into double digits fared with
19 minor problems relative to later cases?

20 MR. GREEN: Again, what we tried to do is go back
21 and look at that, but the problem is that--and I'm not
22 saying we're not still trying to gain this information, but
23 the problem becomes that it wasn't something that was
24 captured, the individual user wasn't captured on the case
25 report form. So it's something you'd have to go back to the

1 patient forms back at the individual institutions in the
2 clinical trial and collect. So it's not something we have
3 available, so it was not an analysis we were able to do.

4 DR. KRUCOFF: Okay. Patients who were enrolled
5 clearly by the structure of the study must have been a
6 subset of patients who were consented, since you had to have
7 a successful angiographic result in order to go on and be
8 randomized. Can you give us a sense of what percentage of
9 patients who were consented for these procedures actually
10 had a successful enough procedure to enroll?

11 DR. POPMA: I can tell you what happened at our
12 site, but, Rick, do you have any specific--

13 DR. KUNTZ: We didn't look at a universal log to
14 look at that percentage, which I think would have been very
15 valuable to see how many patients came in front. I can tell
16 you at our center the vast majority of patients who came
17 back with chest pain after stent placement we felt had
18 clinical in-stent restenosis who were consented before they
19 received the pre-treatment enzymolytic(?) therapy were the
20 general catchment area. Among those patients were people
21 who we verified had in-stent restenosis by angiography, and
22 because of the practice patterns of actually treating
23 patients after their diagnostic angiogram at the same
24 setting, there were patients who would be treated and then
25 qualified for the study.

1 It's my experience that that probably represented
2 close to 90 percent of the patients, that the vast majority
3 of individuals with standard therapy qualified for this
4 analysis, but we don't have any hard data to show that
5 because it would be very, very hard to start from the
6 consent portion and go through, and we prospectively didn't
7 capture each of those logs before the randomization actually
8 occurred.

9 DR. POPMA: In our institution now, either with
10 the trial and with the confines of the compassionate use
11 trial, we have been able to treat 90 percent of patients
12 without putting a stent in before we give radiation therapy.
13 So it's frequent. The answer is we can often get them in.

14 DR. KRUCOFF: Okay. And, Jeff, I heard you
15 respond earlier--if I heard you correctly--the 21 percent of
16 stents that were placed were placed after the Beta-cath--

17 DR. POPMA: That's correct.

18 DR. KRUCOFF: --had been positioned, either mock
19 or real treatment was administered, and then the catheter
20 was removed.

21 DR. POPMA: That's correct.

22 DR. KRUCOFF: Then there was an angiographic
23 deterioration that was of concern enough to do something in
24 addition. Can you tell me how, then, we would understand
25 whether that 21-percent deterioration was just from natural

1 recoil or how we would know that it was or was not a result
2 of sticking the delivery system through the previously
3 dilated artery?

4 DR. POPMA: That's an excellent question. It's an
5 excellent question because I'm not sure that we have
6 definitive data that would tell us the exact circumstances
7 before and after the stent implantation. This was recorded
8 on the angiographic core laboratory sheets, but oftentimes,
9 as you know, in the cath lab the exact occurrence of the
10 events are not actually filmed.

11 The biggest fear would be that there was a
12 suboptimal result before the radiation was done with the
13 investigator knowing that they were going to try to get the
14 radiation in and then see how things looked. I would hope
15 that wouldn't have been a frequent occurrence in the trial
16 and that they were done for real legitimate reasons with
17 respect to the bail-out stenting.

18 The majority of the cases were done for residual
19 stenoses. The minority were done for new dissections. And
20 I think it is reasonable to suggest that there is some
21 reintrusion of plaque within the vessel wall.

22 The message that we'd like to give from this trial
23 is avoid stenting if possible. We want to make sure that we
24 have a successful result first, make sure that we really do
25 have a less than 30-percent residual stenosis and there

1 really are not significant dissections; and if that's the
2 case, then to deliver the radiation therapy as prescribed in
3 the IFU.

4 If after that the patient's in trouble and has a
5 greater than 40 percent stenosis or has a dissection that
6 develops, then to not be afraid to use stenting, use it
7 because you're correcting a complication.

8 My personal feeling is that that number will be
9 actually much less than 20 percent. At least it is in our
10 practice, that we're actually able to not stent often in the
11 vast majority of cases.

12 DR. KRUCOFF: Well, the issue--and I'm sure you
13 can see it--is that while--as we look, for instance, at the
14 acute outcomes with radiation or non-radiation, they're spot
15 on, they're identical. On the other hand, if putting the
16 delivery system across an adequately dilated lesion itself
17 engenders a 21-percent complication rate regardless of
18 whether or not you radiate, then we have a whole different
19 kind of dilemma.

20 DR. POPMA: Right.

21 DR. KRUCOFF: And, you know, I'll say up front
22 this is a Catch-22 because you guys did what I think was a
23 very reasonable study direction to blind this. To really
24 get at the effect of radiation, you got to put the device in
25 or you can't blind it.

1 DR. POPMA: Right.

2 DR. KRUCOFF: But I really just wonder what your
3 comments are, whether 21-percent deterioration of lesions in
4 the cath lab from before putting the device in to after
5 putting the device in, I think you have to at least examine
6 the question: Does it relate to putting a new piece of
7 hardware across an adequately dilated stenosis?

8 DR. KUNTZ: We actually did some analysis on that
9 which I think will put you at ease a little bit. One is
10 that 65 percent of the cases were done for a suboptimal
11 result. And so when we looked at the pre-stenosis, the
12 stenosis after initial treatment but before stent placement,
13 compared to those people who didn't get a stent, there
14 really wasn't much of a difference. What we really saw in
15 this study was a different belief pattern of the use of
16 stents to improve a cosmetic result, and that was--as you
17 recall, when this study was started, there was a huge
18 interest in restenting in-stent restenosis lesions, much
19 more than there is now. So because of that we had a
20 heterogeneity of some sites who tended to use stents more
21 often for the same residual stenosis that other sites would
22 leave alone.

23 So the vast majority, 60 to 70 percent of the
24 cases, were not done because of inducible dissections by the
25 delivery catheter, but were done at different belief

1 patterns as to whether or not you needed to optimize a
2 stent--an in-stent restenosis result with a second stent.
3 And when we analyzed these data, the overall rate was 20
4 percent. When we actually went back and looked at residual
5 stenoses and dissections, only about 20 to 25 percent of the
6 cases could be justified as a dissection. And we're looking
7 at 20 to 25 percent of cases of the 80 or 90 patients who
8 got stented. We're talking about 18 or 19 patients out of
9 470 that had evidence of a dissection induced by the device.

10 DR. KRUCOFF: Okay. Two last quick questions, and
11 I'll be quiet. One of the concerns, I think, again,
12 thinking about the use of this technology, if it came to
13 market, is the later picture, what does happen afterwards,
14 and I have two questions related to that. One is from an
15 animal model. Does anybody--or can anybody describe to us
16 at what point in time, one year, three years, five years,
17 tissue either is normal or at least in a stable, healed,
18 scarred, whatever state, following radiation therapy?

19 My second question is: In human beings who
20 underwent, as in the START study, radiation who still had
21 restenosis, again, after receiving treatment, what do we
22 know, have they been redilated? Is the tissue more friable?
23 Does it dilate well? What happens when you have someone who
24 has a radiated segment that's still restenosis and you
25 approach it again with intervention? Do we have any data on

1 those individuals?

2 MR. GREEN: Maybe we could come back--as far as
3 what the--in the animal model, as you asked, what the
4 breakpoint is for when endothelialization occurs, I don't
5 believe that we can answer that from our animal studies.
6 There are some suggested data out there from other animal
7 models and studies, but I'm not sure that's a clear answer.
8 We can bring someone else up to talk to that as well.

9 I don't know if Dr. King maybe has something to
10 add to that.

11 DR. KING: A short answer. No, I don't think we
12 know the time when everything is normal. Animal models--we
13 don't have any animal models that far out. There is
14 experience longer than four years with radiation,
15 intravascular radiation, the longest being ten years from
16 the experience of Lehrman (ph) in the superficial femoral
17 artery. But I don't think we have any information that
18 tells us exactly what the nature of the arteries are years
19 later.

20 ACTING CHAIRPERSON TRACY: Actually, I think we
21 better move along.

22 DR. KRUCOFF: Okay. Can I just ask the last
23 question? The patients in START who received beta radiation
24 therapy who restenosed within the eight-month follow-up,
25 what happens to them?

1 MR. GREEN: The patients in the START trial who
2 did need reintervention later went through the standard
3 revascularizations--angioplasty, CABG, et cetera--that were
4 available to the placebo patients that failed. They were
5 all available for this.

6 DR. KRUCOFF: Is this an observation? Are there
7 data?

8 DR. POPMA: Maybe Dr. Lansky can speak to this,
9 but the lesion length at follow-up was somewhat shorter in
10 the treated patients than it was in the placebo patients,
11 suggesting that the restenosis that did occur was more
12 proliferative. It was less proliferative with the
13 Strontium-90-treated patients.

14 What that means to me as a clinician, those that
15 we've treated, is it's a simple percutaneous therapy if the
16 lesion length is not quite so diffuse. That's the structure
17 from the data, but if you're kind of asking the question
18 about how we would manage it, if the lesion recurs and it's
19 relatively focal, not diffuse, that allows me then to treat
20 it one more time percutaneously.

21 I don't think we have any of the data so far on
22 the outcomes of the re-retreatments for in-stent restenosis.

23 ACTING CHAIRPERSON TRACY: Dr. Wilson?

24 DR. WILSON: Thank you. Frank Wilson, radiation
25 oncology. I also appreciated the clarity of the information

1 that was in the briefing book. I do have some questions,
2 though, that probably I'm the only person in the room that
3 doesn't know the answer to them, and I apologize for that if
4 that's true. But I think my questions mostly relate to the
5 device itself, if I could--as I think about it.

6 This PMA specifically is asking for approval of
7 the 30-millimeter, 12-seed source train as part of the
8 device. But during the time period of the START trial,
9 there was also a 40-millimeter, 16-seed source train that
10 was utilized, and my questions about that are the following:

11 Is the data that's in this book pertinent only to
12 the 30-millimeter seed train experience? And if not, is the
13 40-millimeter seed train experience analyzed separately? My
14 question is obviously related to the fact that radiation
15 effects are going to relate not just to the dose and
16 fractionation, but also to the volume, in this case length
17 of tissue that is irradiated, whether there are favorable or
18 unfavorable effects. And it isn't clear to me that we're
19 not talking about the experience with both of these source
20 trains in this information.

21 MR. GREEN: You're correct. We're asking for
22 approval here for the 30-millimeter Beta-cath system. The
23 trial did allow for the use of both. There's a very small,
24 about 5-percent use of the 40-millimeter system.

25 Table 3A on page 27 of the clinical report in the

1 START section does look at that, and actually, I think I'm
2 going to let Dr. Kuntz talk about the analysis.

3 DR. KUNTZ: The bottom line is the estimates look
4 about the same, but they're so underpowered it's hard to say
5 if the 40 is going to be all right. The estimates, though,
6 are consistent with the 30. My guess is that 40 is going to
7 be just fine, but I think it's probably safe to say that the
8 company's not going for a 40-millimeter label on this
9 analysis.

10 DR. WILSON: Does the sponsor feel that all
11 eligible patients who might benefit from the procedure can
12 be treated with the 30-millimeter train, or is there going
13 to be the temptation on the part of users to treat lesions
14 that are not necessarily satisfactorily treated with other
15 than the 40-millimeter seed train?

16 MR. GREEN: Of course, we'll only be providing the
17 30-millimeter train, and the instructions for use and the
18 training we'll be providing will be on how to treat with
19 that, and the recommendation for that is that treatment
20 with--lesions that can be treated with up to a 20-millimeter
21 balloon. You can't--because we're looking actually at
22 injury created here that can be covered by the source train,
23 and that will be what the training and the instructions for
24 use recommends, and that's what we will advocate because
25 it's all we can support with the clinical data.

1 DR. WILSON: Along this same line, the Alpha IV
2 device is what's being specifically requested for approval,
3 I believe. But it's unclear to me whether the bench testing
4 of the improvements in--what is it?--the touie borst valve
5 and the LED pressure indicator system. Is bench testing
6 still going on with those, or was bench testing completed?
7 Were any problems related to that valve related to pressure
8 maintenance? Are those now corrected fully to the sponsor's
9 satisfaction with the Alpha IV device?

10 MR. GREEN: We have completed the testing that we
11 submitted in the PMA. The FDA is currently reviewing that.
12 Now, they may have additional questions as the review goes
13 on, as they had suggested. We qualified the arrow sheath.
14 We did the testing to show and support that the pressure LED
15 does, in fact, show or reflect the pressures necessary to do
16 in individual increments what's supposed to be occurring
17 with the device at that time. But, again, it's under review
18 with the FDA currently, and if they have more or additional
19 testing, we will provide it as well.

20 DR. WILSON: Well, also, concerning what's been
21 called the minor device malfunctions, which is on the order
22 of 20 percent, as I recall, most of those seem to relate to
23 source transfer. You can either--and hydraulics is just one
24 way of transferring sources. When you're transferring high
25 dose rate brachytherapy sources, you can do it manually or

1 with projection cables and, in fact, both of those
2 approaches are more common than hydraulics.

3 But if the transfer is interrupted as the sources
4 proceed into the patient, that's one thing, creating no
5 radiation hazard for the patient or users, by and large.
6 But it's another if the transfer coming back is not
7 expeditiously possible.

8 None of these MDMs were of that latter type, were
9 they? There was no transfer problem where the source could
10 not come back home?

11 DR. SPEISER: They were not included in the MDMs.
12 That would be in the removal portion.

13 DR. WILSON: It does say seven where it was
14 aborted.

15 DR. SPEISER: Well, basically what would happen is
16 if you had a small increase in transit because you didn't
17 apply enough pressure or there was a micro kink at the
18 delivery catheter within the touie borst valve. You can
19 slow down the return, the transit time to more than 5
20 seconds.

21 If, however, there was any concern at all, then
22 the radiation oncologist was obligated to remove the entire
23 system, whether there was truly a problem or not, to be on
24 the safe side.

25 DR. WILSON: And the failsafe is separate from

1 extraction of the entire system; is that right? Can you
2 explain--

3 DR. POPMA: The failsafe is in the device to
4 prevent the sources from exiting unless the proper catheter
5 is docked within the device correctly.

6 DR. WILSON: Okay. I think those are the only
7 questions I have.

8 ACTING CHAIRPERSON TRACY: Dr. Najarian?

9 DR. NAJARIAN: Ken Najarian from the University of
10 Vermont.

11 Most of my questions have been answered, but I did
12 have a question about--I was surprised by how many stents
13 were placed, particularly when the study criteria specified
14 that stent placement really would exclude a patient. And I
15 understand you use it for a bail-out, and I, you know, kind
16 of agreed with your explanation. But it does seem quite
17 high, and I have a hard time believing that there were 101
18 cases where bail-out was realized only after the radiation
19 was given.

20 But since you do have the data and you have split
21 it out somewhat, I was wondering, have you looked at the
22 clinical difference between those patients treated with
23 radiation without stents and those patients treated with
24 radiation and with stents? Now, you've broken out the data
25 with restenosis, and it looks like the restenosis rate is

1 higher in patients who were treated with stents compared
2 with those treated without stents. But how about the
3 clinical outcome? Was that different at all?

4 And then my second question is: Why not just drop
5 those patients from the study or at least segregate them and
6 look at only the 375 patients who were treated--I believe it
7 was 375--treated without stents?

8 DR. KUNTZ: We did do analysis of the stent use,
9 and we found basically that when stents were used, the
10 radiation effect was not as good as when the stents weren't
11 used, and that's clear. That went across all the different
12 outcomes.

13 The sample size of 100 out of 476 was not big
14 enough for us to see any significant difference, especially
15 with the clinical results. But there's no question that
16 when the stents were used, the effect of radiation was
17 diminished substantially.

18 However, the comparison of a stent using placebo
19 was still not as good as radiation without stent, so I think
20 ultimately the--why do we have 100 patients? Because there
21 were a couple sites that liked to use stents. That's what
22 happened. And so despite having it in the protocol, they
23 tried to optimize the results of otherwise tolerable small
24 residual stenoses in the 23-percent range that most of the
25 investigators allowed to have in there, and this was during

1 a very controversial time when in-stent restenosis was the
2 focus of a lot of interest and there were two camps. There
3 were camps out that stented these and camps out there that
4 just did balloon angioplasty. And despite the admonition of
5 the study to try to avoid stents up front, some people's
6 tolerances were different levels. And so the vast majority
7 of these new stents used were for cosmetic improvement of
8 residual stenosis, not for dissections. And we can show
9 that by analysis of what the stenosis was before stent
10 placement use compared to those without, and they were very,
11 very similar. So we have to say that a lot of them were due
12 to just belief patterns of the individuals.

13 What wasn't anticipated was that when we looked at
14 patients who received stents, their result actually did do
15 better than when you don't have a stent used. Therefore, it
16 diminished the amount of effect the radiation therapy had to
17 offer for those cases. However, the use of a stent in a
18 placebo patient still was not as good as radiation therapy
19 overall.

20 So without going through too much overanalysis and
21 getting to multiplicity issues of multiple comparisons, I
22 think it's probably safe to say that we can expect the stent
23 use to be low based on the true dissections that we saw and
24 that the admonition should be to avoid stent use except in
25 the cases of dissection that may be threatening about

1 closure and to try not to use stents for improvement of
2 cosmetic results or any other type of suboptimal result
3 because we have data to suggest that when those suboptimal
4 results exist, radiation therapy is very, very effective.

5 DR. NAJARIAN: One other question, kind of a minor
6 question. But, again, inclusion criteria are arteries 2.7
7 millimeters to 4 millimeters, and stenosis or degree of
8 stenosis 50 percent or greater. Yet you do this by visual
9 inspection. Was any measurement performed at all, or was
10 any measurement performed subsequently? Were the angiograms
11 reviewed and actually measured?

12 DR. POPMA: This is a point--and I noticed the FDA
13 asked the same question as well, but this has been something
14 from the core laboratory thing we've been struggling with
15 for 20 years. That is, when one compares the clinical site
16 assessment for reference vessel diameter with what we obtain
17 using conventional quantitative angiographic techniques,
18 there is always between a 0.3 and a 0.5 difference in
19 reference vessel diameter. We know that from selecting
20 balloon sizes. We know that from NACEY (ph), from a variety
21 of different comparative analyses where the site has even
22 done calipers on vessels and then compared to the
23 quantitative angiographic result. And so this is typically
24 seen in every interventional trial that we do.

25 One could say that the clinical sites are wrong,

1 but we know actually by intravascular ultrasound that
2 sometimes we underestimate the size of the vessel using
3 conventional angiographic techniques, and that the reasons
4 why are a little bit complex, but, nevertheless, it happens.

5 So most of what we wanted to do for this trial was
6 to let clinicians use the tools for vessel sizing that they
7 were comfortable with, and clinicians are pretty good about
8 picking out a 3-millimeter balloon for a 3-millimeter
9 artery. We know that because when we do quantitative
10 analysis of the balloon, the balloon-artery ratio comes out
11 to be one to one, which means we're measuring the balloon
12 size smaller as well radiographically.

13 So I think that the points are well taken. All of
14 us want to be more quantitative in our delivery systems, and
15 we want to be more quantitative in assessing the vessel
16 size. It's very difficult to institute in-lab, online,
17 quantitative angiography that will really be useful. And I
18 think we did achieve a good result in the study based on the
19 dosing that was done by the investigators at the clinical
20 sites. The balloon-artery ratios were appropriate. The
21 outcomes were appropriate. The balloon sizings were
22 appropriate. So I think that--I understand the point. It's
23 actually one that we've just noted now for 10 years. But I
24 still think that we should be using the visual assessment at
25 the clinical site to determine what our dosage is going to

1 be.

2 DR. NAJARIAN: I understand in clinical practice
3 we can all more or less do a very educated guess. But it
4 seems like when you enter a clinical study, you know, you
5 have to use a measurement. You know, if someone had a 40-
6 percent stenosis and someone had a 60-percent stenosis,
7 different people see that differently. One way you can do
8 it is just use an internal measurement, just use the
9 coronary artery, the normal diameter of the coronary artery
10 as the baseline, and then compare the stenosis to that,
11 which is done in all the carotid trials. I mean--

12 DR. POPMA: We've done that analysis outside,
13 which you haven't seen the panel pack, but we published it
14 in the American Journal of Cardiology, and that was a
15 comparison of over 800 patients that had clinical side
16 caliper measurements in core laboratory quantitative
17 angiographic measurements, and that's where the 0.3-
18 millimeter difference is coming from that I'm speaking
19 about. So even when you do the caliper--the clinical site
20 caliper measurements and compare then to a separate core
21 laboratory analysis, that discrepancy is absolutely
22 anticipated for a clinical trial.

23 DR. NAJARIAN: I know we all struggle with
24 measurement, and it's taking a living situation and trying
25 to put a number on it. But then, again, that's why we're

1 here, isn't it?

2 MR. GREEN: We also, in designing the protocol, we
3 wanted to make sure we designed it in such a way that they
4 studied it in the way it would be applied when it was
5 actually available to the user. As you said, the visual
6 estimate of the reference vessel diameter was what we used.
7 We were able to come out with a result that we'd hoped for,
8 and now that can actually be applied by a user in a cath lab
9 with the tools they use every day, which is visual estimate.

10 DR. NAJARIAN: Okay. Thank you.

11 ACTING CHAIRPERSON TRACY: Dr. Griem?

12 DR. GRIEM: Mel Griem, University of Chicago. I
13 would like to ask a couple of questions relevant to the
14 transfer device and the response kit.

15 The response kit has equipment to look for the
16 source, to pick it up magnetically. There's a tweezers and
17 so forth. But suppose the loose source is somewhere in the
18 patient. Do you need something like a Geiger counter or
19 something like that to find it, say either on the floor or
20 in the patient? And what do you do when you have this kind
21 of a problem?

22 MR. GREEN: Actually, I think we're going to let
23 Dr. [unintelligible] answer this question.

24 DR. (?) : Mohawn Sinteralangum (?),
25 University of Maryland, radiation oncologist. I was the

1 principal investigator on the START trial. We at the
2 university have done over a hundred cases using this system.
3 I have been paid for my travel expenses to this meeting.

4 In terms of handling worst-case scenarios of a
5 source that has become dislodged from the system within the
6 patient, certainly a Geiger counter would be utilized to
7 identify location of source. But then the more important
8 clinical issue is that if the source is, in fact, in the
9 coronary vessel, then the ischemia that that source might
10 cause is the more pertinent issue that would need to be
11 addressed immediately.

12 So that would be addressed through surgical
13 techniques, again, because this is a beta isotope, in the
14 operating room no special shielding would be required, and
15 you would use just the source container to be able to place
16 the source in a safe place and maintain minimal exposure to
17 patient and personnel.

18 DR. GRIEM: Now, on the transfer device, I'd like
19 to ask a couple of questions. You have the single battery
20 with the low battery voltage problem. You have a pressure
21 monitor with LEDs. Is that voltage sensitive?

22 MR. GREEN: Yes, it is. We actually build in the
23 battery indicator, which is discussed in the panel pack, as
24 a way of ensuring that the items on the transfer device,
25 such as the LED and other items of the sensing system, have

1 adequate power with a safety margin in order to perform a
2 procedure. But as you're pointing out here, yes, it is
3 battery operated, so when you start a procedure, a transfer
4 device would go through a diagnostic. If you have enough
5 battery power to complete a procedure, you'd be allowed to
6 go on. If you did not have enough to complete a minimum of
7 worst-case procedures, you would not be able to go on. So
8 even though they do use the battery power, the system does
9 check itself to make sure that there's adequate power for
10 them to function properly.

11 DR. GRIEM: Why don't you have two battery sets,
12 like on a boat?

13 MR. GREEN: Actually, in the device there are--the
14 battery is composed of two cells.

15 DR. GRIEM: But are they separate?

16 MR. GREEN: There are two cells. I would have to
17 actually bring up--two cells that are actually in connection
18 with one another.

19 DR. GRIEM: So that's one--

20 MR. GREEN: They're individual cells acting as one
21 power source.

22 DR. GRIEM: Okay. But why don't you have two
23 power sources?

24 MR. GREEN: The power source is simply--the source
25 sensing system and the electronics is because of room

1 considerations within the device, making it able to be used
2 in the cath lab, a small device. We only have the one
3 battery. Therefore, we built in the back-up of the battery
4 indicator that would indicate when, say, you had about ten
5 procedures left that you could not do any more procedures.
6 Therefore, there isn't a need for a back-up battery because
7 if you can begin and initiate a procedure, you can complete
8 a procedure because you'll have enough battery power left.

9 DR. GRIEM: We've had the Indian, Pennsylvania,
10 episode where the source finally wandered around the
11 countryside because the detection system failed for various
12 reasons, and such a thing concerns me here.

13 MR. GREEN: It should be noted also that the
14 electronics does not control the containment of the source
15 within the system. If the electronics were not functioning
16 or if anything were wrong, you could remove the entire
17 system. The sources are contained within the system. So
18 you would not be able to--if you will remove the system,
19 leaving the sources within the patient.

20 DR. GRIEM: At what pressure does the catheter
21 explode?

22 MR. GREEN: We've done that testing, which has
23 been submitted to the Food and Drug Administration, on the
24 catheter. The catheter has a (?) pressure of
25 approximately 430, 440 psi. The transfer device itself

1 includes a pressure limiting pressure regulator that would
2 only allow pressures of between 85 and 100 psi to be
3 generated.

4 DR. GRIEM: As far as radiation effects in blood
5 vessels and connective tissue, I don't have any
6 knowledgeable data in heart. There is some excellent in
7 dermis, and that's published in the British Journal of
8 Radiology Supplement No. 19, some of it with Strontium as
9 planar sources and some with point sources in the dose
10 ranges you're thinking about and the 2-year results of that.
11 There's also an article in there on the rate of fibrosis and
12 collagen formation as a function of dose with gamma
13 radiation between 16 and 22 Gray, and how it proceeds in
14 cyclic fashion, and that may be helpful to you.

15 MR. GREEN: Thank you.

16 ACTING CHAIRPERSON TRACY: Okay. Mr. Dillard?

17 MR. DILLARD: I've got one point. Jim Dillard,
18 FDA. Just in terms of one of the earlier questions about
19 some of the animal data, and I believe that Dr. Waxman got
20 up and at least talked about some information that had to do
21 with different types of sources, and I think we've had some
22 other people get up to perhaps talk about some things that
23 either, number one, may not be exactly pertinent to this
24 particular PMA and/or might be data outside the scope that
25 isn't available in the public literature. So I just wanted

1 to make the point that the information you should be using
2 today is that which is in the PMA and/or available in the
3 public literature that you know about. So just to make sure
4 that what you're doing is factoring in that which is
5 absolutely appropriate for this particular beta source.

6 Thank you.

7 DR. BAILEY: Can I ask a question in that regard?
8 Could I ask if the clinical endpoint results and the MACE
9 results were significant with just the 30-millimeter source
10 data?

11 DR. KUNTZ: We did do that analysis, and they were
12 all positive. I think that--did you say what the TVF was?

13 MR. GREEN: It's Table 3A, page 27, START report.

14 DR. KUNTZ: That analysis doesn't address your
15 question directly; that is, if you take those patients out,
16 is there still significant differences between them? That's
17 obviously a question of power. And so what we did so was
18 analyze whether there was a treatment effect associated
19 with--a main effect associated with the 40-millimeter
20 device, which there wasn't. And there was no interaction
21 between the 40-millimeter radiation assignment.

22 So, indirectly, my guess is that--I don't think we
23 actually did this analysis, but since there were only 13
24 cases out of the overall group, my guess is that since the
25 treatment effect was identical, all we'll do is just reduce

1 the pool, the sample size by 5 percent, and we'll still have
2 significant differences among the remainder groups of 30
3 millimeters.

4 DR. BAILEY: I guess the question is: If we're
5 just applying for approval of the 30-millimeter device,
6 shouldn't we be looking at those results?

7 ACTING CHAIRPERSON TRACY: Can we let FDA answer
8 that?

9 MR. DILLARD: Jim Dillard. I don't know if you're
10 looking at me to actually address that question. I think
11 the sponsor's probably more appropriate to do it. But I
12 think that one of the things that we have to look at, we
13 certainly need to look at the overall data set. That's
14 certainly very important in the analysis of safety. And I
15 think in this case the sponsor has put forward an analysis
16 for effectiveness where the predominance of the data is the
17 actual product that they want approval on.

18 So I think one of the things that you might be
19 able to help us with is potentially a recommendation of an
20 analysis. If you think it's important, that could be part
21 of your recommendation to us.

22 ACTING CHAIRPERSON TRACY: Okay. At this point
23 I'd like to take a 5-minute break. We're running a little
24 bit late, so if we could just reconvene in 5 minutes,
25 please?

1 [Recess.]

2 ACTING CHAIRPERSON TRACY: At this point I'd just
3 like to check with the panel members whether they have any
4 burning questions that they are in dire need of asking the
5 sponsor.

6 DR. KRUCOFF: I do. Just relative to the
7 physician from the University of Maryland, again, I just
8 want to make sure I heard this correctly, talking about
9 concerns of a coronary and the ischemia. My understanding
10 from before is that this has not actually happened.

11 DR. : Yes, that's actually a very
12 important point. The question that I was being asked was
13 what if, worst-case scenario. It's important to recognize,
14 I think this system's been used in over 3,500 cases. They
15 have not had one incident of catheter rupture and/or source
16 lost in patient or--it is a closed system that actually
17 prevents that.

18 DR. KRUCOFF: With a blow-out valve.

19 DR. : Right. So I was answering that
20 as a worst-case scenario.

21 DR. KRUCOFF: Thank you.

22 ACTING CHAIRPERSON TRACY: Dr. Simmons?

23 DR. SIMMONS: There's a section in the packet
24 about a stent inside a stent and the radiation delivered to
25 the artery maybe being reduced by as much as 50 percent.

1 Should this be put in as a contraindication? I mean, if
2 you're going to be delivering radioactive brachytherapy to
3 an artery and it's actually going to be reduced by 50
4 percent, is it even worth doing or should it be done? Or
5 should it be left in longer? Do you have any thoughts
6 before we--

7 MR. GREEN: Are you referring to the statements
8 made in the FDA review memos by Dr.--

9 DR. SIMMONS: Mm-hmm.

10 MR. GREEN: --when he was talking about the 20 to
11 50 percent? When we actually did our studies with our
12 source train, we did some studies on the bench with this.
13 Dr. Crocker at Emory University had done some of these, Tim
14 Fox at Emory University. We've come up with slightly
15 different numbers, but numbers we used to predict our
16 dosing. So for the START trial with respect to a non-
17 stented or a non-in-stent restenosis trial. So that was
18 built--that estimate was built into that. Dr. Crocker
19 talked about that briefly earlier. He can go into some more
20 detail about those numbers. But I think what we'd like to
21 do is in our instructions for use recommend that they do
22 the--they use the doses that were studied in the trial and
23 that they select those doses the way they were selected in
24 the trial, and that should allow them to get the same
25 results that were achieved in the trial.

1 DR. POPMA: The issue about contraindication, I
2 think we should--again, we didn't have these stent
3 sandwiches in our trial, so we didn't--we don't know whether
4 radiation is effective or not effective in that subgroup.

5 DR. SIMMONS: So at the very least, it's a warning
6 or a--

7 DR. POPMA: At the very least, however ultimately
8 it comes around. But, again, I'm taking my non--I'm not a
9 regulator, but a contraindication for me from a clinical
10 perspective means that we have data saying this might be
11 harmful. And we don't have any data saying that it might be
12 harmful, but I think it's very reasonable to say that we
13 didn't include stents within stents in our clinical trial
14 and that we don't have any data about the efficacy in that
15 subset. But I think that's a well-taken point. We would
16 want to make sure that we emphasize that these are really
17 just single stents in arteries that we're treating, not
18 multiple stents overlapped on one another.

19 DR. CROCKER: And I think it's also important to
20 add that, you know, a stent only covers a very small amount
21 of the luminal surface, and even if you had a stent within a
22 stent, I mean, the chances that they would be covering each
23 other at one point would likely be very small.

24 DR. SIMMONS: Just one other quick thing. In your
25 training overview, I guess it's page 1, there's going to be

1 this checklist, and it implies here that upon receipt of--
2 that the checklist, you know, the cardiologist, the
3 radiation oncologist, the physicist, the staff are all going
4 to be graded on this checklist to make sure that everything
5 is done right. And then on completion of the checklist,
6 they'll basically be certified. I mean, what is your
7 criteria there? Is it going to be 80 percent, 100 percent?
8 I mean, is it going to be--and what if they don't? I mean,
9 what if it is 80 percent? Are you not going to deliver the
10 radiation--I mean, what--I mean, I'm sort of trying to
11 visualize what's going on here. You're going to bring these
12 people there. You're going to train them. You're going to
13 do your mock trial and you're going to come back to the
14 radiation lab. You're going to do a mock thing there. And
15 then you're going to do three cases, and you're going to
16 watch them and fill out this checklist. And if they don't
17 do it right, you're not going to deliver the radiation to
18 them anymore?

19 MR. GREEN: Actually, there's two points here.
20 One, of course, this is the proposed training that we're
21 submitting to the FDA. However, what we're suggesting here
22 is that the checklist is something that would actually be
23 used in every phase of the training to ensure that each one
24 of the following items is covered, in the regional training,
25 in the on-site training, in the mock procedure and the

1 follow-up. So it's not a grade sheet at the end, if you
2 will, to see if they've passed, but it is--the criteria, the
3 things they need to be trained on and show proficiency in,
4 each one of these individual items before being released.
5 If they don't show proficiency in these core items, then
6 they need to be either trained more in-depth on those or
7 there needs to be an understanding why so they can use the
8 device in the safe and effective manner.

9 Does that answer your question?

10 DR. SIMMONS: I think so. I think basically what
11 you're saying is you don't have any control over it, and,
12 you know, you're going to try to provide them with the
13 information. But whether they use it or not is going to be
14 up to them, it sounds like what you're saying.

15 DR. SPEISER: That's true. There's limited
16 control. One is proposing credentialing for the physicians
17 who don't have the present time have staff privileges. And
18 what we're hoping to do is to say that you need to go
19 through this and be checked off before the company will say
20 that you are proficient for the procedure.

21 The question came up what happens if something
22 happens months later, and I don't think that there's any
23 control that you can control an individual months down if
24 they change their pattern.

25 MR. GREEN: What I would say is that we are--we

1 would be going through these things to make sure they're
2 proficient in these. Both the proctors and other
3 experienced users that are part of the training program for
4 the company we would not be releasing from proctoring.
5 We're suggesting three to five proctored cases. If after
6 five proctored cases a team has not showed proficiency in
7 using the device, they would not be released for, you know,
8 solo use of the device or the system.

9 Again, also, even after the proctored devices, we
10 wouldn't just release the device and then assume that down
11 the road that they were using it proficiently. There would
12 be a need for follow-up visits with the site post-sign-off,
13 if you would call it that, to ensure that they are
14 continuing to use and that they are using the device
15 correctly. And, again, this is all things that would be
16 worked out with the FDA. This has been proposed to them,
17 and they're reviewing it as to how best to implement
18 training for this type of system.

19 ACTING CHAIRPERSON TRACY: Does the sponsor have
20 any clarifying comments they want to make before they step
21 back?

22 MR. GREEN: No.

23 ACTING CHAIRPERSON TRACY: If not, okay, then you
24 can step back, please. We'll move on then to the questions
25 for the panel that the FDA has proposed.

1 Okay. The first question that we were asked to
2 consider is: Based on this information, as stated in the
3 preliminary remarks to Question 1, please discuss your
4 recommendations for antiplatelet therapy for patients who
5 receive a new stent and for patients who do not receive a
6 new stent.

7 Any comments from the panel on this? I know it's
8 my own impression that there does seem to be--there is in
9 the labeling a recommendation for patients who do receive a
10 new stent, which seems to be founded on data--perhaps not
11 data from this particular study, but that does seem
12 reasonable to me. However, it seems reasonable to make some
13 statement regarding patients who have not received a new
14 stent, even if it were a statement such that antiplatelet
15 therapy as indicated by usual clinical practice, but some
16 type of statement like that I believe should be added to the
17 labeling, would be my recommendation on that.

18 Any comments from the panel?

19 DR. KRUCOFF: I would agree. I think the data
20 would support patients who do not receive a new stent should
21 be managed per the routine clinical approach of the center
22 performing the procedure.

23 I guess particularly just on what my own feelings
24 would be, I think for patients who do receive a new stent,
25 particularly with less toxic options currently available, a

1 60- to 90-day or a 90-day use of drug would be a reasonable
2 inclusion precaution.

3 ACTING CHAIRPERSON TRACY: Okay. Anybody else?

4 DR. SIMMONS: Yes, I think, you know, the data in
5 this packet doesn't really support a 90-day, but the data
6 that they've brought in--I've got to trust them that it
7 suggests that it does. I guess I'd go with 90 days for the
8 stents and the usual clinical practice for the non-new
9 stents.

10 ACTING CHAIRPERSON TRACY: Okay. All right.

11 We'll move on to Question 2, then, which pertains to device
12 failures and malfunctions that occurred during this study.
13 Please discuss the clinical importance of the device failure
14 and malfunction events in the evaluation of the safety and
15 effectiveness of the Beta-cath system.

16 Comments?

17 DR. AYERS: I have one. I think the implication
18 is that when the source, other than the minor drift
19 problems, you have problems transporting the source back out
20 or partially into the catheter system through the valve, you
21 have a problem in that you don't know where they're at.
22 Unless they're in the fluoro field or in the safe--in the
23 device, you have no idea here in the vascular the sources
24 are located. And some of the reports we've had have had
25 them free-floating in that basket for upwards of two

1 minutes, and the literature tends to support that radiation
2 doses below the therapeutic amounts can, in fact, induce
3 stenosis. I think it would be difficult to establish that
4 one way or another, but I think there is a clinical
5 potential for some harm.

6 I guess my recommendation would be that that
7 introducer sheath is perhaps the best defense against that
8 and would be an appropriate mechanism to use.

9 ACTING CHAIRPERSON TRACY: Maybe I can--I don't
10 know how this device is used other than what I've been
11 presented here, not being an interventionalist, so I'll turn
12 to an interventionalist to say: Would the problem of
13 delivery be solved by not having a touie but having another
14 type of introducer?

15 DR. KRUCOFF: I almost wonder if there's a more
16 generic way to approach the whole issue. It seems to me
17 that all of the minor delivery issues have approaches either
18 in the training of the user or in engineering or redesign or
19 evolving design, so that it would seem to me that a
20 decrement in the incidence of these events should be
21 documentable. And I know personally to me the eeriest part
22 of all this would be pulling a guide wire at a time that I'm
23 not necessarily sure I'm ready I'd want to pull the guide
24 wire. And ultimately I think the reduction in the
25 percentage, in the rate of these events would be the best

1 agenda from a patient point of view. It seems to me that a
2 lot of these have either ideas or solutions in that a lower
3 incidence than perhaps was seen in the START study could be
4 something we would look for in the evolution of the device
5 and as a result of training.

6 DR. IBBOTT: I'm a bit disappointed that we're not
7 able to review data relating the incidence of the
8 malfunctions with time in the study or from one institution
9 to another or to the training the practitioners received.
10 But having said that, it also appears that the variations in
11 dose received by the target lesion itself are much greater
12 due to eccentricity of the catheter or of the lesion and
13 placement of the sources with respect to the lesion than
14 variations in the dwell time or in drifting of the sources.

15 Still--so I don't--it doesn't seem that the
16 effectiveness measures of the study would be greatly
17 affected by the incidence of the malfunctions. I think
18 they're more likely to be affected by those other issues of
19 centering and so on.

20 ACTING CHAIRPERSON TRACY: So it seems--I'm sorry.
21 More comments down there?

22 DR. GRIEM: The purpose of my query was to look at
23 the transfer device and say what are the possible means of
24 failure, and I tried to identify some of those questions
25 just before the break. And I think that the FDA has

1 sufficient engineering ability and talent here to look at
2 those questions.

3 ACTING CHAIRPERSON TRACY: Okay. So the sense of
4 the panel seems to be that the minor drift does not seem to
5 be a--the minor drift is not a major problem, and that the
6 other engineering issues can be addressed ongoing with the
7 company in monitored--see whether there is a relation to
8 training or experience of the operator.

9 DR. KRUCOFF: I would want to say must be
10 addressed. I mean, I think there are a lot of pointers that
11 they are being addressed. I'd like to see data that they
12 are actually being addressed.

13 I think we have to accept the fact that if this
14 radiation therapy is capable of being effective, that part
15 of its effectiveness is going to be the ability to deliver
16 it accurately and to have it affect the area you're
17 targeting and then get out of Dodge without adversely
18 affecting other areas.

19 So I would want to maybe voice it a little more
20 strongly, Cindy, that it should be either--we should have
21 augmented information over time that these fixes are--that
22 training and that modification of the device and attention
23 to the touie are sufficient to really reduce the incidence
24 of these mal-deliveries relative to the START study.

25 DR. SIMMONS: Those are the kind of things that,

1 you know, could be addressed in a post-market kind of
2 surveillance thing. I guess I'm disappointed--you know, Dr.
3 Zuckerman did an analysis looking at the newest design, and
4 it didn't seem like the lights and the locking stylet and
5 everything else changed the rate of drift or anything else.
6 So I think that's disappointing. So maybe it has to be
7 training. If you're going to do training, I think maybe
8 post-marketing is the way to go.

9 But I liked his idea of making it mandatory that
10 they use the arrow thing. I mean, the whole idea of
11 screwing down on this catheter and putting a kink in it and
12 getting it locked in the--I don't know. It just doesn't
13 seem--it seems like it's a built-in source of error that can
14 be eliminated. I don't know how to put that in words to get
15 it into the protocol other than just to say it out loud, but
16 it certainly seems like that's a very simple fix for--

17 ACTING CHAIRPERSON TRACY: So the answer, then,
18 is--it will probably come up again a little bit later in the
19 discussion, but there is concern at least over the delivery,
20 not so much the fact that there may be 5 versus 7 seconds'
21 worth of delivery or withdrawal. However, the issue of the
22 adequacy, the technical adequacy of the introduction and
23 withdrawal of the active radiation source.

24 DR. BAILEY: I guess the other point was--I guess
25 I'm still not sure. I thought that data were presented on

1 the effect of the mal-delivery on one of the endpoints,
2 anyway--MACE--which seems to conflict with your answer to
3 your question, which was that they couldn't identify the
4 patients who--they couldn't identify which patients had the
5 mal-deliveries. Otherwise, I mean, if they could identify
6 them, then they can say which order they occurred in. So
7 I'm not sure about that issue. Maybe they can speak to
8 that.

9 But I would like to see the most accurate analysis
10 possible of what the clinical effect was, and I'm not sure
11 we saw that. And I think it's very benign, but I'd just
12 like to see more data on that. Even though they're going to
13 get rid of the problem, I'd like to see what, if any, the
14 problem was that they did encounter. They have lots of
15 power to look at the effect of drift or whatever on the
16 change in minimum luminal diameter in the stented segment.
17 So even post hoc I think that would be useful information
18 for us to have.

19 MR. DILLARD: Jim Dillard. I was just going to
20 make the comment, you know, that the sponsor can certainly
21 get up and address that if they'd like to at this point,
22 too.

23 MR. GREEN: I believe your question, Dr. Bailey,
24 was: Could we identify the patients that had the source
25 drift and source transit? And you are correct. We were

1 able to identify those patients, and that's how the analysis
2 was completed by CDAC, and we came up with that.

3 DR. BAILEY: Does that not mean, then, that you
4 could identify factors such as training, learning curves?

5 MR. GREEN: We do have the details of what
6 happened in the cases where those happened, and that's
7 exactly the experiences we're talking about that we're
8 implementing in our training program.

9 DR. BAILEY: But the response to Dr. Ibbott's
10 question was that you couldn't analyze that.

11 MR. GREEN: If you mean after that event were
12 there any more events like that reported at that site, so
13 did they get better with time and experience--

14 DR. BAILEY: Right. He was just asking whether
15 factors such as size of center or experience volume,
16 training, had an impact on that.

17 MR. GREEN: That may actually be one way of
18 looking at that. We haven't done that analysis, but that
19 might be something we could look at.

20 ACTING CHAIRPERSON TRACY: Then it may be worth
21 asking the sponsor to look at that and provide that
22 information.

23 Okay. We'll move on to Question 3, and I'll read
24 the background again here in case anybody's forgotten. As
25 demonstrated by the results included in Table 1 of the START

1 clinical report, page 5, the incidence of the primary
2 endpoint, target vessel failure, was significantly lower at
3 8 months for the treatment arm compared to the placebo. The
4 incidence of target vessel revascularization, target lesion
5 revascularization, and major cardiac adverse events were
6 also significantly lower over the 8-month follow-up period
7 for the treatment arm compared to the placebo. No incidents
8 of stent thrombosis were detected in the treatment arm, and
9 the frequency of total occlusions was comparable between the
10 treatment and placebo arms.

11 The question is: Please discuss whether you
12 believe the probable clinical benefit of the radiation
13 treatment outweighs the probable risks of death, myocardial
14 infarction, total late occlusion, and late stent thrombosis
15 posed by the device in the intended patient population.

16 DR. SIMMONS: Yes.

17 ACTING CHAIRPERSON TRACY: Yes. Any comments,
18 qualifications on that? Yes?

19 DR. WILSON: Frank Wilson. Perhaps that's a
20 qualification. I think we've accepted that it's intuitive
21 that the information in Table 3A doesn't draw any probable
22 distinction between the 30-millimeter and the 40-millimeter
23 source train. But the deal with absolutely accurate data
24 relative to what's in the application for the 30-millimeter,
25 I would probably like to see this table reworked to confirm

1 that that data is what we think it is.

2 ACTING CHAIRPERSON TRACY: I think that's a fair
3 enough addendum to our answer yes, but we'd like to see the
4 information presented specifically with the 30-millimeter.

5 DR. KRUCOFF: I think the other potential addendum
6 to the yes, since the question is posed, Does beta radiation
7 therapy achieve this? where the answer clearly is yes, is
8 that this set of data still leaves the question as to
9 whether the delivery system itself either rubs or irritates
10 the interventional site independent of the delivery of
11 radiation. And I think that awareness of that in this or
12 future device designs, that the device has to be placed into
13 the lumen of a territory that has been designated optimally
14 dilated, and then in 21 percent of cases, by the time the
15 radiation therapy has been administered acutely, another
16 step has to be added, is a potential proviso that would be a
17 reasonable thing to survey over time and with wider
18 experience.

19 So this question as posed for the radiation, which
20 I think the data clearly support, does get a yes, but the
21 delivery device as an intracoronary device I think we still
22 have to recognize was not randomized in this study, and 21
23 percent of patients, after that device was removed, had
24 additional manipulation of the site.

25 DR. SIMMONS: Well, the other thing was something

1 that you brought up: What happened to the patients who had
2 reintervention after the stenosis? I mean, we don't have
3 any data on those either. I was surprised. Those patients
4 appear not to have been followed up, so the patients who had
5 re-restenosis in the radiation group, did they do as well as
6 the patient population that has restenosis without the
7 radiation? Was there excess bleeding, you know, problems
8 with the surgeons finding adequate sites to reimplant the
9 grafts? We have no data on that.

10 ACTING CHAIRPERSON TRACY: So the answer becomes
11 yes, but--

12 DR. SIMMONS: I was looking at the acute--

13 ACTING CHAIRPERSON TRACY: Right. We need the
14 information on the shorter device, and we also recognize
15 that it is not just the radiation but there's the delivery
16 device system. So follow-up on that and understanding of
17 what the mechanics of the delivery system does to the vessel
18 and the late effects of radiation, if there are any late
19 interventions, would be useful information to follow over
20 time.

21 Okay. Question 4 is a multi-part question. One
22 aspect of the pre-market evaluation of new product is the
23 review of its labeling. The labeling must indicate which
24 patients are appropriate for treatment, identify the
25 product's potential adverse events, and explain how the

1 product should be used to maximize benefits and minimize
2 adverse effects. Please address the following questions:

3 4A, Please comment on the indications for use
4 section page 12 as to whether it identifies the appropriate
5 patient population for treatment with the device. And
6 probably we should turn to that.

7 DR. KRUCOFF: Page 12?

8 DR. SIMMONS: Page 12, Section 4.

9 DR. KRUCOFF: I think one of the things that needs
10 to be emphasized in the indications is that the patients
11 tested in this study had successful angioplasty results or
12 successful percutaneous intervention results. And I think
13 the way it's currently worded, patients who have undergone
14 PTCA for discrete lesions, is far less specific to a host of
15 operators than the patients who were, in fact, included in
16 the START study. In fact, as was stated earlier, we don't
17 know how many patients came into the labs with in-stent
18 restenosis who were not included in the study. Roughly, if
19 that's 10 percent or so by the operators' estimates, I think
20 that that's an important element to the indications for use,
21 that these were patients who had a successful angioplasty
22 result, who then underwent beta radiation.

23 DR. SIMMONS: Let me put my foot in there.

24 Successful PTCA with a lesion less than 30 percent? Thirty
25 percent or less? Residual lesion 30 percent or less,

1 something like that.

2 ACTING CHAIRPERSON TRACY: I think that would be
3 what was included in the study, so that seems to be
4 reasonable to include it in the indications here.

5 MR. DILLARD: Jim Dillard. Just an additional
6 question. One thing that we struggle with frequently is how
7 much actually had to do with entry criteria or inclusion
8 criteria in the study, how much of that needs to go into
9 specifically defining the intended use or indication for use
10 versus how much of that should go in the clinical section of
11 the labeling that actually gives us the descriptive
12 characteristics of the clinical study and the outcomes.

13 And so one of the things if you're thinking about
14 where to put it or where your recommendation might be,
15 should it actually be in the indication for use or should it
16 just be a very prominent section contained within the
17 clinical section of the labeling, if you can make some
18 differentiation between the two of those, because what I
19 don't like to see in the direction we're trying to go at the
20 agency is try not to put so much detail in the indication
21 for use statement that you as the clinician stop reading
22 them because they become three pages long and then the
23 important clinical section becomes very tiny. So I know
24 it's a trade-off, but, you know, any recommendation you
25 might have on that would be appreciated.

1 ACTING CHAIRPERSON TRACY: It may be worth being a
2 little bit less specific, then, and perhaps just saying
3 successful rather than specifying a degree of stenosis since
4 different labs have different abilities or technologies for
5 measuring the lumen and the residual stenosis. But this
6 study really did pertain to those patients who had had a
7 successful in-stent restenosis. So I would say maybe just
8 the word successful.

9 DR. BAILEY: Should atherectomy be included in
10 this, or is that implied?

11 ACTING CHAIRPERSON TRACY: I would think it would-
12 -there were a variety of different techniques by which the
13 vessel was opened. Whether it was atherectomy or dilatation
14 or--I don't think we should specify--I would think we
15 shouldn't specify that.

16 DR. KRUCOFF: Actually, this is a small detail,
17 but I guess small can be important. Rather than PTCA, it
18 might be worth just substituting PCI as an indication, that
19 the patients who were enrolled in this study essentially had
20 a reduction of their lesion based on operator discretion,
21 selection of tools, not just balloons.

22 DR. GRIEM: But excluding new stents.

23 DR. KRUCOFF: But excluding stents. That's true.

24 ACTING CHAIRPERSON TRACY: Okay. So we're going
25 to change the word from PTCA to PCI and add the word

1 successful.

2 DR. KRUCOFF: You might want to add excluding
3 stents. That's a good point.

4 ACTING CHAIRPERSON TRACY: Okay. Well, I'm not--
5 maybe we can move on to 4B. Somewhere we've got to deal
6 with the stents, but 4B is: Please comment on the
7 contraindications section, page 12, as to whether it
8 identifies all conditions under which the device should not
9 be used because the risk of use clearly outweighs any
10 possible benefit. And the contraindications, as stated on
11 page 12, say unprotected left main disease and patients in
12 whom antiplatelet and/or anticoagulant therapy are
13 contraindicated.

14 Any comments from the panel?

15 DR. AYERS: Bob Ayers. I noticed one thing that
16 crops up here is that nowhere indicated--and it could bridge
17 contraindications and warnings and precautions. There's
18 nothing there about use that hasn't been established in the
19 trial and that *a priori* would probably be considered a
20 contraindication or potentially harmful, such as treating
21 across a bifurcation or trying to step a source like this.
22 In other words, trying to use a 30-millimeter source train
23 to treat 60 millimeters of artery, which the system's not
24 designed really to do.

25 MR. DILLARD: I'll make a comment. Jim Dillard.

1 Without going into a lot of detail about where we currently
2 view precautions, warnings, and contraindications, let me
3 just give you a little bit of a sense. Contraindication I
4 think in our mind would be that where we have got some
5 negative data, some data that we would know would be adverse
6 to a patient or a patient group. I think that would be very
7 important and that should drive a contraindication.

8 I think generally--and perhaps it's implied,
9 although many times it ends up in a warning about any other
10 patient population or any other subgroup that was not
11 studied in the trial. Of course, there's no safety and
12 effectiveness information known on those patients. Many
13 times statements like that show up. They don't show up
14 generally in contraindications, but a lot of times they
15 would show up in a precaution or a warning type of
16 statement.

17 So I think we're trying to clarify that and not
18 make contraindications when a contraindication is not
19 warranted, but nonetheless, if it's something that might
20 have either an effect on the device or an effect on a
21 patient population where we don't know very much, then that
22 should drive either a precaution or a warning, respectively.

23 DR. SIMMONS: What about a special consideration?
24 I don't think I've heard that term used before. Where did
25 that one come from?

1 MR. DILLARD: Jim Dillard again. I think there
2 can be special considerations, there can be notes, there can
3 be a lot of other sections to a manual, and I think the
4 important thing, at least--you know, maybe we can put this
5 to bed a little bit--is that if your recommendation is that
6 there should be some consideration in the labeling about a
7 certain type of issue or a certain type of item, I think we
8 can work very closely with the sponsor about where to
9 appropriately put it. I think if you can give us a
10 recommendation about how strongly you think it's needed,
11 that will be, you know, very beneficial to us.

12 ACTING CHAIRPERSON TRACY: I think as regards that
13 comment, the issue of the stent perhaps comes up somewhere
14 where you can decide with the sponsor where it should be
15 mentioned, that this study was not specifically meant to
16 deal with radiation therapy for stents placed within stents
17 for restenosis. And the other section that I think that we
18 should think about are the whole group of exclusion criteria
19 for the investigational protocol that did not make it up
20 either as contraindications or warnings and precautions.
21 And I wouldn't think they should be contraindications, but I
22 think it was Dr. Simmons who had pointed it out earlier that
23 certain patient characteristics or ejection fractions were
24 not included in this patient population. That should, I
25 would think, be stated somewhere, called something.

1 DR. SIMMONS: Yeah. How about, you know, the MI
2 less than or equal to 72 hours prior to the procedure?
3 There may not be specific data on that, but it would--you
4 know, certainly that artery is probably not the same as an
5 artery that's, you know, stable, anginal-type symptoms and
6 maybe that should go under precaution just--there may not be
7 negative data, but there's certainly no data and there's
8 certainly implied data, that maybe it isn't a normal artery.

9 ACTING CHAIRPERSON TRACY: Yeah, I think that
10 there is a gradation, it seems, within the exclusion
11 criteria, some of which would probably rise to a precaution
12 level. And I think the infarct is a good example of that.

13 DR. KRUCOFF: Yeah, Mitch Krucoff. I'd sort of
14 extend the list not, again, so much as a contraindication as
15 to helping interventionalists understand where we just don't
16 have data to probably include thrombotic lesions, vein graft
17 segments, stent sandwiches, and at least to the best of my
18 appreciation of the START data, to diffuse proliferative
19 responses that extend beyond the margins of previously
20 implanted stents.

21 ACTING CHAIRPERSON TRACY: Do you think that--are
22 you proposing those as precautions or warnings, or do you
23 think those are just indications of what was not studied?

24 DR. KRUCOFF: Well, I'm actually not sure what the
25 right answer is. I think being cautious in an arena where

1 we don't have data and where we have potentially different
2 physiologic substrates about the use of radiation technology
3 is one of the reasons that I would impute this START study
4 was designed to look at a fairly pristine patient
5 population, and we have data from a fairly pristine patient
6 population, and we have a community of knuckle-dragging
7 interventionalists who will probably run all over that
8 outside of that pristine patient population. So anything we
9 can do to assist them to stay within the boundaries of what
10 we know and have learned from these data I would encourage
11 be in the package labeling.

12 DR. SIMMONS: So maybe under precautions?

13 ACTING CHAIRPERSON TRACY: I'm sorry?

14 DR. SIMMONS: Maybe under precautions rather than
15 warnings kind of thing.

16 ACTING CHAIRPERSON TRACY: Maybe we'll leave the
17 semantics to the FDA.

18 DR. SIMMONS: How about these? Could we look at
19 these? As long as we're looking at--we sort of lump these
20 all together.

21 ACTING CHAIRPERSON TRACY: Which one is this?

22 DR. SIMMONS: What about these special
23 considerations? Do you want to read through those and see
24 what you want to do? I have some problems with those. I
25 don't know what to do with them. Like these vessels or

1 lesions that would preclude revascularization or placement
2 of the Beta-cath delivery system, it's kind of obtuse to me.
3 I don't understand what it's trying to say or what it's a
4 special consideration for.

5 ACTING CHAIRPERSON TRACY: That is a little--I
6 would--I took that as meaning an unsuccessful dilation or an
7 unsuccessful atherectomy.

8 DR. SIMMONS: I don't know...

9 ACTING CHAIRPERSON TRACY: I think we've moved
10 that into the indication--I think, if I'm reading that
11 correctly, that they're talking there about an unsuccessful
12 intervention.

13 DR. SIMMONS: Or a tortuous vessel or a vessel
14 that's too small to get the catheter into or something--

15 ACTING CHAIRPERSON TRACY: It could be, but they
16 have specifically indicated that the study involved 2.7- to
17 4-millimeter vessels, so we shouldn't even be talking about
18 those other types of vessels I would think.

19 DR. SIMMONS: So I think that's vague and--

20 ACTING CHAIRPERSON TRACY: So maybe it's too
21 vague, just leave it out.

22 DR. SIMMONS: How about patients having undergone
23 prior chest radiotherapy? What does that have to do with
24 anything? I mean, maybe one of the radiation oncologists
25 could help us here. If you've had previous radiation

1 therapy, does that preclude you from getting a successful
2 result with this radiation therapy? Or are they worried
3 about cumulative radiation dosages? I don't understand that
4 one.

5 DR. WILSON: I suppose that was the concern. I
6 read that several times and decided it was acceptable where
7 it is. It's a special consideration, should be given all
8 due weight in the thinking of the user before proceeding.
9 But I don't have a strong feeling about it. I doubt this is
10 ever going to be a clinical problem in individual cases or
11 in groups of patients. But it's something to weigh.

12 DR. SIMMONS: And how about the other one, the
13 women of child-bearing potential? Is that just a special
14 consideration? Is that a warning, a precaution? Is it
15 really important if they're having coronary anatomy that
16 needs to be opened up whether they're of child-bearing
17 potential or not?

18 ACTING CHAIRPERSON TRACY: I think it is a special
19 consideration in that you're exposing that woman and that
20 child to radiation of one form or another, whether it's
21 through fluoroscopy and whatever limited radiation at a
22 distance you get from the beta source.

23 DR. SIMMONS: So just leave it in this sort of
24 vague special considerations category rather than a warning
25 or a precaution.

1 ACTING CHAIRPERSON TRACY: I would think so.

2 DR. WILSON: I looked at that also, and I wondered
3 about that. It seemed to me that it's all right where it
4 is. Obviously, if you have a woman who is in the first
5 trimester, that is, during the period of organogenesis,
6 you're going to be very concerned about the dose from
7 fluoroscopy in that patient. But it seems to me it's still
8 something you're going to take under advisement rather--

9 DR. SIMMONS: Yeah.

10 DR. WILSON: --than say it's an absolute
11 contraindication towards.

12 DR. AYERS: Bob Ayers. It kind of supports, goes
13 along with our regulations. We have no prohibition
14 whatsoever as to the practice of medicine of giving
15 radiation to a fetus, but we do have a prohibition against
16 unintentionally giving radiation to a fetus. So if the
17 physician doesn't determine the patient is pregnant and then
18 goes ahead and gives an excessive dose of radiation to the
19 fetus, that's a problem. But if he knows the patient's
20 pregnant and decides it's still in the best interest of the
21 patient and goes ahead, that's okay. So it's unintentional
22 radiation exposures to a fetus that are a problem for us.

23 ACTING CHAIRPERSON TRACY: Okay. So maybe that--
24 under their label section special considerations we would
25 suggest removing the second one, which seems to us to be

1 another statement of unsuccessful or inappropriate, so we'd
2 take that out. And the other comments that we made
3 regarding the inclusion, specific inclusion, and the
4 exclusion criteria from the study should be reflected
5 somewhere, probably for the most part under either an
6 additional statement of inclusion/exclusion criteria of the
7 study or precaution for the particular of acute infarct
8 vessel.

9 DR. KRUCOFF: Cindy, Mitch Krucoff. I guess I
10 should speak up since to me this second one actually does
11 make sense. I should at least voice it. Lesions that
12 preclude revascularization to me is a way of saying to the
13 interventional community this gadget is not magic; you know,
14 that basically it is indicated for use once you've achieved
15 a successful angioplasty result in a vessel that can be
16 revascularized. And maybe more importantly, the second part
17 that precludes placement is a reminder that this is not a
18 supple balloon catheter design. This is a hydraulically
19 protected closed system of tubing that is going to be a
20 little more stiff and potentially ramming it into a coronary
21 anatomic location that's obviously tortuous or heavily
22 calcified would be something you'd be worth taking a special
23 consideration about delivering this device compared to other
24 devices.

25 I would take that as at least the spirit of why

1 it's there and why it's sort of isolated in this section as
2 a way of giving interventionalists an alert that this is not
3 a sleek, supple balloon catheter, this is a larger plastic
4 system that you better think about, and you might not want
5 to slide in through a tiny guide catheter, you might want to
6 use a larger guide catheter, et cetera, et cetera.

7 ACTING CHAIRPERSON TRACY: Is that, then, a
8 contraindication or special consideration?

9 DR. KRUCOFF: Well, for me, I would leave it as a
10 special--it might, for instance, influence me in the
11 selection of the guide catheter that I would use to make
12 sure I had more support or that I might take more time if I
13 had a more moderate turn in a coronary to make with this
14 thing, that I might be a little more aggressive in placing a
15 guide catheter or other sort of technical elements like
16 that.

17 ACTING CHAIRPERSON TRACY: Okay.

18 DR. SIMMONS: Make sense to me. It's great.

19 ACTING CHAIRPERSON TRACY: It's the anti--

20 DR. SIMMONS: It just left me cold. I read it and
21 I went blank.

22 ACTING CHAIRPERSON TRACY: Okay.

23 DR. NAJARIAN: Just as far as leaving it in, I
24 agree with that. But you could add another word like
25 morphology or anatomy, you know, vessel or lesion morphology