

1 different between the two groups, and it was in favor  
2 of PMR with the PMR patients having -- 25 PMR patients  
3 having angina during the one-year follow-up that  
4 required hospital admissions versus 39 for the medical  
5 group.

6 When you look at arrhythmias, there were  
7 11 in the PMR plus medication group versus four in the  
8 medical group. Three of those we've already mentioned  
9 were complete heart block. There was one patient in  
10 each group that had ventricular tachycardia and  
11 ventricular fibrillation, and so it didn't appear to  
12 be a difference caused by the treatment in causing VT  
13 and VF.

14 The other events in the PMR plus medical  
15 group included four instances of atrial fib and  
16 flutter. There were two in the medical group and  
17 three symptomatic bradycardias. All of these patients  
18 were treated with beta blockers, and beta blockers  
19 were needed to be continued in the patients. So two  
20 of these patients -- actually one of the patients had  
21 a permanent pacemaker implanted. We've already  
22 mentioned that one, and the other two had just

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1 adjustment of the medications and didn't need a  
2 permanent pacemaker, but they did have hospitalizations  
3 for the bradycardia.

4 The other events are as listed and not  
5 statistically different between the two groups, and  
6 patients when we look at the total number of patients  
7 with any event, 50 in the PMR plus medical group and  
8 48 in the medical group, not statistically different.

9 Next slide.

10 So in conclusion of the PACIFIC study  
11 data, I think we showed that PMR significantly reduces  
12 angina symptoms, reduces hospitalization for angina,  
13 improves the exercise test duration, and improves  
14 quality of life.

15 And the safety data we spent a great deal  
16 of time on. I believe that there are reasonable  
17 procedural risks for these seriously ill patients with  
18 very limited treatment options.

19 Next slide.

20 The BELIEF study is an extremely important  
21 study to look at the placebo effect in this treatment  
22 group. Professor Nordrehaug was kind enough to let me

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1 present the data. He is here and will be available to  
2 answer any questions you have. For further definition  
3 of the study, I'm going to just show you a very brief  
4 overview.

5 As we said, Class III to IV angina  
6 patients who were turned down for revascularization  
7 were entered into the trial. They were randomized to  
8 either get PMR plus medical therapy or a sham  
9 procedure so that the patient and the operator were  
10 totally blinded as to the treatment.

11 Next slide.

12 The blinding was accomplished by having a  
13 technician behind a lead screen. That was the only  
14 one that knew which treatment that the patient got.  
15 He calibrated two different laser catheters so that  
16 the patient and the physician could hear the laser  
17 firing as the laser catheter was pushed up against the  
18 wall, and both patients, both groups of patients were  
19 treated exactly the same. Neither the operator nor  
20 the patient knew whether or not he had been treated  
21 with laser.

22 The only difference besides this double

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1 blinding in this and the PACIFIC trial was the  
2 ejection fraction could be slightly lower for  
3 enrollment in this trial at 25 percent. No  
4 crossovers, again, were allowed between the two  
5 treatment groups.

6 Next slide. Next slide.

7 The angina assessment I should point out  
8 was done by the same physician at these institutions  
9 who was also blinded to treatment. The same physician  
10 assessed the patient at entry into the study and at  
11 six months.

12 The baseline characteristics are in this  
13 slide. The only thing worth pointing out is the  
14 incidence of diabetes. In Europe, as in most European  
15 studies, it is less than it is in American studies,  
16 with only 12 to 21 percent of the patients having  
17 diabetes. Otherwise the baseline characteristics are  
18 pretty similar to the previous trial, and two-thirds  
19 of their patients also had prior myocardial  
20 infarction.

21 Next slide.

22 The mean number of channels, either sham

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1 channels or real PMR channels was 19 to 20. The PMR  
2 duration was 36 to 37 minutes, and the total procedure  
3 duration was just over an hour in each group.

4 Next slide.

5 The angina assessment in the BELIEF trial  
6 was done differently than the angina assessment in the  
7 PACIFIC trial. The angina assessment was done by a  
8 scripted group of questions asked by the same  
9 investigator at both time points, and then the  
10 investigator, that blinded investigator, graded the  
11 patient's angina.

12 Whereas in the PACIFIC trial, it was  
13 strictly investigator assessment, the majority of the  
14 data that I showed you, although there was an  
15 independent assessment that we showed you some data  
16 about in a limited number of patients.

17 The ETT was done by the modified bridge  
18 protocol, as I showed you earlier in PACIFIC. It was  
19 done by the CAEP protocol in the BELIEF study, but not  
20 only was the protocol different. The patients had a  
21 metabolic stress test. They had an oxygen or a mask  
22 to collect expiratory gas. They were asked to

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1 exercise to exhaustion, and that was proven by the  
2 fact that the patient produced lactate before he was  
3 allowed to stop on the treadmill.

4 So it's a cardiovascular endurance test in  
5 the BELIEF trial, whereas in the PACIFIC trial it was  
6 modified Bruce geared towards topping with the patient  
7 having angina.

8 The quality of life was the same test in  
9 both studies.

10 The only primary endpoint that the BELIEF  
11 study was powered for is improvement in angina, not  
12 for the other two parameters.

13 Next slide.

14 If we look at the baseline features, Class  
15 III angina was the predominant class in the BELIEF  
16 trial with only ten to 17 percent of the patients  
17 having Class IV angina. The majority were Class III  
18 at baseline.

19 Next slide.

20 If we look at angina improvement again,  
21 two class angina improvement by this independent  
22 assessment, at six months 41 percent for the PMR

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1 treated group versus 13 percent for the sham control  
2 group, again, a highly statistically significant  
3 difference in favor of PMR.

4 Next slide.

5 If we look at the PACIFIC data at six  
6 months, 51 percent of the patients by investigator  
7 assessment had an improvement of greater than two  
8 functional classes, 41 percent in the independent  
9 assessment of the BELIEF trial. Both trials show a  
10 very strong advantage for PMR even though the numbers  
11 are slightly different. The numbers for the control  
12 group, since they were different control groups, I  
13 think are also not surprisingly different in terms of  
14 the numbers improving two classes, 13 percent in the  
15 BELIEF trial versus only six percent in the medically  
16 treated control group of the PACIFIC study.

17 But both of these analyses confirm one  
18 another that angina is significantly improved by PMR.

19 Next slide.

20 If we look at the in hospital adverse  
21 events, there was one patient in the sham group that  
22 had a myocardial infarction and died the day of

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1 treatment; 2.4 percent death rate. None of the PMR  
2 patients died.

3 If we look at arrhythmias, most of the  
4 arrhythmias were ventricular arrhythmias, just  
5 isolated PVCs when the catheter was placed up against  
6 the wall. That occurred equally 26 to 27 percent in  
7 the two treatment groups.

8 There was one perforation, free wall  
9 perforation in the PMR group that required  
10 pericardiosynthesis, and then resolved. No other  
11 adverse clinical sequelae of that perforation.

12 There was one TIA, 2.4 percent, in the  
13 sham treated group, and both groups had two patients  
14 that had bleeding complications from the access site.

15 Next slide.

16 If we look at six month adverse events,  
17 there is, again, no great difference between the two  
18 hospital groups, but a couple of differences from the  
19 PACIFIC trial. There were rehospitalizations in 12  
20 percent of these patients over six months. It was  
21 much higher in the PACIFIC trial.

22 And if we look at death, there were two

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1 deaths in the sham treated group versus none in the  
2 PMR treated group. Those are the only differences I  
3 just wanted to point out to you.

4 Next slide.

5 If we look at a Kaplan-Meier plot of all  
6 cause mortality, again, not statistically different at  
7 the end of six months between the two groups.

8 Next slide.

9 And possible reasons for fewer adverse  
10 events in the BELIEF study than in the PACIFIC study  
11 was the PACIFIC study patients at baseline had a  
12 higher ejection fraction. The ejection fraction was  
13 65 percent in both groups versus 50 percent in the  
14 PACIFIC study. There were more Class III patients in  
15 the BELIEF study and many fewer diabetic patients in  
16 the BELIEF study.

17 So we believe that the baseline  
18 characteristics really predicted fewer adverse events  
19 as corroborated by the data.

20 Next slide.

21 So, in conclusion, safety and efficacy,  
22 that is, angina improvement of the Eclipse PMR system

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1 are confirmed and supported by the BELIEF study  
2 results, and the double blinded BELIEF study with the  
3 sham control certainly establishes that angina  
4 improvement with this system is not primarily related  
5 to placebo effect.

6 Next slide.

7 And now Dr. O'Neill will summarize the  
8 risk-benefits.

9 DR. O'NEILL: Dr. Tracy, ladies and  
10 gentlemen, members and guests of the panel, I am  
11 William O'Neill. I'm the Director of Cardiology at  
12 William Beaumont Hospital in Royal Oak, Michigan.  
13 I've been involved with new device evaluation for  
14 approximately 20 years and have been involved with  
15 multiple PMA submissions, most recently with the Tech  
16 and the Rotoblader (phonetic) arthroectomy device in  
17 the early 1990s.

18 I have no conflict of interest to  
19 disclose. I have no ownership, and the only  
20 reimbursement I'm receiving is for travel expenses  
21 that I have during the visit this morning.

22 The reason that I'm here testifying for

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1 the company is because I do have a firm belief that  
2 there is clinical efficacy with this procedure. I've  
3 been involved initially as a skeptic. In the early  
4 1990s, I thought that this procedure really was  
5 totally silly until I had many medically refractory  
6 patients with no other treatment options that almost  
7 in desperation we referred for surgical evaluation,  
8 and lo and behold, in follow-up to us, we found that  
9 these patients had an extraordinary relief of  
10 symptoms.

11 And based on that, our own institution  
12 began developing and researching this procedure. We  
13 were involved with Dr. Allen in the New England  
14 Journal article on the randomized trial with surgical  
15 TMR, and since then we've been involved with  
16 percutaneous evaluation.

17 So based on my own experience over the  
18 last six years treating many, many patients that are  
19 medically refractory, following them and seeing them  
20 back in the office, I have a strong belief in the  
21 clinical efficacy of this device, and that's really  
22 the reason that I'm here to testify on their behalf.

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1 Can I have the next slide, please?

2 The clinical problem that we're dealing  
3 with is patients that have diffused atherosclerotic  
4 end stage disease, and again, I want to characterize  
5 the gestalt of this overall population of patients for  
6 you.

7 These patients have relatively well  
8 preserved ventricular function. Their ejection  
9 fractions are 50 to 60 percent, but they have diffuse  
10 inoperable coronary disease. Many of these patients  
11 have diabetic arteriopathy. Many of these patients  
12 have previous bypass surgeries or previous  
13 interventions. They have well preserved ventricular  
14 function, but they are very, very limited because of  
15 the severe, profound angina, and this results in a  
16 great debilitation. The patients have a sense of  
17 hopelessness that nothing can be done for them, and  
18 the physicians certainly have a great deal of  
19 frustration with these patients.

20 In this particular population of patients,  
21 60 percent of the patients that had two  
22 hospitalizations in the year before for refractory

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1 angina. So that really characterizes the group of  
2 patients that we're dealing with.

3 Next slide, please.

4 If we look in the literature at what  
5 proportion of patients could this technique be  
6 valuable for, there are 500 patients that were  
7 prospectively evaluated by the Cleveland Clinic and  
8 published in the JACC in 1999. These patients were  
9 referred to symptomatic coronary disease. There were  
10 a panel of three cardiologists that reviewed the  
11 medical history and angiographic films, and 11 percent  
12 of these patients, or one out of ten of these  
13 patients, had inoperable coronary disease.

14 And remember at the Cleveland Clinic these  
15 were obviously one of the foremost surgical sites and  
16 percutaneous sites in the world. So even in that  
17 center, 11 percent of these patients had inoperable  
18 coronary artery disease, and approximately six percent  
19 of these patients could be eligible for PMR and TMR.

20 So, again, it's a minority of the patients  
21 that are referred for symptomatic evaluation of  
22 coronary disease, but a very, very significant

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1 subgroup of patients that consume a great deal of  
2 resources with regards to repeat hospitalizations and  
3 have a very, very poor quality of life.

4 Next slide, please.

5 The indications that we recommend Eclipse  
6 PMR system is indicated for use of percutaneous  
7 myocardial vascularization procedures to decrease  
8 angina and increase exercise tolerance in patients  
9 with chronic angina.

10 I think Dr. Whitlow had demonstrated  
11 consistent information with regards to both the BELIEF  
12 and the PACIFIC trials that angina is decreased, and  
13 in the PACIFIC trial we've demonstrated significant  
14 improvement in exercise tolerance.

15 Again, this is for chronic Class III or  
16 Class IV angina, which is refractory to medical  
17 treatment and secondary to objectively demonstrate a  
18 coronary artery disease with a region of the  
19 myocardium with reversible ischemia not amenable to  
20 direct coronary vascularization.

21 We'd like to re-emphasize that this is not  
22 an alternative for traditional revascularization

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1 techniques. Patients that are eligible for coronary  
2 bypass surgery or eligible for PCI should have those  
3 traditional revascularization techniques performed.

4 But we do feel that there are a subgroup  
5 of patients that have medically refractory angina with  
6 no other viable percutaneous or surgical treatment  
7 options for which this approach is indicated.

8 Next slide, please.

9 If we look across the board at the  
10 improvement of symptoms of both TMP and PMR in the  
11 published series, in a risk reduction analysis you can  
12 see that both the surgical experience in the yellow  
13 and the percutaneous experience in the green -- we've  
14 presented the PACIFIC and the BELIEF, but the company  
15 has also done the TMR-10 study. In all of these  
16 there's a consistency of benefit with both TMR and  
17 PTMR demonstrating a significant improvement in  
18 angina, which is highly significant and is very, very  
19 consistent across the published studies that have been  
20 reported.

21 Next slide, please.

22 We think that we have demonstrated that

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1 there is a significant benefit of this procedure with  
2 a Class II improvement in symptoms. A majority of  
3 these patients end up being Class I or Class II, and  
4 again, this greatly improves their quality of life and  
5 improves their exercise capacity.

6 Very importantly these patients have  
7 repetitive hospitalizations prior to the procedure,  
8 and we've demonstrated a significant decrease in the  
9 rate of hospitalization in the one-year follow-up in  
10 the U.S. study, and again, this is an enormous impact  
11 for these patients both in quality of life and  
12 decrease in length of stay and hospitalizations.

13 We have demonstrated that this technique  
14 significantly improves exercise duration in the  
15 modified Bruce protocol, and we have demonstrated a  
16 significant improvement in the quality of life.

17 Next slide, please.

18 If we look at this technique as an  
19 alternative to the FDA approved surgical TMR, the data  
20 is presented on the left of the already approved TMR  
21 Eclipse protocol in which a significant decrease in  
22 angina occurred with the surgical treatment in

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1 patients that are Class IV.

2 In the PACIFIC study, again, a highly  
3 significant decrease in symptoms in patients that have  
4 Class IV, which is very equivalent to the surgical  
5 approach, and we feel that this approach should be  
6 viewed as an alternative to the already FDA approved  
7 surgical approach for TMR.

8 Next slide, please.

9 But it's important to understand that  
10 there's a comparison, although the two appear to have  
11 equal efficacy in Class IV symptoms. The surgical  
12 approach requires an open thoracotomy. It requires  
13 general anesthesia, a great deal of pain to the  
14 patients, where as the percutaneous approach is  
15 obviously just percutaneous.

16 The length of stay for a surgical approach  
17 is six days where it's 1.2 days in the PTMR group.

18 The recuperation because of the open  
19 thoracotomy is going to be two to three weeks, where  
20 it's only one to two days for the PMR patients.

21 And then the mortality, the 30-day  
22 mortality in the surgical approved protocol was five

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1 percent, whereas in this approach the surgical  
2 mortality is one percent.

3 So we feel that the comparison between the  
4 surgical approach is going to be a significant  
5 decrease in length of stay, a significant decrease in  
6 pain and debility to the patients, an improvement that  
7 occurs much more quickly and a trend towards a  
8 favorable improvement in 30-day mortality.

9 Next slide, please.

10 We do feel that in order to decrease the  
11 risk of this procedure that labeling recommendations  
12 are required. Dr. Whitlow has demonstrated a  
13 substantial risk with complete heart block occurring  
14 when the upper septum is treated, and physicians and  
15 patients need to be warned about that potential risk,  
16 especially in patients with preexisting right bundle  
17 branch block.

18 We would recommend strict adherence to ACT  
19 protocols to try to maintain ACTs of greater than 250  
20 seconds, in order to decrease the risk of  
21 thromboembolic events during the procedures, and then  
22 because of the finding, which is quite interesting,

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1 that three of the patients had pericardial effusions  
2 demonstrated on routine screening out-goes, we would  
3 recommend that a routine pre-discharge out-go occur to  
4 assure that pericardial effusions are not present post  
5 procedure.

6 Next slide, please.

7 In terms of physician recommendations, a  
8 great deal has been learned about this procedure. A  
9 great deal now can be recommended for physician  
10 training. We feel that Board certified interventional  
11 cardiologists are required, but there should be a  
12 commitment to perform no fewer than ten cases per  
13 year, with a referral base that is appropriate to  
14 assure that that kind of volume occurs at the  
15 institution.

16 A lecture format can occur on much of the  
17 data that we have demonstrated today, certainly with  
18 regards to the safety and complications, should be  
19 taught. Laser safety issues need to be taught, and  
20 the clinical results need to be demonstrated. Patient  
21 selection and avoidance of complications can occur in  
22 lecture format.

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1           In addition, because this device is a new  
2 device, some hands on is required, and we think that  
3 this can be accomplished with a procedural model. We  
4 think that the operators need to observe at least one  
5 or two clinical cases.

6           And then very importantly, the first two  
7 cases should be performed in conjunction with an  
8 experienced proctor, and I think this would be a very  
9 good and safe way to train new operators on this  
10 device.

11           Next slide.

12           So in conclusion, we think there is  
13 overriding benefit of decreased angina and related  
14 hospitalizations for these patients. There's a  
15 consistency of the PACIFIC and the BELIEF studies that  
16 established that the anginal improvement that we've  
17 seen in the PMR group is not primarily related to  
18 placebo effect.

19           There is a significant improvement in both  
20 the PACIFIC study and in the BELIEF study in anginal  
21 symptoms.

22           The procedural risks are well

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1 characterized. They're reasonable for this medically  
2 refractory treatment group, and this, in conclusion,  
3 is a less invasive approach than surgical TMR for  
4 patients who really have very limited other treatment  
5 options.

6 Thank you very much for your attention.

7 CHAIRPERSON TRACY: Does that complete  
8 your presentation? Okay.

9 We will take any brief clarifying  
10 questions at this point from the panel members.

11 DR. PINA: I have several questions,  
12 particularly for Dr. Whitlow who was presenting the  
13 data.

14 How is maximal medical therapy defined?

15 DR. WHITLOW: The patients had to be on at  
16 least two doses of a beta blocker, a nitrate or a  
17 calcium antagonist. Two of those three you had to be  
18 on maximally tolerated doses.

19 DR. PINA: Defined by blood pressure,  
20 heart rate?

21 DR. WHITLOW: Defined by the clinician,  
22 but, yes, I mean, blood pressure and heart rate were

1 the two parameters.

2 You know, nitrates, a lot of patients are  
3 intolerant to nitrates because of headaches. I  
4 suppose that would be another consideration, but for  
5 beta blockers and calcium antagonists, it would be  
6 blood pressure and heart rate.

7 DR. PINA: My next set of questions sort  
8 of relate to the exercise testing protocol. We didn't  
9 see the BELIEF data. Hopefully you have some of that  
10 data. Do you have the VO-2 and the RARs to document  
11 really either a near maximal stress test?

12 My experience has been that anginal  
13 patients never really get to a maximum point because  
14 they develop chest pain. Do you have EKG data? Do  
15 you have time to one millimeter ST segment depression?

16 This is very similar to the old anginal  
17 trials when we were looking at drugs for angina.

18 DR. WHITLOW: Yeah. Because the protocols  
19 were so different and because we haven't seen a lot of  
20 the data, Professor Nordrehaug maybe can answer your  
21 question. I can't answer it.

22 DR. PINA: This should be protocol

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1 independent. If you're doing the O<sub>2</sub>s it's protocol  
2 independent.

3 DR. WHITLOW: Right, but as far as the  
4 data goes maybe he could. These patients were  
5 exercised to exhaustion. I mean, that was by  
6 definition. I'm not sure that the O<sub>2</sub>s were  
7 appropriate.

8 DR. NORDREHAUG: I'm, again, Jan  
9 Nordrehaug. I thank you for letting me speak here.

10 I have no conflict of interest, no  
11 financial interest in the company. Reimbursement will  
12 be given for my tickets to come here today. That's  
13 all.

14 We had oxygen uptake in the two groups.  
15 That was similar. There was no difference between the  
16 groups. The RAR was 103 in both groups. So that is  
17 a similar exercise level. Time to chest pain was the  
18 same between the groups. I cannot remember which  
19 level at the moment, but there was no difference  
20 between the groups, and time to ST depression was the  
21 same. All patients had ST depression, and that was in  
22 the protocol.

1 DR. PINA: So they exercised through their  
2 angina to this maximal endpoint?

3 DR. NORDREHAUG: Well, 103 is probably  
4 submaximal.

5 DR. PINA: No, it is submaximal. So they  
6 stopped because of angina.

7 DR. NORDREHAUG: It could be 120; it could  
8 be 130, at the very maximum.

9 CHAIRPERSON TRACY: I think I'm going to  
10 break this off at this point to allow for lunch, and  
11 then we'll resume with the full panel discussion after  
12 lunch.

13 MS. MOYNAHAN: We'll meet back at 1:30?

14 CHAIRPERSON TRACY: Let's meet back at  
15 1:30.

16 (Whereupon, at 12:33 p.m., the panel  
17 meeting was recessed for lunch, to reconvene at 1:30  
18 p.m., the same day.)

AFTERNOON SESSION

(1:33 p.m.)

1  
2  
3 CHAIRPERSON TRACY: All right. At this  
4 point, the FDA, we will call on them for their  
5 presentation review of this PMA.

6 DR. BERMAN: Good afternoon. My name is  
7 Michael Berman. I am the FDA lead reviewer for this  
8 PMA supplement.

9 Next slide, please.

10 This is a list of the team members who  
11 were part of the review. If I've omitted any of the  
12 FDA folk or if I've given them improper credentials,  
13 I apologize.

14 Next please.

15 Let me remind you that this device  
16 consists of a laser console, an ECG monitor, and a  
17 delivery system. The laser console contains the  
18 laser, which is going to provide the energy for  
19 ablating the endocardium, and it contains also  
20 appropriate circuitry so that the laser will work  
21 properly.

22 The ECG monitor serves to trigger the

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1 laser so that it fires appropriately during cardiac  
2 systole. The delivery system consists of an aligning  
3 catheter and a laser catheter. The two are called  
4 axial, and the laser catheter contains an optical  
5 fiber. The laser console and the ECG monitor are both  
6 external to the patient. The delivery system is  
7 placed inside the patient.

8 Next please.

9 These are the preclinical concerns that  
10 the agency considers with such a device system.  
11 Basically we have concerns about the engineering, the  
12 biocompatibility and the sterility, and this is what  
13 we direct our review at.

14 Next, please.

15 Some of the engineering issues are  
16 electrical safety. This device plugs into the wall.  
17 It has electronics and electrical circuitry in it.  
18 The sponsor has tested this device to demonstrate  
19 compliance to EN-60601-1. This is a European norm.  
20 It is the equivalent of IEC-60601-1, which is an  
21 international standard which is recognized by the FDA.

22 The sponsor has performed the appropriate

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1 testing. They have provided the agency with  
2 documentation to support the testing. We have no  
3 concerns remaining about electrical safety.

4 EMC has electromagnetic compatibility.  
5 This device will be used in a cath. lab. There will  
6 be other electronic equipment working concurrently  
7 with this.

8 We need to know that this device does not  
9 produce electrical or electronic interference that  
10 will interfere with the operation of other equipment  
11 in the lab, and we need to know that the operation of  
12 other equipment will not interfere with the operation  
13 of this device.

14 So, again, they have tested to EN-60601-1-  
15 2. This is a collateral of 60601-1. Again, it is  
16 equivalent to the IEC standard, which is recognized by  
17 the FDA. The sponsor has done the appropriate testing  
18 for this device under its expected conditions of use.  
19 They have provided us with sufficient documentation to  
20 demonstrate that this device neither emits interfering  
21 radiation, nor is it susceptible to radiation in the  
22 environment.

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1           The device contains a laser, emits a  
2 certain amount of energy. The device, again, has been  
3 tested to an EN, a European norm. This is a  
4 particular standard within the 60601-1 family. The  
5 testing is appropriate. This is recognized by the  
6 agency that the sponsor has demonstrated laser safety.

7           Next, please.

8           The delivery system is a catheter, and  
9 there are mechanical issues involved with such a  
10 device. The sponsor has done the usual and customary  
11 cold bend and twist testing, which they have used  
12 limits specific to their device. They have  
13 satisfactorily demonstrated to us that the joints in  
14 the device will not come apart when the device is  
15 either inserted or withdrawn from the patient.

16           They have done bending to demonstrate that  
17 the device, especially at the tip, can be bent as  
18 appropriate during the procedure, and it will not  
19 fail, and they have demonstrated the device can be  
20 twisted without failing.

21           This device can be torqued. The laser  
22 catheter can be torqued or the optical fiber can be

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1 torqued within the laser catheter as part of the  
2 procedure, and they've done sufficient testing and  
3 provided us with documentation to demonstrate that all  
4 of the appropriate mechanical testing has been done,  
5 and the mechanical integrity of the delivery system  
6 has been demonstrated.

7 The laser console and the ECG use  
8 software. The software has been validated. There is  
9 no specific standard for that as yet. It has been  
10 validated appropriately to the performance  
11 specifications for the device.

12 The ECG monitor is a commercial device.  
13 It's clear to market under a 510(k). So it's been  
14 validated previous to this use.

15 The system has been tested for shipping so  
16 that it arrives alive at the hospital, and it's been  
17 tested according to an ASTM standard, which is  
18 appropriate for this use, and the device will, in  
19 fact, arrive alive.

20 Next please.

21 Because the delivery system is inserted in  
22 the patient, there will be blood and tissue contact

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1 short term. The procedure length is an hour probably  
2 at the outside.

3 The sponsor has tested the device, all of  
4 the patient contact parts of the catheter to ISO,  
5 which is International Standards Organization, 10993.  
6 This is the recognized standard for biocompatibility  
7 testing. All of the appropriate testing has been  
8 done. All of the data has been furnished to the  
9 agency. We have reviewed it. The device has been  
10 shown to be biocompatible when used as intended.

11 Next, please.

12 Because the device has patient contact, it  
13 needs to be sterile. It is shipped sterile by the  
14 sponsor. The catheter, the patient contact part is  
15 sterilized using ethylene oxide, which is a standard  
16 sterilant. It's done by a contract sterilizer.

17 We have documentation furnished by the  
18 sponsor to demonstrate that the residuals subsequent  
19 to ethylene oxide sterilization are less than the FDA  
20 recommended limits, and the sterilization process has  
21 been validated by an independent laboratory not  
22 connected with the sterilization facility, and it's

1       been tested according to that ANSI-AAMI spec., which  
2       is something that the FDA recognizes.

3               So the sponsor has addressed the sterili  
4       issues, and in with the sterili issues, the sponsor  
5       has also demonstrated a two-year shelf life for the  
6       sterilized components.

7               Next please.

8               A summary of the preclinical work for this  
9       PMA supplement, the sponsor has performed the  
10      appropriate preclinical testing. The test results  
11      have been provided to the agency. We have reviewed  
12      them. They are adequate. There are no remaining  
13      preclinical concerns at this time.

14              I'm going to turn the microphone over to  
15      Dr. Lesley Ewing, who will present the FDA clinical  
16      review, following which I will come back and address  
17      specific questions to the panel.

18              DR. EWING: Good afternoon.

19              Next slide, please.

20              As you've already heard, the sponsor has  
21      provided two clinical studies to support their PMA  
22      supplement. One is the larger study, PACIFIC, which

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1 is an open label, unblinded study, randomized control  
2 comparison of PMR and medical management. Belief was  
3 also provided and is a randomized double blind  
4 controlled study with a sham procedure control group.

5 Next slide.

6 In PACIFIC, there are 200 patients studied  
7 at 11 sites and randomized into PMR or medical  
8 treatment. All of the patients had Class III or Class  
9 IV of Canadian Cardiovascular Society angina score.  
10 Most of the patients, two-thirds of the patients were  
11 Class III; 38 patients were Class IV. They all had  
12 angina refractory to medical treatment. As you  
13 already heard, these are patients that do not have any  
14 other option for treatment, and they all had an area  
15 of myocardium with reversible ischemias documented by  
16 thallium testing.

17 Next slide, please.

18 The effective endpoints for the study were  
19 greater than or at least or greater than two class  
20 improvement in angina and improvement in exercise  
21 time. The angina assessment has previously been  
22 discussed, but all patients had a baseline assessment

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1 by the investigator at the site and some patients had  
2 an independent assessment of angina class at baseline,  
3 but that was begun after the study had already  
4 started.

5 All patients had a 12-month assessment of  
6 angina class, performed both independently and by an  
7 investigator at the end of the study.

8 A secondary endpoint for effectiveness in  
9 this study is quality of life measured by the Seattle  
10 Angina Questionnaire.

11 Next slide.

12 The inclusion criteria are as stated and  
13 have been previously discussed.

14 Next slide.

15 Exclusion criteria also are here, include  
16 a recent myocardial infarction, and the patients all  
17 had to have wall thickness at least eight millimeters  
18 in the PMR area. They were excluded if they could not  
19 perform an exercise test or they did not have angina  
20 during the exercise test.

21 Next slide.

22 This slide is difficult to see, especially

1 from the back of the room, but it outlines the  
2 accountability of the patients and basically shows  
3 that there are 200 patients randomized into treatment  
4 and control group. The treatment group was PMR, and  
5 the patients continued to be on maximum medical  
6 therapy, and the control group was on maximum medical  
7 therapy alone.

8           There were ten patients who received a  
9 reintervention in the study group or the treatment  
10 group, and 14 patients had a reintervention in the  
11 control group and the reintervention consisted of  
12 surgery, PTCA, or one patient had surgical laser  
13 procedure or TMR.

14           And there were nine patients that were  
15 withdrawals in the study group. The patients were  
16 assessed as has been previously described in the last  
17 observation carried forward, and the reintervention  
18 patients were carried into the analysis as were the  
19 withdrawal patients as their last measurement before  
20 their reintervention or withdrawal, and the patients  
21 who died in the study were measured as worst case, as  
22 has been previously discussed.

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1 Next slide.

2 This slide details the adverse events seen  
3 in PACIFIC as measured out to 12 months, and these  
4 have been previously described in much more detail  
5 than I will do here because it's been previously  
6 discussed.

7 This slide shows the adverse events with  
8 angina taken out of the table. So it is essentially  
9 the same data as was previously shown, and with angina  
10 removed, as angina is counted in the effectiveness  
11 criteria, the total adverse events in the treated  
12 versus the control group is higher.

13 When each individual serious adverse event  
14 is analyzed, the p value is not significant for each  
15 individual, but the total is.

16 As has been previously discussed, in the  
17 arrhythmia group, it includes three patients who are  
18 part to be paced. There are seven deaths in the PMR  
19 group versus two in the control, and the three  
20 perforations have been also previously discussed.

21 Next slide.

22 In the effectiveness results in PACIFIC,

1 in the group of patients that were assessed by the  
2 investigator both at baseline and at 12 months, 42  
3 percent versus eight percent in the control group; 42  
4 percent of the treated group versus eight percent in  
5 the control group achieved at least two class or  
6 greater angina improvement.

7 The numbers that we have in our slide for  
8 the independent assessment are slightly different  
9 because of a reanalysis by the sponsor, and they  
10 previously showed those numbers.

11 Next slide.

12 In the exercise tolerance improvement at  
13 12 months using a modified Bruce protocol, in the  
14 PACIFIC group when analyzed to see what percentage of  
15 patients achieved a clinically significant improvement  
16 over their baseline, a significant increase was seen  
17 in the treated versus the control group.

18 Next slide.

19 In the Seattle Angina Questionnaire  
20 improvement, as was previously discussed, there are  
21 five subscores in this questionnaire. The first four  
22 are shown in this slide. The fifth subscore is in the

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1 next slide, and when analyzed to see the percentage of  
2 patients that had a clinically significant improvement  
3 in SAQ score, these five subscores did show a  
4 clinically significant improvement, and the next slide  
5 shows that in the angina stability score, this is the  
6 subscore where greater than 50 is the score that shows  
7 that patients have an improvement in their angina.  
8 Fifty-four percent of the treated group versus 25 of  
9 the control group had improvement compared to  
10 baseline.

11 Next slide.

12 So in the second study that was provided,  
13 the BELIEF study is a randomized double blind study,  
14 as has been previously discussed, with the sham  
15 procedure control group. The assessors were blinded.  
16 The people who assessed the angina class were blinded  
17 to the treatment. The patients and the treating  
18 physician were blinded also.

19 There were 82 patient that were randomized  
20 in the study at two sites and followed for six months.  
21 Essentially the same inclusion and exclusion criteria  
22 specific and the device used is identical.

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1 Next slide.

2 The study endpoints are essentially the  
3 same, although the study was set up to show primary  
4 effectiveness endpoint of improvement of at least one  
5 angina class. We'll show the data that has been  
6 previously shown for two angina classes.

7 And the secondary study endpoints were  
8 exercise time using the CAEP protocol, and quality of  
9 life measured by the Seattle Angina Questionnaire.

10 Next slide.

11 And this slide also shows the progress of  
12 the patients though the study. Forty patients were  
13 treated and 42 patients had the sham procedure. There  
14 were not withdrawals, and two deaths seen in the  
15 control group, only no deaths in the treated group.

16 Next slide.

17 The patients with peri-procedure adverse  
18 events has been discussed, and in this group of  
19 patients in the first 30 days after the procedure  
20 there is essentially no difference in adverse events,  
21 with one death seen in the control group -- next slide  
22 -- and in the adverse events follow-up up to six

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1 months, numerically there's essentially no difference  
2 between the treated and the control group.

3 Next slide.

4 The total number of patients with serious  
5 adverse events in the treated group in BELIEF compared  
6 to the control group, numerically there's not a  
7 significant difference. There was one perforation  
8 requiring drainage in the patients treated with PMR  
9 and no acute myocardial infarction in either group.

10 Next slide.

11 In showing at least two classes of angina  
12 improvement at six months, the PMR treated group had  
13 41 percent with two class or more angina improvement  
14 versus 13 percent in the control group.

15 Next slide.

16 The SAQ results in BELIEF were not  
17 analyzed to show percentage of patients that had a  
18 clinically significant improvement, but when you look  
19 at the mean and standard deviation of the scores,  
20 there was not a significant improvement, although  
21 angina stability analyzed this way did show an  
22 improvement compared to control.

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1 Next slide.

2 In the exercise results seen in BELIEF  
3 using the CAEP protocol, the information that we have  
4 is also the mean and standard deviation of the times  
5 that were achieved, and there were not a significant  
6 difference in the increase in exercise duration seen  
7 between the control and the treated group.

8 In the patient population description  
9 within the study and compared to each study compared  
10 to each other, for the full details there is a table  
11 that's on page 17 in the clinical review, in the Panel  
12 pack.

13 But to summarize the patient population  
14 differences between the studies. In PACIFIC there are  
15 more patients that had diabetes. More patients were  
16 hypertensive. More had Class IV angina at baseline,  
17 although there was only 38 patients in each group in  
18 PACIFIC that had Class IV angina. So it was a third  
19 of the patient population even in PACIFIC.

20 More patients in PACIFIC had lower SAQ  
21 scores other than angina frequency, and also in BELIEF  
22 more patients were on lipid lowering medicines and

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1 more were current smokers.

2 So in summary, the cardiac adverse event  
3 rate minus angina in treated patients versus controls  
4 was higher in PACIFIC, but not in BELIEF. In both  
5 PACIFIC and BELIEF, a significant percentage of the  
6 treated patients had an improvement greater than or  
7 equal to two angina classes compared with control  
8 patients.

9 In PACIFIC, there's an improvement in SAQ  
10 scores from baseline in treated patients compared with  
11 medical management, which is not seen in BELIEF except  
12 in one subscore. Exercise duration improved the PMR  
13 in PACIFIC, but not in BELIEF, but the studies use  
14 different exercise protocols.

15 And in both studies some patients improve  
16 their angina scores without PMR treatment.

17 And I passed out to all of you just a  
18 description of the modified Bruce protocol and the  
19 CAEP protocol, and that's what these slides show, just  
20 in case you were interested in it.

21 Dr. Berman will go over the questions for  
22 the panel.

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1 DR. BERMAN: Okay. After the FDA  
2 presentation finishes, which it will after these  
3 questions, the panel will deliberate on this PMA  
4 supplement.

5 Panel, these are questions that were in  
6 your Panel pack. These are things that we ask that  
7 you please keep in mind during your deliberations, and  
8 at the end hopefully you will provide us with answers  
9 to these questions.

10 What I will present now, there have been  
11 some wording changes for clarity, and so the questions  
12 would fit on a slide, but the content has not changed.

13 Next please.

14 This is background for Question 1. Tables  
15 3 to 5 in the FDA clinical review in Tab 3 on pages 7  
16 and 8 of that review list adverse events associated  
17 with PACIFIC. Table 18 in the FDA clinical review  
18 lists adverse events associated with BELIEF.

19 Please note that PACIFIC had a 12-month  
20 follow-up versus six-month follow-up for BELIEF. Both  
21 of those times were designed in, but they're  
22 different.

1                   So Question 1(a): the total of serious  
2 arrhythmias, heart failure, myocardial infarction,  
3 thromboembolic events and deaths in PACIFIC was higher  
4 for the treated and for the controlled patients. In  
5 BELIEF there was only one such adverse event in the  
6 treated patients. We would like you please to discuss  
7 or consider the implications of these findings for the  
8 assessment of safety for this device system.

9                   Next.

10                   1(b): we ask you to please discuss and  
11 consider the clinical importance of the adverse events  
12 observed in these patients.

13                   Next.

14                   Question 2: the primary effectiveness  
15 endpoint in both studies was an improvement in angina  
16 as measured by the Canadian Cardiovascular Society  
17 anginal score. The co-primary endpoint in PACIFIC was  
18 an improvement in exercise time. A secondary endpoint  
19 in both studies was an improvement in SAQ.

20                   Considering that, Question 2(a): in  
21 PACIFIC the CCSAS improvement was assessed by the  
22 investigators, although some patients had a blinded

1 assessment both at baseline and at 12 months. All  
2 CCSAS assessments in BELIEF were blinded. Please  
3 discuss the possible impact of investigative bias on  
4 the evaluation of improvement in CCSAS.

5 Next please.

6 The percent of patients meeting the  
7 criteria for improvement in CCSAS -- that's two  
8 classes or more improvement -- for SAQ and for  
9 exercise time were all significantly greater for the  
10 treated than for the controlled patients in PACIFIC.  
11 In BELIEF, the treated patients did out perform the  
12 controls for an angina score, but not for SAQ and not  
13 for exercise time. We ask that you consider and  
14 discuss this apparent difference.

15 The CCSAS score and the SAQ score are both  
16 ways of assessing aspects of angina. In PACIFIC, a  
17 higher percentage of treated patients as compared to  
18 controls showed improvement in CCSAS and in SAQ. In  
19 the BELIEF study this was true for CCSAS, but not for  
20 SAQ. We will ask that you please consider and discuss  
21 this apparent difference.

22 Question 3: patients in both PACIFIC and

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1 BELIEF had severe refractory angina. However, some  
2 patients in the control group in each study met the  
3 criteria for improvement of angina. Please comment on  
4 this improvement in the control patients as it relates  
5 to the effectiveness of PMR as a treatment for angina.

6 Next.

7 There are three statistical analyses  
8 provided for PACIFIC: the last observation carried  
9 forward, all survivors, and all survivors without  
10 reintervention. We ask that you please comment on the  
11 inclusion or exclusion of patients who received  
12 reintervention subsequent to enrollment, and should  
13 those patients be counted as failures of PMR if the  
14 patient had been treated with PMR?

15 Next.

16 We ask that you please discuss and  
17 consider whether the data in this PMA supplement  
18 provide reasonable assurance of effectiveness for this  
19 device in the patient population studied.

20 We are required to evaluate the device  
21 labeling to determine whether it properly indicates  
22 which patients are appropriate for treatment,

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1 identifies potential adverse events with use of the  
2 device, and explains how the product should be used to  
3 maximize benefits and minimize adverse events.

4 If you recommend approval of this PMA  
5 supplement, please address the following labeling  
6 questions. This is a copy word for word, if I typed  
7 it right, from the Panel pack, Tab 2, page 2. This is  
8 the sponsor's proposal for labeling.

9 "The Eclipse PMR system is indicated for  
10 use in percutaneous myocardial revascularization  
11 procedures to decrease angina and increase exercise  
12 tolerance in patients with chronic angina, CCSAS III  
13 to IV, which is refractory to medical treatment and  
14 secondary to objectively demonstrated coronary artery  
15 disease, and with a region of the myocardium with  
16 reversible ischemia, not an interval to direct  
17 coronary revascularization."

18 Keeping that in mind, Question 6(a): the  
19 indications portion of the labeling states that this  
20 device is indicated to increase exercise tolerance.  
21 Please comment on whether the information presented  
22 today provides adequate justification for this claim.

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1 Next.

2 Please provide any other recommendations  
3 or comments regarding the indication statements or any  
4 other aspects of the device system labeling for this  
5 device.

6 Question 7: please identify and discuss  
7 the items that you believe should be contained in a  
8 physician's training program for this device.

9 Question 8: this is looking towards the  
10 future. Is additional clinical follow-up of the TMA  
11 cohort needed to evaluate the long-term effects of  
12 PMR?

13 And (b): please discuss the possible use  
14 of PMR in combination with other modalities. Would  
15 additional clinical trials be appropriate?

16 CHAIRPERSON TRACY: Thank you.

17 Any brief questions for clarification?

18 (No response.)

19 CHAIRPERSON TRACY: If not, then I'll ask  
20 Dr. Ferguson to give his review and begin asking  
21 question of the sponsor.

22 DR. FERGUSON: Again, my name is Thomas

1 Ferguson. I'm a cardio-thoracic surgeon from  
2 Washington University, St. Louis, just to refresh your  
3 memory.

4 Dr. Whitlow, first, I want to say that  
5 that was a remarkable -- where are you there? There  
6 he is -- a remarkably lucid presentation, and we want  
7 to thank you for that.

8 I've had from the surgical side a great  
9 deal of experience with the TMR, and it seems to me  
10 that we always need to look at what we're doing to the  
11 patient with respect to what results we're obtaining.

12 Now, my problem is not with any of the  
13 issues you brought up. My problem is with the fact  
14 that when TMR was approved in its present state, the  
15 number of usages of the laser device was anywhere from  
16 20 to 40. Most people, I think, if I quote the  
17 literature correctly, do at least 30 penetrations.

18 Those penetrations are full transmural  
19 penetrations, have to be to be registered as  
20 effective.

21 The system we have here has a mean, as I  
22 understand, again, the data correctly, has a mean of

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1 16 penetrations. The penetrations are five  
2 millimeters in depth. Five millimeters is not very  
3 deep.

4 The issue, and I'm not being facetious  
5 here at all; please believe me. The issue is here why  
6 does the data with fewer penetrations, less deep  
7 penetrations give the same results that you get with  
8 TMR, or put it another way: what is the fewest number  
9 of penetrations that you have to have for this system  
10 to be effective, which gets to one of my questions to  
11 you?

12 Has that issue been looked at? Have you  
13 looked at how well or how poorly the patients did  
14 based on the number of interventions that they had at  
15 the time?

16 I know there are a lot of factors that  
17 would influence this. I understand that, but the fact  
18 of the matter is we have to have some kind of baseline  
19 judgment of how much or how little we need to do to  
20 the patient to change their lifestyle and their  
21 angina.

22 DR. WHITLOW: Thank you very much for that

1 question.

2           It's true that the surgery technique, the  
3 TMR and PMR, have very different channels, and that's  
4 by design. With TMR it is visual. You can see the  
5 channels you put in. It leaves a mark. So you don't  
6 overlap the channels.

7           This technique that we described is guided  
8 by fluoroscopy to the area that the investigator  
9 believes is ischemic as judged from a thallium scan.  
10 I mean that's his target, as well as from coronary  
11 arteriograms.

12           There's a definite down side, we believe,  
13 to putting two channels right on top of each other.  
14 If you had a five millimeter hole to begin with and  
15 then you slip the laser catheter into that hole, you  
16 might create a hole that goes all the way through the  
17 myocardium and causes perforation.

18           So we intentionally had fewer channels  
19 with PMR to maximize the safety. That was the  
20 theoretical reason that there are fewer channels.

21           When we looked at the data to look at  
22 whether or not the number of channels predicted who

1 would improve and who would not, there was no  
2 relationship at all that could be demonstrated.

3 There aren't that many channels. I mean  
4 16, as you said, was the mean number of channels, and  
5 it didn't seem to make any difference whether you got  
6 six or seven, which was --

7 DR. FERGUSON: Some of the patients had  
8 six penetrations only.

9 DR. WHITLOW: Yes, that's correct. That's  
10 correct.

11 DR. FERGUSON: And they did just as well  
12 as the others?

13 DR. WHITLOW: Some of them did well.

14 Now, you know, we don't understand well  
15 enough to answer your question completely the  
16 mechanism of improvement perhaps. We don't know how  
17 many channels you have to put in, but in this group,  
18 we know that 42 percent of the patients got two  
19 functional classes better.

20 In Professor Nordrehaug's study, in  
21 BELIEF, they did put in a few more channels and took  
22 an extra five or ten minutes in order to do that. It

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1 shows a similar amount of angina relief.

2                   So we can't say that if we put in double  
3 the number of channels would we get better angina  
4 relief. We don't know that. Perhaps that would be  
5 worth some more study later, but we simply can't  
6 answer the question from the data we have.

7                   DR. FERGUSON: That's one of the things  
8 that puzzles me about this, and it gets back to the  
9 fact that we don't really know what the mechanisms  
10 are. I understand that, too.

11                   And pursuant to that second comment, I am  
12 a little bit upset with the lack of objective data on  
13 the patients that died in terms of what you found at  
14 autopsy, and I'd like to explore that just a bit with  
15 you.

16                   Was a concerted effort made to look at  
17 this? I saw no histologic studies, if I read the  
18 material correctly.

19                   DR. WHITLOW: Yes. There was only one  
20 patient in the group that had an autopsy that we got  
21 data on, and that was the one that I did show just a  
22 gross description. As far as I can tell, that

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1 pathologist did not look for angiogenesis and other  
2 factors. He just looked for perforation and adverse  
3 events. It was one month, 29 days. He died 29 days  
4 after treatment, but there was no intensive look  
5 through there for angiogenesis as far as I could tell.  
6 I read the autopsy report, and there was nothing  
7 mentioned about it, other than some scarring was seen.

8 DR. FERGUSON: Thank you very much.

9 Dr. Tracy.

10 CHAIRPERSON TRACY: Thank you.

11 Dr. Domanski, any questions?

12 DR. DOMANSKI: The thing that occurred to  
13 me in looking at these data, you know, again, this  
14 business of pushing mechanisms is, you know, a  
15 longstanding discussion, not one we're going to  
16 resolve here, and probably shouldn't be pushed very  
17 hard for this PMA.

18 But I guess I was intrigued by the BELIEF  
19 study -- I'm sorry -- in the PACIFIC study by the  
20 mortality, and I'd like to go back to that. It's one  
21 of your slides, and I pulled it out.

22 You know, it's true that there isn't a

1 statistically significant difference, but you know, it  
2 looks like there's a trend, an unfavorable one, in  
3 terms of mortality, and I wonder if you could discuss  
4 with us the power to see a difference in mortality in  
5 this study, you know, which has a pretty strong trend.

6 DR. WHITLOW: Certainly the number of  
7 deaths in the PMR group is concerning, and in order to  
8 put that into some greater perspective, perhaps we  
9 could show the deaths. We've got a slide that shows  
10 the deaths in the PMR and TMR studies in the control  
11 group or the treated group.

12 Certainly in the PACIFIC study seven  
13 versus two should raise some concern. It does raise  
14 some concern, but it is a limited sample size. I  
15 mean, the study was powered to look for angina  
16 improvement in exercise time and not for death  
17 specifically. So I think we need to look at some  
18 other studies and look at all the data maybe to help  
19 with that perspective.

20 DR. DOMANSKI: Yeah, but I'm not all that  
21 smart about these sorts of things. So I guess maybe  
22 I need to -- you know, but I'd like to know what the

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1 power was to see the mortality difference that  
2 occurred, the power to see at the .05 level because I  
3 suspect the power is very, very low in this, very low  
4 in this study, and I think that those numbers do raise  
5 some concern because I think it appears that there is  
6 angina relief by whatever mechanism, and the question  
7 is are we detriminting these people in terms of  
8 safety.

9 DR. O'NEILL: Yeah, Mike. I don't think  
10 that any of these studies could really be shown to  
11 show a mortality difference. I mean, fortunately  
12 mortality is a very low --

13 DR. DOMANSKI: That's not the question  
14 though, Bill. I'm sorry, but I guess I'm concerned  
15 just as a safety issue that there's a difference that  
16 shows a strong trend. Admittedly it does not reach  
17 the p equal .05 level, but it does reach a p equal .09  
18 level in a study that would be grossly under powered  
19 to show a mortality difference.

20 And I'd like to pursue that a little bit  
21 and understand what the power was, even though I know  
22 the study was powered for its primary endpoint rather

1 than this one.

2 I mean the statistician probably knows  
3 that, don't they?

4 I'm not suggesting you do a mortality  
5 study. I'm just seeing safety data that looks like a  
6 strong trend towards increased mortality in a study  
7 that, in fact, is under powered to show a mortality  
8 difference whether it existed or not.

9 DR. O'NEILL: Again, in very serious  
10 adverse events, whether it's intracranial bleeding  
11 with thrombolytic therapy or any other device, I think  
12 that there always has to be a concern, and a way of  
13 looking at it would be looking at larger numbers to  
14 see whether or not there is a disturbing trend in all  
15 studies that would end up to being a very significant  
16 safety difference.

17 I think that in a 200 patient trial, you  
18 can be very unlucky, or there could be a valid  
19 concern. That's one reason why large numbers of  
20 patients are going to have to be looked at. When you  
21 look at the combination of the PACIFIC, the TMR-10,  
22 and the BELIEF study, there really isn't a trend

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1 towards a mortality difference in the first year of  
2 follow-up.

3 DR. DOMANSKI: I guess I wouldn't combine  
4 those studies a priori. I'd just look at the one I've  
5 got in front of me, and I suppose I think that that's  
6 of some concern. I think people need to at least give  
7 it some thought, and I take it that you're not going  
8 to give me a power.

9 DR. WHITLOW: No, we just looked up the  
10 power.

11 Actually we don't have the power yet. The  
12 power is here. So with this sample size, there was  
13 only a 27 percent power to detect a difference in  
14 mortality.

15 DR. DOMANSKI: But what worries me is not  
16 that you were --

17 DR. WITTES: Excuse me. What magnitude of  
18 difference?

19 DR. O'NEILL: What magnitude of  
20 difference? Seven percent versus two percent.

21 DR. DOMANSKI: So, I mean, they have  
22 essentially no power to see even a massive difference

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1 in mortality, and my concern is not so much that they  
2 were unlucky and got a trend. My concern is that they  
3 may have been lucky and not gotten more of one.

4 DR. WHITLOW: Well, I think we have to  
5 look outside the study to help see whether or not this  
6 is a matter of chance.

7 DR. DOMANSKI: Sure.

8 DR. WHITLOW: We made an awful lot of  
9 statistical comparisons for a small number of events,  
10 and you're going to see some by way of chance.

11 DR. DOMANSKI: Sure, sure.

12 DR. WHITLOW: You're going to see some  
13 things that look funny. So I think it is perfectly  
14 valid to look at the BELIEF study where there were two  
15 deaths in the sham control group and none -- and  
16 that's over one year, and actually there were a few  
17 more deaths in the sham control that we know about.  
18 The one-year data are not complete.

19 But no one to this point has died in the  
20 treated group in the BELIEF study, but it's something  
21 that's important.

22 CHAIRPERSON TRACY: Mike, I think Dr.

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1 Wittes has a clarifying question or comment.

2 DR. WITTES: Well, I don't know that it's  
3 clarifying, but it's related.

4 I think it's very hard to look at  
5 individual serious adverse in a study that's this  
6 small, but what seems to jump out is if we look at the  
7 slide that you showed us of the total number of  
8 serious adverse events, removing those that are  
9 specifically angina related, the split we saw was 45  
10 to 16. Now, I suspect that's 45 events and 16 event,  
11 not 45 people and 16 people, but I think that's what  
12 we should be looking at.

13 And then that feeds into the question  
14 about mortality, and I think the mortality is the  
15 strongest signal, but the sample size is too small.  
16 So do you have that number?

17 DR. O'NEILL: Well, again, I guess we  
18 would raise a little bit of an objection about  
19 removing refractory angina that required the patients  
20 to be rehospitalized as a serious adverse event. We  
21 think that that is a very serious adverse event.

22 Remember these patients are very

1 symptomatic, and they have such severe debilitating  
2 symptoms that they have to be hospitalized, again,  
3 primarily for use of intravenous nitroglycerine. So,  
4 I mean, that is a serious adverse event that should be  
5 reported in the analysis.

6 DR. WHITLOW: And it was defined in the  
7 protocol that that would be analyzed as a serious  
8 adverse event. The FDA reviewed that before and  
9 agreed with that.

10 DR. DOMANSKI: Yeah, they may have  
11 reviewed it, but I'm not so sure that when it comes to  
12 safety that that is a reasonable, you know, serious  
13 adverse event. Perhaps in terms of how well your  
14 procedure worked to make people feel better, but not  
15 in term, I think, of the safety.

16 So I think the question she asks is  
17 probably a pretty reasonable one. It would be  
18 interesting to hear the answer.

19 DR. WHITLOW: I think the data, Joe, that  
20 the FDA slide presented, was that per patient or was  
21 that per event? Do you remember? It was 45 versus  
22 19. I just don't remember.

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1 DR. EWING: The information is per  
2 patient, patient number.

3 DR. WITTES: Are you sure? I can't  
4 believe that. At the bottom, that bottom line is  
5 number of patients?

6 DR. EWING: The bottom line is not.

7 DR. WITTES: I think we need that number.

8 (Pause in proceedings.)

9 DR. WHITLOW: So it's our consensus  
10 amongst the doctors that helped present this data that  
11 we believe that hospitalization for angina is a  
12 serious adverse event, and if you start cutting up the  
13 adverse events to fit a purpose, you can probably come  
14 up with other things also, but you're having to really  
15 change the design of the study for analysis to do  
16 that.

17 DR. DOMANSKI: That might not be a bad  
18 idea.

19 DR. WHITLOW: Well, you can do it. I  
20 mean, it's your alternative.

21 I think you also have to consider that  
22 these patients have no other alternative, as well,

1 other than TMR, and TMR, perhaps we should look at the  
2 risk of TMR versus the risk of PMR. If we could  
3 perhaps show that slide then.

4 DR. WITTES: Well, can we just make a  
5 clarification?

6 DR. WHITLOW: Yes.

7 DR. WITTES: On this slide where it says  
8 45 to 16, I'm interpreting that as 45 is the sum of  
9 PMR and 16 is the sum of control. What I'm asking is  
10 a very simple question. If you ask what is the total  
11 number of people who have one of those above events,  
12 all I'm asking for is those two numbers, the numbers  
13 at the bottom, not the number of events; the number of  
14 people.

15 MS. MOYNAHAN: Can I ask the sponsor to  
16 please introduce themselves because the  
17 transcriptionist can't see you from there.

18 DR. WHITLOW: Yeah, at this end of the  
19 table, it's Dr. Knopf, Dr. Nordrehaug, Dr. Whitlow,  
20 Dr. O'Neill, Dr. Schaer.

21 Yeah, in this slide, I agree with you. If  
22 you add up the numbers, those are the total number of

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1 events. That's not patients with events.

2 The total number of patients would be 37  
3 versus 14.

4 DR. DOMANSKI: You know, I would also  
5 hasten to add that the point is an important one, that  
6 if you're dealing with people who have no alternative  
7 in terms of their lifestyle, then you may be willing  
8 to accept more complications to get people some  
9 relief. So I'm not offering it as a deal killer or  
10 anything. I'm just trying to hone in and make sure I  
11 understand the safety side of it. It's not to bury a  
12 spear under anything. I'm just trying to understand  
13 it.

14 DR. WHITLOW: If we could then show the  
15 data of TMR, the adverse events of TMR just to give  
16 you some background compared with the data from the  
17 PACIFIC trial.

18 These are peri-procedural adverse events  
19 out to 30 days. Is that the one we're going to show?

20 You can see that death in the TMR study,  
21 death 13 percent peri-procedural versus seven percent.  
22 So this is one year data. I'm sorry. It is one-year

1 data.

2 Arrhythmia is 23 percent versus 11. Heart  
3 failure, five versus eight. Myocardial infarction, 14  
4 percent versus 11 percent, and stroke was not  
5 specifically collected after the hospitalization in  
6 the TMR study. So we can't comment on that, but five  
7 percent in PMR.

8 So the alternative certainly has a greater  
9 morbidity and mortality than the PMR.

10 DR. PINA: Could I ask a point of  
11 clarification on here, Dr. Tracy?

12 CHAIRPERSON TRACY: Yes.

13 DR. PINA: What was the ejection fraction  
14 of the TMR group? We heard that the PMR group has an  
15 ejection fraction pretty high.

16 DR. WHITLOW: Yes, 51 percent, and TMR --

17 DR. PINA: Right. What was it in TMR?

18 DR. WHITLOW: TMR, it was 45 percent.

19 DR. DOMANSKI: All right. Well, I have  
20 another question. I think this more underscores the  
21 need to make sure the patients really are medically  
22 refractory before you start the procedure, but it's

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1 probably not a point that anyone would argue with.

2 CHAIRPERSON TRACY: Dr. Krucoff.

3 DR. KRUCOFF: I certainly want to echo the  
4 quality of the sites who have participated in these  
5 investigations and the investigators here today  
6 presenting the data. It's noteworthy.

7 I think, in part, that is a reflection of  
8 just the level of mystery that this patient population  
9 can entertain, but I do want to sort of hold you guys'  
10 feet to the fire a little bit because to me were roles  
11 reversed, I think the main agenda that I would have  
12 liked Pat and Bill, in particular, but all of you to  
13 do is to help us understand a little bit more the  
14 depths of some of this information rather than let the  
15 enthusiasm and the passion for trying to find a way to  
16 help these patients without getting surgical involved  
17 in the mix.

18 In particular, I think in the absence of  
19 understanding the mechanisms of this at all, I think  
20 some of Dr. Ferguson's questions to me are very  
21 salient, and if we're going to look at the morbidity  
22 issues with TMR versus PMR, I would like to have done

1 that in the context of a trial that looked at TMR  
2 versus PMR.

3 The ability to put 30 or 40 transmural  
4 channels in a very discrete geographic pattern under  
5 an open surgical opportunity in a non-anti-coagulated  
6 patient to me is potentially a source of palliation  
7 that mechanistically could be very different than the  
8 fluoroscopic exploration of on average 16 sites, five  
9 millimeter depth in an anti-coagulated patient through  
10 a ten French or nine French access site.

11 So I would have liked to have heard a  
12 little bit more if we're going to compare morbidities  
13 about a study that would have compared the therapeutic  
14 efficacy of an unknown mechanism in this patient  
15 population, and that's not what we're looking at in  
16 either PACIFIC or BELIEF.

17 These are patients who are randomized  
18 against medical therapy, and with medical therapy, I  
19 think that the burden of SAEs is a real one, and just  
20 to come back briefly to the question, can one of you  
21 guys tell me if I'm wrong? To me the angina relief  
22 endpoint was counted as an efficacy endpoint. Is that

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1 not correct?

2 DR. WHITLOW: The two endpoints are  
3 different. Angina relief was counted as an efficacy  
4 endpoint, absolutely, but hospitalization for angina,  
5 for medically refractory angina requiring  
6 hospitalization, was the serious adverse event that we  
7 showed.

8 DR. KRUCOFF: Okay.

9 DR. WHITLOW: So two different endpoints.

10 DR. KRUCOFF: I'm definitely on the side  
11 of saying you can have it one way or the other, but  
12 what you're trying to do is both, and that's probably  
13 not a smart way to do it for us to understand the  
14 impact on patients, and I think if angina relief is an  
15 efficacy endpoint, then the SAEs that we're looking at  
16 probably are more accurate as the list minus  
17 rehospitalization for angina. That's just my  
18 particular interpretation.

19 The other things that get me a little bit,  
20 when you talk about BELIEF, about blinding the  
21 operator, as I've seen and touched this gadget, the  
22 handle of the gadget lights up when laser energy is

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1 delivered. Was that different in the overseas  
2 experience or was that covered up or blinded?

3 That's not really mentioned. If you don't  
4 connect it to the laser source, does the operator not  
5 see the flashing light at the end of the catheter  
6 head?

7 DR. SCHAER: If I can just address that  
8 comment, my name is Gary Schaer. I have no financial  
9 or equity stake in this company. I'm just having my  
10 expenses covered.

11 But, Mitch, what you're getting at there  
12 is with the Axcis system, there is no feedback to the  
13 operator that there's any laser energy going through  
14 the catheter. The catheter is not transparent in  
15 terms of laser.

16 I think you may be considering the Eclipse  
17 system, where the TMR system --

18 DR. KRUCOFF: So that system. Okay.

19 DR. SCHAER: So there are two separate  
20 systems.

21 DR. KRUCOFF: And secondly, in maybe the  
22 older system, please tell me if it's different. When

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1 you deliver laser energy to the ventricle there, PPCs,  
2 is that not visible?

3 DR. KNOPF: Right. Mitch, this is Bill  
4 Knopf, and I also have no equity interest in the  
5 company except for the expenses paid for this trip.

6 Again, this is a gated system. So with  
7 the cardiogenesis system, you did not elicit PVCs when  
8 you fired this laser energy source, unlike the Eclipse  
9 older system which was not gated, and you did indeed.

10 DR. KRUCOFF: So you really could blind  
11 the operator.

12 DR. KNOPF: Correct.

13 DR. KRUCOFF: Thank you.

14 DR. O'NEILL: Can I go back to your  
15 questions, I guess? I'm not sure if we're going to  
16 come to a conclusion, but I want to make sure that  
17 perhaps the characterization of angina is incorrect in  
18 the serious adverse events. It's not just the  
19 patients are having symptoms. It's that they are so  
20 severe that they are requiring repeat hospitalization  
21 primarily for intravenous nitroglycerine  
22 administration.

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1           Now, that could occur at any time from  
2 discharge to the follow-up, and so if they were  
3 rehospitalized, say, at a month and then six or seven  
4 months later when they were called their anginal  
5 classification was assessed.

6           You aren't double counting the same thing.  
7 They really are truly different things. The efficacy  
8 is anginal status at the time of follow-up, but if  
9 they've had an event between them, that's counted both  
10 for the medical treatment group and for the PTMR  
11 group.

12           So I think there are slight differences.

13           In terms of the surgical technique, we're  
14 training the operators basically to go in and look at  
15 the size. I mean, many patients have very large  
16 anterior lateral wall of ischemia that require large  
17 numbers of laser channels in order to cover the target  
18 area. Typically we're asking them to go down to the  
19 apex, pull back to four or five laser channels, then  
20 go back down, redirect, try to get at least 12 to 16  
21 channels into the patient.

22           So some of the patients because of the

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1 size of the ventricle and the myocardium that's  
2 jeopardized don't really -- you really can't safely do  
3 that without assuming that there's overlap.

4 So although it sounds empirical, there is  
5 some format involved. In addition to that, during the  
6 procedure itself, we actually are using maps to try to  
7 overlap and really try to characterize the location of  
8 the numbers of channels that we're given.

9 So there is with biplane angiography, with  
10 the use of fluoroscopy, with the use of masking, you  
11 really can relatively carefully tell the areas where  
12 you're treating with the laser, and we are trying to  
13 get a fair number of channels placed.

14 With more experience, such as with Dr.  
15 Nordrehaug's data, more channels are being applied,  
16 but I think at the start of this procedure, people  
17 were very concerned about overlapping and the risk  
18 that if you created channels too closely, you might  
19 perforate.

20 DR. WHITLOW: Just to go to the mechanism  
21 idea, the only mechanism that was examined in these  
22 two studies was placebo, the effect of the sham

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1 controlled placebo, and we felt that that was  
2 necessary in order to try to get some kind of a  
3 feeling for whether or not the serious adverse events  
4 could be worth it.

5 And I think what the BELIEF study showed  
6 pretty clearly is that the relief of angina is  
7 dramatically better than one gets with a placebo sham  
8 control.

9 It doesn't tell you whether it is  
10 angiogenesis or denervation or any of the other  
11 mechanisms, and now that we know that there is  
12 compared to placebo a big effect, then perhaps some  
13 more can be done to elucidate the mechanisms, but we  
14 didn't plan on doing that with these trials.

15 DR. KRUCOFF: Well, all I'm trying to say  
16 is the other way around. In the absence of  
17 understanding the mechanism, I think our obligation in  
18 applying this to patients is to be very meticulous  
19 about safety and efficacy data to bring these gadgets  
20 to market.

21 And there my point on TMR, Bill, is it's  
22 very clear this is not too different from coronary

1 revascularization. In the surgical environment, you  
2 have a more controlled environment, but you pay a  
3 price in doing the procedure in an open chest.

4 The obligation then is to use that  
5 morbidity comparison with the efficacy comparison  
6 between surgery and percutaneous techniques, and I  
7 think it's no different here.

8 If we're going to justify the SAEs that  
9 we're seeing with the percutaneous approach by saying  
10 it's about the same as or better than a surgical  
11 approach, then we should be looking at the efficacy  
12 between the surgical approach and we're not. We're  
13 looking in both of these trials at the efficacy  
14 between a medical approach and this percutaneous  
15 approach.

16 And at that level, I think we have to be  
17 honest and say that's also then the comparison of  
18 adverse events or the results of doing a procedure  
19 that have to be the locus of comparison, and we just  
20 need to keep those separate, again, particularly in  
21 the absence of a mechanism.

22 And lastly, I think the placebo issue here

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1 is a huge one, and with all respect and everything  
2 else, I disagree with you that these two studies  
3 resolve that. In fact, your own slide, looking at  
4 angina improvement at six months between BELIEF and  
5 PACIFIC, to at least one observer could be taken as  
6 actually a measure of the degree of the placebo  
7 effect, both positive and negative.

8 So as you see in Pacific with unblinded  
9 patients, 51 percent improvement compared to BELIEF,  
10 41 percent improvement in the treatment group. That's  
11 a 20 percent difference that might just result from  
12 the placebo effect of the patients in PACIFIC knowing  
13 that they got therapy.

14 On the flip side, if you were to in your  
15 own slide see the six percent in PACIFIC who did not  
16 get treated who improved versus the 13 percent in  
17 BELIEF who didn't know what they go who improved, you  
18 could say that's a 50 percent difference just by at  
19 least one possible mechanism being that the patients  
20 in PACIFIC knew what they go, could be either  
21 disappointed that they didn't get laser or could be  
22 excited that they did.

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1           So I think the placebo effect here is a  
2           very open problem, and unfortunately from the trial  
3           design where the main pivotal study was not blinded,  
4           you have both the positive and the negative placebo  
5           effect. You have the patients who got laser. Laser  
6           is not radiation. It's very sexy. Patients come in  
7           and they ask for it. They like it. It sounds good.

8           If they got it, I think the motivating  
9           factor there as a positive placebo effect needs to  
10          really be looked at, and I don't think that it was.

11          The flip side, patients who didn't get it  
12          and how demoralizing that was and how disenchanting  
13          that was after being consented that you're suffering  
14          beyond all current technology, so we're going to put  
15          you in this randomized clinical trial looking at  
16          laser, but you randomized to medicine. The negative  
17          placebo effect there is equally probably profound.

18          When you blind both in BELIEF, it looks  
19          like that's, in fact, measurable just by your own  
20          primary endpoints and very significant, and that in  
21          light of the morbidity of putting a ten French system  
22          in gets to be a very hazy area, and I wish you guys

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1 could have spent some more time helping us sort some  
2 of that out.

3 In the BELIEF study, as well, I think the  
4 reality is to do a sham procedure, you're still  
5 putting in a ten French or a nine French guide.  
6 You're still taking a catheter and poking it around  
7 inside of the ventricle. So it's silly to me to  
8 divide up vascular complications between the sham  
9 group and the treatment group when you're putting a  
10 ten French guide.

11 I mean, those vascular complications  
12 should be pooled, not divided, if we're going to  
13 understand relative to a medical therapy strategy what  
14 the potential down side of these technologies are.

15 So that's --

16 DR. WHITLOW: We agree with you that the  
17 adverse events are related to the procedure in the  
18 sham control group, and we're not saying that that is  
19 the equivalent of a medical treatment group, which we  
20 got in the PACIFIC trial. They are different kinds of  
21 controls. It's simply another comparison that we  
22 made, and it just shows that without the laser there

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1 still are adverse events just from putting the guiding  
2 catheter in.

3 And I agree with you. Those are things we  
4 have to take very seriously.

5 DR. KRUCOFF: Okay. My last questions are  
6 about supporting data. In our Panel pack, there was  
7 some data from TMR-010. As I read through it, in  
8 PACIFIC sites were also allowed a fairly substantial  
9 number of roll-in patients, that while all of the  
10 specifics weren't given, it looks like somewhere  
11 between 40 and 100 treated patients were used in the  
12 roll-in phase.

13 Is there any safety data in these  
14 individuals? Are there any other supportive trials  
15 that might help us understand better whether the  
16 vascular complications and other problems potentially  
17 related from a safety perspective of this gadget or  
18 the efficacy, particularly any efficacy with objective  
19 measures attached rather than just self-perceived  
20 angina scores; is there any other supportive data that  
21 could be compiled to help understand just what the  
22 risk-benefit balance really here is?

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1 DR. WHITLOW: There were a number of roll-  
2 in patients, as you say, the operator doing some cases  
3 before the patients were randomized, and those  
4 complications were essentially the same as what was  
5 seen in the trial.

6 DR. KRUCOFF: Is there data?

7 DR. WHITLOW: Yeah, we have that data. So  
8 we can show it. We can put it up for you.

9 So this is, I mean, the learning curve of  
10 a number of different operators, but the learning  
11 curve may be longer than what was seen in the PACIFIC  
12 trial because they didn't seem to get a whole lot  
13 better as time went by, but you know, it's a new  
14 procedure for everyone.

15 There were 11 different centers with a  
16 couple of operators at each center. That may mask.  
17 Maybe later we'll see that there was a learning curve  
18 that we get over some of the complications, but we  
19 haven't seen it so far.

20 I think we need to go back a little to the  
21 difference between BELIEF and placebo, BELIEF and  
22 PACIFIC. In the BELIEF trial, I mean, the sham

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1 control is a different kind of control, and the  
2 difference in angina between the two groups was still  
3 dramatic, and that's despite the fact that the  
4 patients in the BELIEF trial primarily had Class III  
5 angina.

6 If you go to the BELIEF study and the  
7 PACIFIC study and do multivariable analysis for what  
8 predicts success in terms of greater than or equal to  
9 two functional classes, treatment is the first, the  
10 most important variable, and second is Class IV status  
11 at baseline.

12 So we still see that significant a  
13 difference in the BELIEF trial, despite the fact that  
14 most of the patients were Class III and not Class IV,  
15 but in the PACIFIC trial, a very dramatic effect and  
16 very powerful effect was whether or not the patient  
17 was Class III and whether or not he improved two  
18 classes.

19 I think that it's important to have both  
20 different kinds of controls, the medical treatment  
21 control, because then we lose the complications of the  
22 procedure itself, and the sham control where we see

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1 what complications might be related to the laser part  
2 of the procedure, and we can see the potential benefit  
3 in terms of angina relief with a sham control, which  
4 is quite different than the medical control.

5 There are other kinds of studies that  
6 could be done and other placebo groups that could be  
7 used, but we believe that these two groups really  
8 provide strong evidence for angina relief.

9 DR. KRUCOFF: I guess what I'm trying to  
10 sort out is is angina relief with this instrument by  
11 this unknown mechanism like taking PPCs off of a  
12 Holter with a potential safety profile lurking behind  
13 that that we're never going to know because nobody is  
14 ever going to do a large enough trial to tell us, or  
15 is this angina relief that comes from some sort of  
16 therapeutic benefit?

17 Again, if we knew that there was  
18 angiogenesis, it might be different than being  
19 concerned, but actually your one death who did have a  
20 post mortem from what appears to be a sudden death  
21 didn't have a very heterogeneous electrical myocardium  
22 that was a result of poking a lot of laser holes in

1 it.

2 There's just no way of telling. So I  
3 think our obligation -- it would be a big help to me  
4 if the objective functional parameters, the treadmills  
5 in both PACIFIC and BELIEF supported the symptomatic  
6 relief. That would be a big help, but that's not what  
7 the data show.

8 So we're left with basically symptom  
9 relief, which I agree with you looks pretty consistent  
10 in the blinded and unblinded, although the degree to  
11 me does indicate a significant placebo effect. It  
12 doesn't erase the overall effect.

13 But the question of whether that relief of  
14 symptoms which makes patients' lives and our lives as  
15 their doctors a little less miserable isn't just  
16 another foray into erasing PPC off a Holter where the  
17 real price that's paid by patients from unknown  
18 mechanism with the mechanics involved compared to  
19 medical therapy leaves actually patients more at risk  
20 than we can appreciate from these studies.

21 CHAIRPERSON TRACY: Dr. Klocke.

22 DR. KLOCKE: Yes, thank you.

1           You know, when Dr. O'Neill was talking I  
2 think we all do recognize that there is a subset of  
3 patients with this sort of problem that are terribly  
4 distressed and that we're all trying to help, but to  
5 be honest, I also worry about the placebo effect  
6 because I think that understandably this group of  
7 patients is potentially extra suitable to it, and I  
8 suspect that as a lot of them do well, they develop  
9 the personal support we give them.

10           So in terms of trying to assess that, one  
11 thing that did catch my mind, and I tried to start  
12 with BELIEF, and the BELIEF three-month data are  
13 really very different for symptom relief than the six-  
14 month data. The three-month data, which is the slide  
15 you showed that p is 24, there's a 25 percent  
16 improvement in the treated and a 15 percent  
17 improvement in the sham, and at six months, whereas if  
18 I understand correctly, that's the one that you're  
19 really hanging your hat on, the approval is up to 41  
20 percent. The sham is still at 13 percent.

21           Perhaps there's some reason. I think in  
22 the PACIFIC data you thought the findings were

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1 consistent all the way through, but I'm not quite sure  
2 what to do with the fact that if it was a three-month  
3 endpoint, it would have been a, quote, negative  
4 symptom relief study if I understand correctly.

5 At six months it would have been positive,  
6 and I'm not sure that I understand a reason why the  
7 improvement would occur between three and six months  
8 as opposed to between zero and three months.

9 The other thing is that in the BELIEF, and  
10 perhaps we might talk about that and then come back to  
11 PACIFIC, but obviously as you point out with the  
12 exercise tolerance, there was, in fact, no difference  
13 with exercise tolerance, and I think also there also  
14 was no difference in BELIEF if I've got this right  
15 with rehospitalization, the other point that we've  
16 been discussing.

17 So I'm not sure. So BELIEF for me, at  
18 least if I'm understanding, I'm not sure how  
19 conclusive it really is.

20 DR. WHITLOW: I understand your concern  
21 about the difference between three months and six  
22 months, and the same kind of trend was seen in the

1 surgical studies, that there was improvement, the  
2 maximum improvement occurred later than three months,  
3 up until six months in TMR.

4 Looking at the PACIFIC study also, there  
5 was an improvement between three and six months.

6 DR. KLOCKE: Are you sure about that?

7 DR. WHITLOW: Actually I'm pretty sure  
8 about that.

9 DR. KLOCKE: I thought I had a graph -- I  
10 may be mistaken, but I thought the graph that I had  
11 said --

12 DR. WHITLOW: I mean since the endpoint  
13 was one year, we didn't specifically focus on that for  
14 the PACIFIC study, but we've got the data. We'll find  
15 that data for you in just a few minutes.

16 But I think the most logical explanation  
17 for this is that it takes time for whatever the  
18 mechanism is to develop. It's not something that  
19 happens immediately in all patients. The patients do  
20 -- for instance, if you were thinking that  
21 angiogenesis were important, the angiogenesis may  
22 become more profound over time and plateau. That

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1 would be logical. We don't have any histologic data  
2 to show that, but it would be somewhat logical.

3 And for the patients that improve  
4 immediately, and certainly we've seen patients that  
5 the next day tell you, "I feel much better," walking  
6 around, perhaps you can invoke the mechanism that's  
7 been seen with TMR that at least some patients show  
8 denervation. If you do dehydroxy ephedrine scans,  
9 they're quite different.

10 So we believe -- I mean, right now we  
11 don't have enough about the mechanisms to say, but  
12 denervation may play a part. Angiogenesis may play a  
13 part. Certainly there seems to be some time dependent  
14 factor that increases the patient's satisfaction with  
15 the treatment over time.

16 DR. KLOCKE: Okay. One of the points I  
17 wanted to be sure I understood about PACIFIC, and  
18 obviously, first of all, I guess the -- hang on.  
19 Yeah, in terms of the additional exercise treadmill  
20 time analysis where -- well, actually let's start with  
21 the anginal improvement in PACIFIC. My concern there  
22 was that it seemed to me that the degree of

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1 improvement between the investigator assessment and  
2 the blinded assessment, I understand that they were  
3 both a difference, but as I look at it, the magnitude  
4 of the difference is only half as great in the  
5 independent assessment.

6 And what I'm looking at is the angina  
7 improvement at 12 months, the two class improvement in  
8 PMRs as either seven out of 33 or seven out of 29.  
9 It's about 20 percent, and for the overall trial, of  
10 course, you're speaking about 40 percent.

11 Now, I don't know if those -- I understand  
12 that the n's are not the same at 69 and one joining  
13 the other, but it sort of again suggests to me, and  
14 understandably, that -- it leaves me a little bit  
15 uneasy about the objectivity of the investigator  
16 assignment.

17 The independent assignment, you have  
18 smaller numbers, and again, with the smaller numbers,  
19 not recognizing the difference at the same time, so if  
20 I'm talking to a patient and I'm trying to just go  
21 through them and help them understand the risks and  
22 benefits, I guess one interpretation that one could

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1 take -- I'm not sure it's the right one -- would be to  
2 say through the procedure that on the basis of PACIFIC  
3 there's a 21 percent chance of your improving two  
4 classes balanced against the other points that we've  
5 been talking about.

6 The second thing is also even with the  
7 exercise treatment in PACIFIC, which again, I think I  
8 understand the data correctly, but I believe that the  
9 magnitude of the difference, while systematic, and  
10 again I want to be careful. I'm not trying to  
11 minimize it, but I think we're talking about  
12 qualitative differences, but I also think that somehow  
13 the physician taking care of the patient. I have to  
14 look at the magnitude of the difference that I'm  
15 likely to offer the patient.

16 And the improvement in exercise test  
17 analysis for 40 and 60 seconds, as you've pointed out  
18 for us, it is -- it's 54 percent in the PMR treated,  
19 but it's 37 percent in the medical treated.

20 So again, I guess what I'm sort of trying  
21 to struggle with are figures that indicate to me  
22 modest gains, and primarily in a symptom circumstance

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1 that has the problems of interpretation that we've  
2 talked about, and I'd appreciate any thoughts or  
3 comments you might have in terms of helping me with  
4 that.

5 DR. WHITLOW: Let's see. You mentioned  
6 several different points. Let me start out with the  
7 exercise time.

8 The study was powered with the sample size  
9 to look at mean exercise time in the groups. It was  
10 not powered to look at anything else, and there was a  
11 difference. I mean, the different dichotomous  
12 endpoints, you would need larger numbers in order to  
13 really see a big difference.

14 The fact that there was a difference, you  
15 know, is important, I guess, but the magnitude of the  
16 difference is very difficult to rely on that because  
17 of the numbers that were there.

18 We can be very confident that the mean  
19 time in treadmill time increased in the treated group,  
20 the PMR treated group. I think that's about all we  
21 can say.

22 If you want to look at the placebo effect,

1 I think you really have to go to the BELIEF study, and  
2 you mentioned earlier that the placebo effect, you  
3 wanted to look at the exercise tolerance in BELIEF.  
4 I think if we could show some of the exercise data,  
5 the exercise time and belief, the time to angina, and  
6 the time to ST segment depression, that all of those  
7 things -- the study was a small study that wasn't  
8 powered to look at those, but you can look at them and  
9 see that there are trends in each of those.

10 DR. KLOCKE: Are they in the material we  
11 have?

12 DR. WHITLOW: Were they in the PMA  
13 supplement? They were not. We just got them  
14 recently. So maybe we can show those three slides.

15 You can see that the sham -- okay. Leave  
16 it on one. Okay. This is time to ST segment change.  
17 Is that? No, we have one that's time to ST segment  
18 change. Time to ST segment change is what I was  
19 looking for, that slide.

20 So you can see at baseline the two groups  
21 ere very similar, and over time they both did improve.  
22 If we could stay on that.

1 DR. WITTES: Wait a minute. We seem to be  
2 missing something. They look the same.

3 DR. WHITLOW: Yeah, they do look the same.  
4 I'm sorry. You're right there. They do look the  
5 same.

6 Time to chest pain we also have. Time to  
7 chest pain, do you have that slide? time to chest  
8 pain. Okay.

9 So the time to chest pain, I guess,  
10 there's a trend toward an improvement with PMR, but  
11 it's just not -- I don't know if these data help you  
12 any. It's a small number of patients.

13 DR. KLOCKE: No, I understand, and I guess  
14 I'm sort of trying to find myself trying to weigh on  
15 the basis of the data that we have, realizing that the  
16 limitations you point out. I just sort of find myself  
17 trying to visualize how I would put it to a patient  
18 with the information I best have in terms of whether  
19 or not -- what the risk-benefit tradeoff would be.

20 DR. WHITLOW: I guess if I were talking to  
21 a patient today what I would tell them is that you're  
22 going to have a catheter that's being put into your

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1 heart. You have a one to two percent chance of death  
2 with it during the first 30 days, and you have about  
3 a 70 percent chance that you're going to have some  
4 improvement in your angina.

5 DR. KLOCKE: Seventy?

6 DR. WHITLOW: In the PACIFIC trial, 70  
7 percent of the patients had one class improvement of  
8 angina at the follow-up.

9 So there is risk with the procedure.  
10 There's no question. There's no question that there  
11 is risk, and there is some benefit, and then at that  
12 point a benefit-risk analysis has to occur.

13 DR. KLOCKE: I had just a couple other --  
14 I'm sorry.

15 DR. WHITLOW: I think we also wanted to  
16 talk about the potential, the differences in the  
17 independent assessment and the investigator  
18 assessment.

19 DR. KLOCKE: Sure.

20 DR. WHITLOW: There are baseline  
21 differences in the characteristics of the patient as  
22 well. The independent observer did between six and

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1 ten percent of the patients depending on which group  
2 you look at, were Class I or II at baseline by the  
3 independent assessment. Yet the investigator  
4 classified them as Class III or IV.

5 Now, with the independent assessment, with  
6 up to ten percent of patients already being in Class  
7 I or II, he can't improve. I mean, he just can't  
8 improve two classes.

9 DR. KLOCKE: Do you have those 69  
10 patients? Do you have the direct comparison of the  
11 independent versus the dependent, versus the  
12 investigator for those 69?

13 You must. You probably can get that if  
14 you don't have it.

15 DR. WHITLOW: Yeah, we don't have it  
16 currently.

17 DR. KLOCKE: I don't know if you can get  
18 it instantly, but I guess I hear what you're saying.

19 DR. WHITLOW: And that's just part of the  
20 difference. It certainly is not the entire  
21 difference, but it's part of the difference in the  
22 patients. And there are just two different methods to

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1 evaluate the patient, and some of these patients, by  
2 the definition, if you want a two class improvement  
3 could not improve.

4 DR. KLOCKE: Right. And a couple of minor  
5 things, but the reasons for withdrawal, I guess, could  
6 have either been physician or patient. Is there more  
7 information on the reasons for withdrawal in the two  
8 groups in PACIFIC? Were they balanced?

9 DR. WHITLOW: Yes. They were balanced,  
10 and it was basically virtually all of the patients  
11 that withdrew had treatment failure. Their angina was  
12 worsened, and they wanted some other kind of treatment  
13 or they just got fed up with it and didn't want to be  
14 part of the study anymore, whether it was medical or  
15 in the PMR arm.

16 So the withdrawals, it was eight and nine  
17 for the withdrawals, basically very balanced.

18 DR. KLOCKE: And I really just want to be  
19 sure I understood. On the baseline characteristics in  
20 PACIFIC, I think it was hyperlipidemia. The medical  
21 people had more, but your answer was that the  
22 regression -- you had a -- anyway, the question is the

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1 difference in baseline characteristics with regard to  
2 hyperlipidemia, which I understand is a small point.

3 DR. WHITLOW: Yeah, by multivariable  
4 analysis, hyperlipidemia did not have an effect on the  
5 outcome. That's correct.

6 DR. KLOCKE: But it was very strong. I  
7 think it was 003 on the p value for that.

8 DR. WHITLOW: That's correct. it was very  
9 significantly different.

10 DR. KLOCKE: And statin treatments and  
11 things, do we know anything about them in those  
12 groups?

13 DR. WHITLOW: The number of patients in  
14 the medical group, a higher percentage of those were  
15 on statin therapy than in the PMR group. The exact  
16 percentages I can probably find out for you, but  
17 they're clearly different.

18 DR. KLOCKE: Thanks.

19 CHAIRPERSON TRACY: Dr. Pina.

20 DR. PINA: I want to reiterate the fact  
21 that I realize the investigators here were very, very  
22 good and well known and very experienced, which then

1 pushes me to ask for more data on the exercise test.

2 Francis has really honed in on the  
3 differences between the investigator assessment and  
4 the independent assessment, and I think it becomes  
5 even more marked in that Class III or IV angina, but  
6 you've got objective data. You have exercise tests.

7 And having done this for many years and  
8 being a big believer in exercise tests, I want to see  
9 the objective numbers, and you don't have any  
10 differences in BELIEF in the exercise. You have wide  
11 standard deviations. The standard deviations, as a  
12 matter of fact, for PACIFIC are in the order of 187  
13 and 195 seconds, very wide.

14 And we know that there are always patients  
15 who will do a bit more after pain and some who will do  
16 nothing after they start having pain, and the pain is  
17 the last thing that happens. EKG changes first and  
18 blood pressure and heart rate, and we haven't seen any  
19 blood pressure or heart rate ST segment changes time  
20 to ST, and you've shows us total exercise duration.

21 So I would like to see the physiologic  
22 data that accompanies exercise durations since I

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1 consider exercise duration the least reliable of all  
2 these.

3 You've got VO-2 data that we also haven't  
4 seen, and I'd like to know if there was some patients  
5 that improved dramatically and some that didn't and  
6 that's why your mean is being pushed to improvement.

7 So if you had a table that would show, you  
8 know, the pre and the post of the individual patients  
9 and we saw that most of them went in the right  
10 direction, that would help me, understanding that some  
11 of these other things may be very subjective and  
12 understanding the placebo effect and the unblinding  
13 and all that kind of stuff.

14 But I'd like to see objective numbers.

15 DR. WHITLOW: Yeah, we simply don't have  
16 time to ST depression and time to chest pain. In the  
17 PACIFIC trial those data were not collected. The core  
18 lab that ran the study did not collect those  
19 parameters. They believed that the most important  
20 parameter from their point of view was time on the  
21 treadmill, and that's what the study was powered to.

22 So I'm sorry. I tried to find those for

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1 you. We just don't have those data to show you.

2 DR. PINA: Do you have blood pressure and  
3 heart rate at the peak of exercise? Again, if you  
4 show me more exercise of the same double product, then  
5 I can say this must be supply and not demand.

6 DR. WHITLOW: Yes.

7 DR. PINA: Do you have those data?

8 DR. WHITLOW: We do not have them plotted.  
9 It was kind of an annihilistic approach of our core  
10 lab to only look at one parameter, but that's the  
11 parameter that that they focused on, was time on the  
12 treadmill.

13 DR. PINA: How about the individual  
14 numbers of the patients? Do you have that for  
15 exercise duration? In other words, some patients  
16 improve a lot. Some patients don't.

17 DR. WHITLOW: Yeah, we certainly have  
18 that. That data we have. We don't have it plotted in  
19 the way that you suggested, which would be very  
20 interesting to do. We do not have that available.

21 DR. PINA: Because I think the same thing  
22 in the BELIEF trial. Your means may not be

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1 significant, but if we look at the trends and the  
2 trends are going in the right direction, it could  
3 happen because of your wide standard deviations, which  
4 are pretty huge in both.

5 DR. WHITLOW: No, you're certainly  
6 correct. We just don't have the data plotted in that  
7 way. I'm sure we can get them plotted.

8 DR. PINA: I have one other question. Do  
9 you have any dosing of medication that these patients  
10 were on? Do you have like mean nitrate dose, mean  
11 beta blocker dose?

12 DR. WHITLOW: Yeah.

13 DR. PINA: Again, I've taken care of some  
14 of these patients. I know that they're tough to treat  
15 and they're tough to deal with, especially if they  
16 have side effects, but I'd like to see the amount of  
17 medications that they were on.

18 DR. WHITLOW: Yeah, we do have some  
19 information on that. Let me just see if I can find  
20 something to show you.

21 Yeah, we've got baseline the number of how  
22 many meds. they're on, but we should have it also at

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1 one year.

2 Here are the baseline data. Actually but  
3 we'd like to see how it changed over time.

4 DR. PINA: Do you have dosing in here? Do  
5 you have any dosing?

6 DR. WHITLOW: We do. I have seen the data  
7 about increased, decreased, or the same. So we od  
8 have that data somewhere.

9 DR. PINA: And one more thing. Sine you  
10 do have more diabetics in this group and diabetics  
11 tend to have less angina, I'd like to see, you know,  
12 how much medications they were on.

13 DR. WHITLOW: Okay. We're looking.

14 Okay. Why don't we show this slide?  
15 These are the data with very simple designation of  
16 increased, decreased, or unchanged, and you can see  
17 there was a trend for the medical group to be more  
18 increased than the PMR group, but analyzing this  
19 statistically, I mean, there are certainly no dramatic  
20 differences.

21 DR. SCHAER: In the protocol for the  
22 PACIFIC trial, the investigators were specifically

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1 told not to alter if possible the medication regimen.  
2 We were told to try to keep it as stable as possible.  
3 The concept was to try to get them on maximum therapy  
4 and keep them there throughout the 12-month period.

5 So we did as best as we could, but  
6 obviously clinical situations sometimes dictate  
7 changes.

8 DR. PINA: I realize it's hard because  
9 there are lots of beta blockers. There's lots of  
10 different nitrate preparations, but it would be nice  
11 to see what maximum medical therapy was to the  
12 community that took care of these folks who were very  
13 experienced investigators.

14 DR. WHITLOW: Your point is well taken.  
15 We basically in analyzing the data just took it for  
16 granted that most of the patients -- the instructions  
17 to the investigator were to try to keep the  
18 medications the same, and the investigator, I'm sure,  
19 didn't change the dose, but the patients' referring  
20 doctors would change the dose. Patients complain  
21 about cost of medication, side effects, and I'm sure  
22 some of the alteration was done for reasons that we'll

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