

1 never find out.

2 DR. PINA: I have no further questions.

3 DR. KNOFF: I just want to make one other
4 comment about that because I think that as you can
5 imagine, most of these patients that were referred to
6 this trial came from other physicians who really had
7 exhausted their means of taking care of these
8 patients.

9 So I think that it's difficult, I think,
10 in the protocol design to have maximal medical therapy
11 in quotations because there are so many issues, as you
12 know, with maximal medical therapy.

13 I think the take home message basically is
14 these patients were tried on the types of medicines
15 that their physicians felt were tolerable to them or
16 that the patients themselves felt were tolerable to
17 them, and those were the types of patients who really
18 were referred for this therapy.

19 CHAIRPERSON TRACY: Dr. Laskey.

20 DR. LASKEY: I think unfortunately I'm the
21 halfway point here, but I'll try and be concise. Much
22 of this has been alluded to, if not addressed,

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1 already, but it strikes me there are three endpoints
2 in this study. There are two co-primary endpoints for
3 efficacy, and there's one endpoint for safety.

4 How you go about doing sample size
5 calculations and consequent power analysis for this is
6 difficult at best, and to come up with one nice, round
7 number of 200 patients just makes me raise my eyebrows
8 at how the sample size was arrived at and what it was
9 directed towards, which of these endpoints it was
10 directed towards, and I didn't find any of that stuff
11 in here.

12 So that has something to do with Mike's
13 question about power, and I mean, we all know that
14 post hoc power analysis is not really relevant here,
15 but I would like to start with my concerns about the
16 safety and just park a number of things about efficacy
17 since much of this has been addressed.

18 So to safety, was it powered towards
19 patients or events?

20 DR. WHITLOW: Safety issues were not
21 considered in the power analysis. Both studies were
22 powered for efficacy, and there were two co-primary

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1 endpoints in the PACIFIC trial, the improvement in
2 angina and the improvement in total exercise time, and
3 both of those, it was powered to those two events and
4 not to safety.

5 DR. LASKEY: Okay, and I'd still be
6 curious to see how you did that.

7 DR. WHITLOW: Certainly we can put that
8 up.

9 DR. LASKEY: Maybe the statistician has
10 that. Okay.

11 DR. WHITLOW: I mean, these are how the
12 power analyses were done.

13 DR. LASKEY: Okay, and I don't want to
14 hold the group up here, but if I could just see that
15 off line. Do you have a copy of that slide?

16 DR. WHITLOW: Sure.

17 DR. LASKEY: That would be great.

18 DR. WHITLOW: Yeah, we can make that.

19 DR. LASKEY: To Table 11, actually to this
20 issue about leaving the angina requiring
21 hospitalization in or out, let's just leave it out for
22 a second, and can we give an answer to whether these

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1 were events or patients that we're comparing the
2 fraction of?

3 I don't think it matters because the chi
4 square is significant either way, but it would be nice
5 to clarify that.

6 DR. WHITLOW: Yeah, in the FDA
7 presentation, it was the number of events, 45 -- yeah,
8 those are events, not patients, but patients was 37
9 versus 14.

10 DR. LASKEY: Okay. Either way it doesn't
11 look too promising in terms of safety, but let's go
12 down the list for an interventional cardiologist at
13 three percent perforation rate. A tad high.

14 Agreeably you're manipulating large bore
15 instruments in the left ventricle, and agreeably the
16 risk is understood, but this is not a prospectively
17 defined endpoint either. Was echo cardiography done
18 routinely to --

19 DR. WHITLOW: Yes.

20 DR. LASKEY: It was?

21 DR. WHITLOW: No, it was, and I went over
22 those very quickly in my analysis, but there was one

1 perforation. There were three asymptomatic
2 pericardial effusions that were noted on mandated
3 protocol done, echo cardiography that never would have
4 been noticed any other way.

5 Now, why did those occur? We expect and
6 saw in some animals that was occasionally an
7 inflammatory response around the hematoma without a
8 perforation, and we expect that that happens some in
9 patients, that not all of these were perforations. We
10 believe that the one BSD clearly was a perforation and
11 that the one free wall perforation in the BELIEF study
12 clearly was a perforation and responded to
13 pericardiosentesis in stopping the heparin.

14 So perforation itself, the investigator in
15 two of these cases, the investigator said that those
16 were perforations when they found the asymptomatic
17 effusion. I have some doubts whether or not those
18 were real perforations, but that's where we got the
19 three percent.

20 The perforations in reality were one for
21 sure in the PACIFIC trial and one in the BELIEF study.

22 DR. LASKEY: So it's a conservative number

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1 then, but were there paired echoes? In other words,
2 you did a pre-procedural echo and a post procedural
3 echo?

4 DR. WHITLOW: That's correct.

5 DR. LASKEY: So we can be somewhat
6 relieved that it's really not a three percent rate,
7 but one percent?

8 DR. WHITLOW: Yes, yes.

9 DR. LASKEY: Okay. Great.

10 Heart failure, eight versus two in a group
11 of patients with overall preserved systolic function,
12 50 percent mean in both groups. You have eight folks.

13 DR. WHITLOW: Yeah.

14 DR. LASKEY: Eight folks or eight events
15 of heart failure versus two? What's going on there?

16 DR. WHITLOW: Yeah, those were eight
17 events. And all I can say is the majority of these
18 patients at baseline had at least -- we have the data.
19 About 20 percent had baseline congestive heart failure
20 with very well preserved ventricular function, 50
21 percent or great ejection fraction. So diastolic
22 dysfunction was present and prevalent in this group at

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1 baseline.

2 And you know, I don't know if their
3 medications were changed or certainly one of the
4 patients for sure in the treatment group got all of
5 their medications stopped. Angina was gone away. The
6 patient's medications, dig., everything else was
7 stopped, and he was admitted a few days later with
8 heart failure. That was one of the events.

9 DR. O'NEILL: Could I add something also?
10 We have to really characterize this carefully because
11 we didn't really specifically ask whether or not it
12 was systolic or diastolic dysfunction. The vast
13 majority of these patients came in with well preserved
14 ejection fractions. A lot of them were diabetics, and
15 we presume that a lot of this, quote, unquote, heart
16 failure was either anginal equivalence or diastolic
17 dysfunction.

18 When we looked at the echoes at three-
19 month follow-up, there was no deterioration of
20 systolic ventricular function. So you can be
21 relatively assured that in this group there wasn't
22 myocardial damage causing systolic dysfunction as a

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1 sequelae of the procedure.

2 DR. LASKEY: However, you have more folks
3 succumbing to, quote, heart failure for some unknown
4 reason. So for myocardial infarction, 11 versus five.
5 Again, I know these are all the individual components
6 of the composite MACE here, but, again, they all trend
7 in a not very favorable way.

8 Now, is 11 -- is this the famous post
9 procedural CPK myocardial infarction, or is this a
10 real MI?

11 DR. WHITLOW: Yeah.

12 DR. LASKEY: What are these MIs?

13 DR. WHITLOW: Yeah, a couple of different
14 comments. It is important to realize that a lot of
15 these events were clustered in the same patient. For
16 instance, one patient had an infarct that also had
17 congestive heart failure that had atrial fibrillation.
18 I mean multiple events do tend to run in some of these
19 patients.

20 If you look at the myocardial infarction,
21 one of the centers that enrolled a lot of patients,
22 every time a patient died a cardiac death, an

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1 unwitnessed cardiac death, they were said to have an
2 MI. When there was no evidence of an MI, they were
3 found dead.

4 So the patient is counted not only as
5 dying for four of the patients, but having a
6 myocardial infarction when that wasn't documented, but
7 that was just the routine of that particular center.

8 DR. LASKEY: Pat, that's exactly to the
9 point. Could we see -- I think we need to see either
10 some clear-cut tabulation of statistical comparisons
11 either by events or by patients, and better yet, by
12 hierarchical categorization because this is very
13 confusing, particularly when we get to the numbers of
14 angina requiring hospitalization.

15 DR. BERMAN: We ask to make a correction,
16 please. The question was brought whether the heart
17 failure events, the eight heart failure events were
18 events of patients, and the response was they were
19 events. That's true, but it's also eight patients.
20 That data was provided to the agency in the PMA. This
21 data was presented in your Panel pack as well, but,
22 yes, it's events, and, yes, it's also patients.

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1 You guys, that's Table 32 in the original
2 PMA.

3 DR. WHITLOW: In the slide that I showed
4 for adverse events, which included hospitalization for
5 angina, the number of patients with events, including
6 hospitalization for angina, was 48 in one group and 50
7 in the other group. I don't remember which was which,
8 but they were certainly very close in the number of
9 patients with an adverse event.

10 DR. LASKEY: I'm sorry. I'm looking at
11 Table 11, the first line, angina, 25 versus 39, and
12 I'm reading that because the column heading says
13 number of subjects.

14 DR. WHITLOW: Yes.

15 DR. LASKEY: So the next, the unit of
16 analysis here is number of subjects. When you compare
17 25 in the PMR group to 39 in the med. group, you get
18 a p value of .048. So that barely, barely makes it as
19 statistically different, and that's not even adjusted
20 for multiple comparisons, what you're doing here.

21 DR. WHITLOW: Yes.

22 DR. LASKEY: So it just barely makes it,

1 and then can I then go over to BELIEF and in BELIEF
2 say there was no difference? They're almost dead on
3 in terms of the -- so do you guys still feel strongly
4 that these data are strongly in support of angina
5 relief, which I guess we're going around in circles
6 here, but I believe belongs in MACE?

7 I think if you hospitalize a patient after
8 intervention for a recurrence of what got them in,
9 that's a MACE.

10 DR. O'NEILL: We'd agree with you.

11 DR. WHITLOW: Yeah, that's our point as
12 well.

13 DR. LASKEY: Okay.

14 DR. O'NEILL: We completely agree with
15 you. That's why it should be counted as a serious
16 adverse event.

17 DR. LASKEY: But not all together. I mean
18 these are not all -- again, the hierarchical
19 categorization is key here. Angina is not the same as
20 death. It's not the same as heart failure. I mean,
21 these are not all equivalent.

22 If you're going to do that, then you need

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1 to at least weight them or do something to alter the
2 relative importance. They're not all the same.

3 DR. WHITLOW: You're certainly right. We
4 did not perform an hierarchical analysis.

5 DR. O'NEILL: Dr. Laskey, I think you
6 might be asking us to do something that others aren't
7 required. I mean, for the glycoprotein receptor
8 blockers, death and infarction, you know, there's a
9 whole controversy about silent CPK elevation, and a
10 lot of other FDA approved protocols don't really
11 require a hierarchical analysis of adverse events.

12 DR. LASKEY: Agreed. I don't want to go
13 back to Mike's point, but again, this all started --
14 this all started with looking at seven versus two with
15 a p of .09, which I think got you into trouble in the
16 first place.

17 The trend is there, and it's a disturbing
18 trend, and it tracks right with increased heart
19 failure, increased MI.

20 DR. WHITLOW: But now with the results of
21 the BELIEF study where there were more deaths in the
22 control group and not in the PMR group.

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1 DR. KNOPF: It doesn't really speak to
2 chance whether the -- although there is a trend. If
3 you look at some of the other trials, the treatment
4 group -- I mean, the control group is disproportionate
5 low in my experience and with participating in many of
6 these other trials than what was seen in this
7 particular trial.

8 And I think that needs to be taken into
9 consideration because I don't think that the treatment
10 arm is disproportionately high to what has been seen
11 in some of these other trials.

12 DR. LASKEY: All right. Well, that's very
13 useful. That's why I wanted to see your assumptions
14 about sample size calculations because some of this
15 could be you live or die by the toss of a coin, and
16 things pretty close here.

17 I only have one thing to ask about the
18 efficacy. I mean much has been addressed already
19 about the effect of placebo, but in PACIFIC, there
20 were a number of folks that started to drift backwards
21 between six months and 12 months. What should we make
22 of that and is 12 months really where we want to be

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1 looking?

2 If we looked at 18 months for this sort of
3 thing where there are other humors that might be
4 floating around that might be responsible for which
5 way patients go, do you have a feel for people moving
6 between categories?

7 DR. WHITLOW: When I showed the slide of
8 the PACIFIC and BELIEF at six months, that 51 percent
9 improvement, that was by patients, let's see,
10 surviving patient analysis, whereas the one year data
11 we showed was last observation carried forward. We
12 did that just to match that that's the way that the
13 PACIFIC data was captured.

14 But it looks like there's a deterioration
15 from 51 to 41, I think it was.

16 DR. LASKEY: Yeah.

17 DR. WHITLOW: But it's a different
18 analysis.

19 DR. LASKEY: But there is a movement in
20 the wrong direction.

21 DR. WHITLOW: Yeah, and if you analyze, if
22 you give the six month data as last observation

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1 carried forward, it was actually 45 percent. There is
2 still some movement, and with the TMR data, there was
3 a slight decrease between six months and one year, but
4 Keith Allen can address this better than any of us,
5 but with the PLC CO₂ laser, the effect was still very
6 profound at five years. It didn't fall off
7 dramatically.

8 We don't have that data. Anything more
9 than one-year data we just simply don't have with PMR.

10 DR. LASKEY: Right, and that's probably
11 the last thing I'll say. It's not what you want to
12 hear, but I think one-year data may not be enough for
13 this. These are not hard endpoints, and I think the
14 softer the endpoint the longer you need to look
15 because of how things behave in these kinds of patients
16 who are not going to die. They're certainly going to
17 suffer, and they suffer to varying degrees at varying
18 times.

19 So I think expanding the window may be
20 important for post approval issues.

21 Thank you.

22 CHAIRPERSON TRACY: Thank you.

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1 Just a couple of quick points hopefully.
2 I think we've sort of hammered on the issue of us not
3 being powered to look at some of the safety issues
4 that we all would in an ideal world like to have more
5 information about.

6 In terms of trying to look at the efficacy
7 then, the efficacy based on really a couple of things,
8 the symptom score and the angina, and it is sort of
9 striking the difference between the independent
10 assessment versus the investigator assessment. They
11 are fairly different.

12 I don't see, and maybe I missed it,
13 something that's the equivalent for the belief trial.
14 What would it look more like, the independent
15 assessment or the investigator's assessment? What
16 does it look like if you plot out the angina
17 distribution at six months?

18 DR. WHITLOW: I agree with you. It's a
19 point worth some clarification, and we just don't have
20 all the answers, but I think when you bring in for a
21 subgroup in a study, in a study that's two-thirds
22 over, a new evaluation, it's hard with only a third of

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1 the patients having the assessment at baseline and
2 follow-up; it's difficult to know what that means.

3 The BELIEF trial in that way is a much
4 stronger trial because everybody had the assessment
5 independently at the beginning and at the end. So
6 there's no equivocation about that, and the study was
7 powered to look at the independent assessment, to look
8 at one class or two class improvement in angina.

9 In the BELIEF trial the study is very
10 strong, and that was an independent assessment.

11 CHAIRPERSON TRACY: Did people in the
12 BELIEF trial -- did any of the sham people move over?

13 There's a significant improvement in the
14 PACIFIC trial. If you compare baseline, everybody is
15 Class III or IV, but by 12 months, a significant
16 number of the medication people are Class I or II.
17 Did that same phenomenon happen in the sham group in
18 the BELIEF trial?

19 Did anybody with the sham procedure get
20 better?

21 DR. WHITLOW: Thirteen percent improved
22 two classes, yes.

1 CHAIRPERSON TRACY: Okay, all right. And
2 in the BELIEF trial, the overall symptom assessment
3 was not better? I mean, the anginal parameters were
4 better, but the overall symptom assessment,
5 satisfaction with the procedure, overall quality of
6 life?

7 DR. WHITLOW: Yeah, the Seattle Angina
8 Questionnaire, especially each individual component of
9 the angina questionnaire would have taken a lot more
10 power to see differences even if the differences are
11 there. The only differences we saw were there was a
12 significant improvement in anginal stability. There
13 was a trend toward improvement in angina frequency.

14 Since the patients were really randomized
15 double blind, treatment satisfaction, for instance, we
16 didn't really expect to see any difference in that
17 part of the Seattle Angina Questionnaire in the BELIEF
18 study.

19 So the two things dealing with angina,
20 angina stability and angina frequency, were either
21 improved significantly or trend toward improvement.
22 The other three parameters were not.

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1 CHAIRPERSON TRACY: Just out of my own
2 curiosity, how did people, back to the PACIFIC trial,
3 how did people who were deemed to be inoperable or
4 unrevascularizable, how did a total of 24 of them end
5 up being revascularized or reintervened on?

6 DR. WHITLOW: Yes, that's an important
7 issue. There were 14 in the medical group, ten in the
8 PMR treatment group, and a couple of things happened.

9 There were a few of the patients that had,
10 you know, bypass grafts that were okay when they
11 entered that had new lesions. There were a few like
12 that, but that was the minority.

13 The majority were patients who had
14 unsatisfactory relief from what they were treated
15 with, and the referring doctors then offered them some
16 kind of an intervention. For instance, a patient with
17 a chronic total right occlusion that didn't get any
18 better, well, they went and then tried to open the
19 right. It wasn't successful, but they tried to open
20 it.

21 One patient had TMR, which had become
22 approved during the course of the study. So that

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1 patient got moved over to TMR when he simply just
2 didn't respond to whichever treatment he had.

3 So some of these patients, depending on
4 how bad their angina got, were offered higher risk
5 procedures that wouldn't have been done under normal
6 circumstances, but the patients were doing so poorly
7 the physicians tried to do something else.

8 And most of these were done by the
9 referring physician, not the study physician, and
10 there's a mixture between both groups, but there were
11 more in the PMR group than in the TMR.

12 CHAIRPERSON TRACY: As an
13 electrophysiologist, I think that the arrhythmias are
14 fully understandable that it happened here. You start
15 boring holes in the high septum. You're going to
16 knock out some of the conduction system.

17 There seems to be less arrhythmic death at
18 follow-up in this versus TMR, and I think that may go
19 back to the fact that there's less damage being done
20 by PMR than TMR in terms of amount of tissue area
21 that's being disrupted and potential for
22 arrhythmogenic lesions.

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1 Do you have any information on -- I know
2 you didn't present it here -- but any animal
3 information that you could share in terms of the size
4 of these lesions compared to TMR lesions or any
5 speculations on that?

6 DR. WHITLOW: I mean, we've got animal
7 data on PMR, and the hole are generally four to six
8 millimeters, 5.1 plus or minus 1.1 millimeters, in
9 depth. the width of the channels is fairly uniform.

10 There's some contraction when you fire the
11 laser. So they're not 1.8 millimeters by the time you
12 section the heart. They're less than that, but a
13 fairly consistent size. I don't remember what the
14 size was, but pretty consistent kind of channel.

15 I haven't seen the same data for TMR. I'm
16 sure the data exists. I just don't have it.

17 CHAIRPERSON TRACY: You may not have.
18 It's just interesting. That was one concerning thing
19 about TMR to me, was the high risk of arrhythmias. It
20 just in general seems less here, and what you have
21 seems explicable, and you mentioned one patient during
22 the procedure had a prolonged time to resuscitation

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1 from bradycardia, and I'm curious to know whether it
2 was part of the routine to have a temporary pacemaker
3 in place during the procedures.

4 DR. WHITLOW: It was not part of the
5 protocol to have that in place. I think especially if
6 the septum is one of the targeted areas, certainly it
7 would be the recommendation of this group that that
8 patient have the pacemaker placed.

9 There was one bradycardia. Those were the
10 three heart blocks. Those are the ones that in the
11 procedure had problems with hypotension and
12 bradycardia.

13 There was one that occurred 29 days later
14 that's hard to pin on the exact laser procedure,
15 although certainly it could have been related.

16 CHAIRPERSON TRACY: Okay.

17 DR. WITTES: Well, I have five questions.
18 Two are very short, technical ones. One is kind of
19 amusing about risk-benefit. One is about diabetics,
20 and one is a kind of try to understand the
21 relationship between BELIEF and PACIFIC. I was going
22 to say "symphony." I knew that was wrong.

1 The first small question is came up on the
2 slide here. Your slide for power calculations said
3 that the p values were going to be one sided, but are
4 these all one sided p values that you cite?

5 DR. WHITLOW: No, they're two sided p
6 values.

7 DR. WITTES: They're two sided?

8 DR. WHITLOW: Yes.

9 DR. WITTES: So we don't have to multiply
10 them by two.

11 DR. WHITLOW: No.

12 DR. WITTES: Even though that says one
13 sided?

14 DR. WHITLOW: That's right.

15 DR. WITTES: Okay. That's what I figured,
16 but I just wanted to make sure that I wasn't
17 forgetting to multiply.

18 The second question I just wanted to
19 confirm. Somebody raised this before, but I just want
20 to confirm this. Is it true that you don't have a
21 table that shows for the people who have both
22 investigator classifications and blinded

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1 classifications, a cross-classification of those two
2 categories?

3 DR. WHITLOW: Yeah, we can --

4 DR. WITTES: You really don't?

5 DR. WHITLOW: No, we can get that.

6 DR. KAPTCHUK: Doesn't your Lancet article
7 have it? Doesn't your Lancet article have that table?

8 DR. SCHAEER: The Lancet article includes
9 a subset of patients from Papworth in England. So
10 it's a larger cohort, but it's similar.

11 DR. KAPTCHUK: I'm sorry. I didn't mean
12 to take -- did that answer your question?

13 DR. WITTES: Well, if you have it, I'd
14 like to see it. that's the next part of the question.

15 DR. WHITLOW: It will take just a few
16 minutes, we will get that for you.

17 DR. WITTES: Okay, great. Okay. Then the
18 musing. The musing actually has to do with trying to
19 quantify benefit versus risk. I mean, I'm
20 interpreting the data as a clear indication that
21 you're reducing anginal pain and symptoms of angina
22 and a clear indication that there's an excess of other

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1 serious adverse events.

2 And to me the issue is: how do you
3 quantify both of them and how do you balance them?

4 Now, I look at the PACIFIC data, and I see
5 -- and I did a very small -- my little calculations.
6 We have 42 versus eight people with improvement in
7 angina on this two-point scale. But it seems to me,
8 given the nature of the discussion we had today and
9 given what we see in the BELIEF, that we have to
10 discount that by probably about a third to reflect the
11 fact that these were unblinded assessments and that
12 they were -- and placebo effect.

13 So I see an observed difference of 34
14 patients, 34 percent issues. It comes out to be about
15 23 percent, which turns out to be patients because of
16 this nice, equal sample size.

17 If I look at the anginal SAEs, which is a
18 benefit for the treatment, it's 25 versus 39 for a
19 benefit of 14. So there's 23 people that I count as,
20 you know, an estimated 23 percent who benefit in
21 angina, and an estimated 14 percent on the symptoms
22 that would bring you to the hospital.

1 By contrast -- oh, and about 17 percent
2 who show improvement in exercise tolerance -- by
3 contrast, if you look at the non-anginal SAEs, and I
4 persist in saying that you have to separate them.
5 Because one can think of -- the worst case one can
6 think of is that having angina is a warning signal,
7 and what this is doing is cutting away the warning,
8 hiding the warning.

9 So I see there's a 23 percent difference
10 in the number of patients who have at least one
11 serious non-anginal SAE, and that looks like pretty
12 much of a balance to me, and I need to hear why that
13 isn't equal, why it's beneficial to the patient to
14 have the relief in angina that's going to be offset
15 almost exactly by an increased risk of other serious
16 cardiac events.

17 DR. WHITLOW: Again, we don't want to be
18 melodramatic, but on a daily basis, patients that have
19 very severe medically refractory symptoms have a
20 miserable quality of life. They can't do what they
21 want to do. They can't perform their normal
22 activities of daily living. They're restricted and

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1 require a lot of medications to the point where very
2 frequently they have to be hospitalized again for
3 refractory angina.

4 So on a day-by-day basis, that's something
5 that a patient feels -- at the end the patient is
6 going to have to make an informed decision about
7 whether or not they are going to be willing to subject
8 themselves to a surgical procedure with a finite and
9 quantitative risk in order perhaps to benefit from an
10 improvement in anginal symptoms and quality of life.

11 I meant that's really the end analysis of
12 the risk-benefit, and I think as long as the patients
13 are properly informed about this known quantitative
14 risk, they can judge for themselves whether or not
15 they're willing, as with any other surgical procedure,
16 to take that risk, to have the symptomatic benefit.

17 And also in your analysis, you can't
18 expect that all of the adverse events are the same.
19 I mean death and myocardial infarction and stroke are
20 certainly bad events, but perforation that's
21 asymptomatic and found on an echo is not such a bad
22 event as far as we can tell.

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1 Left ventricular dysfunction in a patient
2 who had previous heart failure, it's hard to know
3 exactly how relevant that is, but it's counted as an
4 adverse event.

5 So you know, your strict calculation in
6 addition and subtraction, I think, doesn't quite work.

7 DR. WITTES: Well, I agree, but that's
8 exactly the reasons why you need to do it
9 hierarchically, because if the patients with
10 perforation then went on to have something else,
11 that's one thing. If they have perforation and
12 nothing else, that's another.

13 And I think that's part of what we're
14 struggling with. We don't know which clusters of
15 events happen with which --

16 DR. WHITLOW: Right, and one other thing,
17 I think, with the very rigorous training plan for
18 instituting PMR in the community where we teach
19 doctors to avoid the kinds of procedures and patients,
20 where complications are likely to occur, for instance,
21 lasing the septum, patients with recurrent CVAs, I
22 think are at higher risk for a CVA during this

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1 procedure. This is another group of patients we may
2 wish to select against this procedure.

3 So there are issues that can reduce the
4 complication rates, I think, and kind of tip the
5 balance in the favor of the procedure.

6 DR. WITTES: Let me then ask about
7 diabetics. Because that actually, I think, is one of
8 the groups that I wondered about. PACIFIC had, I
9 think, a third diabetics.

10 Were the benefits and adverse events --
11 how did they play out in the diabetics?

12 DR. WHITLOW: We did a multivariate
13 analysis. We did diabetes, predict adverse events.
14 In some of the adverse events it was predictive, but
15 in others it wasn't, and overall diabetics -- the
16 diabetics improved as often as non-diabetics, I
17 believe, overall.

18 You know, this patient population in the
19 United States, 40 to 50 percent of all of the studies
20 we showed are diabetics. In Europe it's more like 15
21 to 20 percent for most of the studies, but diabetics
22 do respond to this treatment. The diabetics with

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1 angina do seem to improve just like non-diabetics with
2 angina seem to improve.

3 There were the adverse events that -- I
4 don't remember which, in the multivariate analysis of
5 some of the adverse events. They were higher in
6 diabetics. Do you remember, Joe, which events those
7 were?

8 DR. WITTES: Well, you'd expect them to be
9 higher. The question is: is there an interaction
10 between the events and treatment?

11 DR. WHITLOW: Yeah, there was no
12 interaction in any of these multivariate analyses.

13 DR. WITTES: Okay. Then my last question,
14 and this has to do with the struggling to figure out
15 the difference between BELIEF and PACIFIC. One of the
16 questions, there's actually two small questions.

17 One is: do you have data, six months data
18 on adverse events in PACIFIC in order to calibrate
19 against BELIEF?

20 I mean, one of the questions is are the
21 events that you're seeing basically occurring in the
22 second half of the year so that the apparent huge

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1 difference is a temporal thing? That's one question.

2 And then in the BELIEF study, there seems
3 to be no data on hospitalization for angina, and is
4 that because there were none or is that because it
5 wasn't collected or is that a reflection of something
6 about the unblinding of symphony -- see, I'm going to
7 do it over again -- of PACIFIC.

8 DR. WHITLOW: Yeah, the hospitals that you
9 saw were cardiac hospitalizations. Some of those were
10 for angina, but some were for other cardiac reasons.

11 Do you have it broken down by angina, Dr.
12 Nordrehaug?

13 That analysis for angina specifically
14 hasn't been done. I think, you know, a lot of things
15 are different. It's a different health care delivery
16 system that we're dealing with, and the
17 hospitalizations are fewer for sure.

18 We showed you the baseline characteristics
19 that were different between the two patient groups,
20 the diabetics, Class IV, the number of Class IV
21 patients, and the ejection fractions were quite
22 different.

1 So, I mean, it's hard to compare them
2 directly, but I think that the baseline
3 characteristics at least partially explain the los
4 hospitalizations and, I think, the difference in the
5 health care delivery system which is unquantifiable
6 also may play into this difference.

7 Now, we should be able to answer the
8 question about adverse events in PACIFIC though. What
9 percentage of the adverse events actually occurred
10 between six months and one year? And it was --

11 DR. WITTES: The cardiac adverse events.

12 DR. WHITLOW: The cardiac adverse events,
13 and it was not -- yeah, initially they were clustered
14 in the first month, the major events, and that's the
15 reason I spent so much time going through them, but
16 there certainly were some events between six months
17 and one year. It was not as many as in the first six
18 months, but it's not -- we just don't have that broken
19 down in that way.

20 DR. BORER: You have them in these Kaplan-
21 Meier plots here.

22 DR. WHITLOW: Yeah, they're in the Kaplan-

1 Meier plots. You're right.

2 DR. BORER: Page 540.

3 DR. WHITLOW: Yeah, the Kaplan-Meiers go
4 out to one year.

5 CHAIRPERSON TRACY: Okay. Thank you.

6 Okay. Dr. Borer.

7 DR. BORER: As you might expect, with the
8 illustrious group sitting around the table, virtually
9 every question I had has been answered, and I'm not
10 going to ask them to you again.

11 I have just a couple of remaining
12 clarifying questions, and then I would like to make a
13 comment based on what you say.

14 First, because I think it's important in
15 interpreting the lack, the apparent lack of
16 improvement in exercise tolerance in BELIEF, and in
17 fact, nominally the data go to the wrong way. The
18 exercise improvement was greater in the medicine plus
19 sham than the medicine plus laser treatment group.

20 I would like to ask again the question
21 that Ileana began to ask earlier, and that is about
22 the stopping criteria during exercise testing. Pat,

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1 you said that this was basically a cardiac endurance
2 test, but that's not what the protocol says.

3 On page 5-46, the stopping criteria for
4 the ETT in BELIEF sound like the stopping criteria
5 for, you know, standard exercise testing. So you
6 know, it would be important to know whether it was the
7 one or the other.

8 And then taking it one step further, and
9 you may not have these data, and that's okay. Rightly
10 or wrongly, when we evaluate anti-anginal, anti-
11 ischemic drugs, the criteria that are collected
12 include time to onset of angina, time to angina of
13 sufficient severity so that it would normally stop the
14 patient's activity, and then total exercise duration.

15 I'm not sure whether you collected those
16 data. I'd be interested to know if you did. So there
17 are two questions in one there, and I'll let you
18 answer that before I go on.

19 DR. WHITLOW: The other variables on the
20 exercise test, time to onset of chest pain, time to
21 one millimeter ST depression, time to two millimeters
22 ST depression, those data were not collected in

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1 PACIFIC at all.

2 DR. BORER: No, but we have them in
3 BELIEF. With regard to BELIEF, I was talking about
4 the stopping rules because that's the section, Section
5 5, page 46, that sounds pretty standard.

6 DR. NORDREHAUG: Yeah, I think you're
7 right. It is quite standard. We use moderate chest
8 pain as a stopping point and hypotension, the normal
9 things that according to the protocol like you read
10 it.

11 DR. BORER: Okay.

12 DR. NORDREHAUG: But we did also Oxygen
13 uptake and RAR values to assure comparability,
14 especially at baseline.

15 DR. BORER: Now, the second question, with
16 regard to the angina hospitalizations about which I
17 would like to make a comment in a moment, do we know
18 how many of these patients who were hospitalized
19 because of their angina had electrocardiographic
20 variations, transient ECG variations during the
21 hospitalization and how many came in with pain alone?

22 DR. WHITLOW: We don't have that specific

1 data tabulated in the database. We just didn't --

2 DR. BORER: It's not possible for you to
3 go back? I guess it would be difficult to get them
4 retrospectively.

5 The reason I ask is that in PACIFIC, the
6 people who had chest discomfort or didn't have it knew
7 whether they had a laser treatment or not, and you
8 know, as Mitchell articulated so well just a little
9 while ago, if they know they didn't have the treatment
10 and they had chest pain, they might get scared and
11 might tend to come to the hospital.

12 They might. They might not. I don't
13 know. But if they did and they had ST segment
14 changes, that would be perhaps more meaningful than if
15 they have that perception, that symptom that brought
16 them to the hospital and they didn't have evidence of
17 active ischemia.

18 And one of the reasons why that question
19 keeps recurring to me is that despite the increased
20 number of hospitalizations for angina, there wasn't an
21 increased propensity for myocardial infarction in the
22 group that came in with more angina. In fact, it went

1 the other way.

2 So I'm not sure how to evaluate that
3 angina stuff, hospitalization for angina, and I, too,
4 like Janet, I tend to look at that as a measure of
5 efficacy. You were trying to prevent angina. You
6 prevented it. That's good.

7 Okay. Having asked those final two
8 questions there, it occurs to me that angina is a
9 symptom and not a disease, and so I like your response
10 to this. Angina is a symptom. It's not a disease.

11 Now, of course, it can be very
12 frightening, very disabling, but nonetheless it's a
13 symptom, and absent some other benefit, you'd hope
14 that the risk to leave or prevent the angina would be
15 relatively modest, and that's exactly what Bill was
16 saying just a couple of minutes ago.

17 Now, having said that, just as Bill said,
18 if the risk is known and it's communicated to the
19 patient, the patient can make a reasonably informed
20 judgment as to whether he or she wants to accept the
21 risk to get the relief of the symptoms.

22 Here the people have intractable symptoms,

1 and you know, they complain of those symptoms less
2 frequently after the PMR than without the PMR. I
3 mean, I think that I'm willing to accept that from the
4 data that you've presented.

5 But that apparent reduction in symptoms,
6 the magnitude of which I'm not quite sure about for
7 all the reasons that Fran mentioned and Janet did,
8 though there's a reduction in complaints, that
9 reduction in complaints doesn't seem to be translated
10 in the blinded study into an improvement in exercise
11 tolerance. So that's a little concerning.

12 And the ST segment data that you showed us
13 from belief suggests that it's not due to an anti-
14 ischemic mechanism that you're relieving those
15 symptoms, and that's a concern because of the
16 possibility of masking ischemia and causing the
17 events, you know, actually having people, you know,
18 exercise more than they otherwise might have. They
19 had a warning system, and now they have bad things
20 happen to them.

21 Maybe that's what's happening. Maybe it's
22 not, but you know, if we are masking symptoms or we're

1 just minimizing the likelihood that someone will
2 perceive a disturbing feeling, a very disabling
3 feeling, if that's all we're doing, you know, if all
4 we're doing is giving analgesia, if it is, and I don't
5 know that it is, you know, why wouldn't you compare,
6 for example, this therapy with other types of
7 therapies that are given to people with chronic pain
8 like methadone, I mean, if it's just an analgesic?

9 So, you know, I think that's why the issue
10 of mechanism becomes so important, and although I
11 would have suggested that it would be good to go back
12 and get the ST segment data, you have them, and so we
13 saw them.

14 Now, ST segment data aren't the only data
15 or the best data, and these people, two-thirds of them
16 had myocardial infarction, et cetera, et cetera. So,
17 you know, it's hard to know how to interpret those
18 data.

19 But the data we see don't suggest an anti-
20 ischemic mechanism underlying this anti-anginal
21 benefit, and so that's of concern to me. So I'd like
22 to hear what you think about that.

1 DR. O'NEILL: Can I just briefly start
2 with that? I think that the patients that were
3 typically seen are patients that have predominantly
4 total occlusions of coronary arteries that have well
5 developed or moderately well developed collaterals and
6 well preserved ventricular function. A prototype
7 would be a patient with a patent Lima (phonetic), with
8 an occluded right coronary artery with an occluded
9 vein graft to the right coronary artery, who had well
10 preserved ventricular function, but are very, very
11 limited because the collaterals are inadequate.

12 So you really wouldn't expect that
13 particular kind of patient to be predisposed or at
14 risk of having a myocardial infarction. There isn't
15 a culprit lesion that's going to occlude and then
16 cause an infarct.

17 I think you are minimizing the overall
18 physiologic benefit of pain relief. The patients
19 suffer severe symptoms. Therefore, they become very
20 inactive. Therefore, their large muscles atrophy, and
21 therefore, they do less and less physical activity.

22 So pain relief alone does improve their

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1 ability to exercise, again, manifest by the fact that
2 the patients in the PACIFIC trial, their exercise
3 duration was able to be increased. They were able to
4 be more physically active.

5 So it's not just method they're on.
6 There's a very important physical benefit to be
7 obtained from pain relief.

8 DR. BORER: Would not some other form of
9 analgesia give you the same benefit or mightn't? And
10 why would it be beneficial in PACIFIC and not
11 beneficial in BELIEF?

12 DR. NORDREHAUG: Well, I suppose it could,
13 but laser is a one-time procedure. It takes about an
14 hour to do it, and with other therapy you have to use
15 it every day, and you would have complications from
16 that therapy as well.

17 As far as the anti-ischemia effect is
18 concerned from the BELIEF trial, the study was
19 designed because we thought that laser could be only
20 a placebo effect, and we were very skeptical to the
21 whole therapy.

22 So a study was designed to elucidate the

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1 pain effect of the device, and everything else were
2 secondary endpoints like exercise, ECD and the
3 cultural life questionnaires.

4 We designed it to show an effect, and we
5 had power to show a difference between the groups
6 after six months, and we succeeded in doing that, and
7 we were just as surprised as anybody else. So as was
8 mentioned several times, there is a placebo effect.
9 That would exist in both groups. And what we've shown
10 is that laser is definitely better than placebo.
11 There's no doubt about it.

12 I mean, there are no covariates --

13 DR. BORER: I think it is, too.

14 DR. NORDREHAUG: There are no covariates
15 anywhere, and the study is just showing that. So much
16 to my surprise.

17 DR. KNOFF: Also, I think that the whole
18 issue of the mechanism is very interesting and
19 intriguing, and we can discuss that ad nauseam, and I
20 think that there are many patients who have ischemia
21 that are not necessarily manifested by EKG changes,
22 and there are many people that have ischemia that

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1 might be manifested by other things, as you know, with
2 nuclear testing or stress echo cardiography, and
3 clearly even now we're looking at MR perfusion as ways
4 of documenting ischemia that, you know, clearly
5 weren't designed into this trial, but still these
6 patients may, indeed, and probably do have ischemia
7 without some of these other more objective types of
8 things that we know of as objective right now.

9 And I think that as Bill has said, I think
10 that minimizing the symptoms of chest pain and
11 ascribing it solely to just an analgesic approach, I'm
12 not sure that is correct. I just don't know the
13 answer to that, but I think that we should focus in on
14 the symptomatology because I think we do see that
15 every day.

16 These patients are critically ill. They
17 take a large burden of time in anybody's practice, a
18 large burden of the economic dollar that we have to
19 look at in the United States, and I think for all
20 those reasons, I think that approaches such as this
21 are very important in terms of giving these patients
22 back to a life style that's satisfying to them.

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1 Whether that improves mortality benefits
2 or not, as long as it doesn't hurt mortality benefits,
3 I think that's where we need to be.

4 DR. WHITLOW: Dr. Borer, we do have ETT
5 data looking at silent ischemia both in the BELIEF
6 trial and in the PACIFIC study, and both studies show
7 a slight increase in silent ischemia, but we're
8 talking about just a few percent after the treatment
9 or the sham in both groups. There's no difference
10 between the groups, and there's no significant
11 increase in silent ischemia throughout the study.

12 We can show you those slides if you want
13 to see them, but they're just a few patients that have
14 silent ischemia.

15 DR. BORER: This was from the ETT or some
16 other?

17 DR. WHITLOW: By the ETT. Silent ischemia
18 is measured by no chest pain, but ST changes that were
19 significant, greater than one millimeter.

20 DR. BORER: Sure, I'd like to see them if
21 you have them.

22 DR. WHITLOW: Okay. Here's the BELIEF

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1 study. So these were patients who did not complain of
2 chest pain during the exercise test, but had EKG
3 suggestion of ischemia, one millimeter change.

4 DR. DOMANSKI: What's the total number
5 here? The number of patients?

6 DR. WHITLOW: Yeah, this was 40 patients
7 in one group and 42 in the other.

8 DR. DOMANSKI: Why doesn't that suggest
9 that there may be some benefit or no benefit at six
10 months? Is that significant?

11 DR. SCHAEER: The point is that it's not
12 showing that there's more silent ischemia in the
13 treated patients. I mean, the concern is that, you
14 know, they're going to get out and start doing a lot
15 more, and they're going to run into problems.

16 DR. DOMANSKI: Well, I jumped into
17 somebody else's thing, and I apologize. But I don't
18 see why it shows that. That's done on an exercise
19 treadmill, isn't it?

20 DR. WHITLOW: Yes.

21 DR. DOMANSKI: What does that have to do
22 with what they're going to do outside?

1 DR. O'NEILL: Well, if it had an analgesic
2 effect, then what you would expect is that you would
3 see a lot more patients having silent ischemia while
4 they're exercising.

5 CHAIRPERSON TRACY: Is that it?

6 DR. BORER: All done.

7 CHAIRPERSON TRACY: Okay. Dr. Kaptchuk.

8 DR. KAPTCHUK: I think you guys are doing
9 a good job, but I wanted to ask. I didn't see in this
10 data, but in the Austrial (phonetic) study in Lancet,
11 it said that the magnitude of the difference between
12 people who were blinded to the procedure versus people
13 who were not blind to the procedure was a difference
14 of 28 percent improvement in the angina. The
15 difference is 28 percent.

16 And so the magnitude of detection bias is
17 important, and there was an earlier question about
18 whether the laser machine was -- the sham procedure in
19 the BELIEF trial was transparent, that is, you could
20 tell the machine was off or not, and the answer was
21 you couldn't tell.

22 But in the data here, it mentions that

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1 music was needed in order to obscure a noise. I
2 didn't understand what the noise was and what you were
3 trying to obscure and who you were trying to blind
4 with the music.

5 Was it the physician? Was it the patient
6 or people in the -- I just wanted to ask that first.

7 There was music going on in the trial.

8 DR. WHITLOW: Yeah.

9 DR. KAPTCHUK: And it was an attempt to
10 blind, and I didn't know what it meant.

11 DR. WHITLOW: When you step on the laser
12 pedal, you can hear the laser fire.

13 DR. KAPTCHUK: Okay.

14 DR. WHITLOW: And both groups had a laser
15 firing. So that noise was there. The music would
16 have hopefully covered up where the laser -- you know,
17 if you wanted to localize exactly where the laser was
18 firing, it was behind the lead screen.

19 So I don't believe anybody could try to
20 use that information to decide what.

21 DR. KAPTCHUK: Then I don't understand
22 what the music was for. Help me out again.

1 DR. SCHAER: The music was used not in
2 PACIFIC. It was used --

3 DR. KAPTCHUK: In BELIEF. I understand,
4 but what was it trying to obscure? What were you
5 playing music for?

6 DR. NORDREHAUG: Well, in some very
7 slender subjects you may hear a sound inside the chest
8 of the patients.

9 DR. KAPTCHUK: Oh, I see. Okay, okay.

10 DR. NORDREHAUG: Yeah. So we would mask
11 that. Not in very many patients, but in some
12 patients, we may hear it.

13 DR. KAPTCHUK: So it was for increasing
14 the blindness, the masking of the patient. Okay,
15 great.

16 DR. NORDREHAUG: We were skeptics. So we
17 wanted --

18 DR. KAPTCHUK: That's very good, very
19 smart.

20 DR. NORDREHAUG: -- to absolutely blind it
21 in any way.

22 DR. KAPTCHUK: Okay. The second question

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1 I wanted to ask was around the question of informed
2 consent, not because I don't believe you got an
3 informed consent, but I'd like to know the exact
4 wording of the informed consent in both the PACIFIC
5 and the BELIEF trial, and especially concerning how
6 that may impact on the BELIEF trial because of the
7 fact that only one of -- only the angina pain was
8 improved, and yet the treadmill and other parallel
9 outcomes didn't change.

10 So I'm really concerned about how
11 potentially the wording of informed consent. For
12 example, I assume that patients -- can I ask a little
13 about that, how it was presented to the patients in
14 both trials? I'm mostly interested in the BELIEF
15 trial.

16 DR. NORDREHAUG: Well, we had a three-page
17 informed consent telling them about possible
18 complications and possible effects of the procedure.
19 It was very neutral, not a bit optimistic in form and
20 tone, and it was accepted by the FX Committee in the
21 health region, which is government run. It's not part
22 of the hospital.

1 DR. KAPTCHUK: I'm meaning to question the
2 ethics. What I want to know, did the patients know
3 they may receive a sham procedure?

4 DR. NORDREHAUG: Oh, yes. Oh, absolutely.

5 DR. KAPTCHUK: Absolutely, right.

6 DR. NORDREHAUG: Absolutely.

7 DR. KAPTCHUK: The third question I wanted
8 to ask along that line is -- most trials don't do
9 this, but I just wanted to ask. Did you ask at any
10 point the patients after the procedure whether they
11 thought they got the real procedure or the sham
12 procedure? Was that something that was done?

13 It's usually not done, though sometimes it
14 is.

15 DR. NORDREHAUG: Well, that was a part of
16 our blinding as well. We wanted to -- we didn't want
17 to speak about laser or sham at all. So we wouldn't
18 do that because in case --

19 DR. KAPTCHUK: Fine.

20 DR. NORDREHAUG: -- if they were guessing
21 and if we didn't answer them, then they may take that
22 as an acceptance, that we agreed with them. So we

1 didn't want to bring in that question at all.

2 DR. KAPTCHUK: Okay. Thank you.

3 DR. WHITLOW: In the general outline each
4 individual center had a different informed consent.
5 The same elements though. The patient was told of all
6 the risks, and that he might have angina relieved by
7 the procedure. No other promises were made. If he
8 got the procedure, he might have angina relieved, but
9 that this hadn't been tested yet.

10 CHAIRPERSON TRACY: Yes.

11 MR. MORTON: Well, thanks. This has been
12 a fascinating discussion this afternoon. I appreciate
13 being a part of it and hearing it.

14 I'd simply like to respectfully remind the
15 Panel as you begin to consider voting not to base your
16 voting on what you might have liked to have seen, for
17 instance, a comparison with TMR, because as valid as
18 that might be, I'd encourage you to consider what the
19 sponsor has brought here, what evidence, and I would
20 echo the FDA's question to you.

21 There we go. I'd simply echo the FDA's
22 question to you: does the sponsor present reasonable

1 assurance of safety and effectiveness based upon the
2 indications that the sponsor has recommended?

3 CHAIRPERSON TRACY: Anything, Mr. Dacey?

4 MR. DACEY: Very quickly. The nice thing
5 about being last is all the tough efficacy and safety
6 questions have been asked, and I represent the
7 consumer, the patient, and I guess in some ways I've
8 been there. I know from personal experience what
9 you're describing. So my observations really are
10 partially based on the fact that I was present for the
11 TMR PMA and recall that quite clearly, and I want to
12 salute you for the work that you've done.

13 And this is really not so much an efficacy
14 and safety issue as it is, I guess, a practice issue,
15 but there's a real dilemma, a patient-doctor dilemma,
16 that troubles me, and there's no answer to it because
17 I looked over the information for patients considering
18 PMR, and you know, how does a physician respond to a
19 patient who ask some questions? Because what you're
20 saying to the patient is we're going to enter your
21 body and we're going to do this to you, but we don't
22 know how it works or why it works, but we have

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1 evidence that it does work.

2 And for some folks that would be
3 comforting. Some folks, I think, are going to need
4 some more information, and they certainly have to have
5 a lot of trust in the physicians they're dealing with.

6 And in also looking over this information
7 for patients because I've spent a good part of my
8 career in patient education and information, I run and
9 hide when I see a lot of compound, complex sentences
10 aimed at patients, especially as we look at the
11 extremely diverse population in this country and
12 around the world where this information has to be
13 translated.

14 And I've spent some time trying to get
15 information translated, medical information, and the
16 more compound, complex the sentence, the much more
17 difficult it is to get it translated into languages.
18 They don't even have words that are comparable to the
19 ones we're using.

20 So I hope you would pay special attention
21 to those kinds of issues that end up touching the
22 patient because we assume a high level of literacy,

1 and it's not always there, and we assume a high level
2 of understanding when what's really needed is some
3 one-on-one extra time.

4 So with that, thank you very, very much.

5 CHAIRPERSON TRACY: I think we'll --

6 DR. BORER: May I ask Mr. Dacey a
7 question?

8 CHAIRPERSON TRACY: Sure.

9 MR. DACEY: Certainly.

10 DR. BORER: I think you've raised an
11 extraordinarily important issue here, and so I'd like
12 to have you respond and maybe you'll translate it back
13 to the sponsor here.

14 I think most people assume if you do
15 something to their heart when they have angina, that
16 that's going to be good. I mean, you know, you're
17 not just going to make them feel better. Somehow
18 mystically there's some goodness in there. It's
19 better, not necessarily you're going to live longer.

20 But how do you tell somebody that you may
21 live shorter, you may have a heart attack, you may
22 have a stroke, you may have all these other things

1 that you might not have had? You know, I don't want
2 to go through the whole litany that we've had already.
3 We don't know the magnitude, small samples, et cetera,
4 et cetera, but it sounds like you sort of have to
5 somehow get that point across to people.

6 Maybe we can do this and make you feel
7 better, but we may do some bad things to you. How do
8 you do that? I mean, can you do that in an effective
9 way for most people?

10 MR. DACEY: If I knew that, I think I'd be
11 a multimillionaire.

12 Again, I have to go back to that word of
13 trust between the patient and the physician and the
14 other providers. I've experienced some horrendous
15 complications, and I've also participated in designing
16 informed consent documents. You can't cover all the
17 bases all the time for everybody, which is why I
18 stress in patient education what I call skill
19 training, but it's why I also stress that if the
20 patient has some basic trust and if the physician
21 understands that patient and respects that patient and
22 they reach agreement that they will or will not do it,

1 and I know a lot of patients, myself included, who
2 have chosen not to have an intervention and done quite
3 well.

4 These are moments of truth that it's a
5 moving target, and all I can ask is that the sponsors
6 and physicians work hard at trying to make it work,
7 and I don't know that there's really any magic.

8 CHAIRPERSON TRACY: Thank you.

9 At this point we will take a 15-minute
10 break, which brings us to 4:15 to reconvene.

11 (Whereupon, the foregoing matter went off
12 the record at 4:00 p.m. and went back on
13 the record at 4:17 p.m.)

14 CHAIRPERSON TRACY: Okay. If everybody
15 could gather back to your seats, please, I'd like to
16 proceed going through the FDA questions specifically
17 directed at the panel.

18 Okay. Why don't you go ahead and proceed
19 with Question 1.

20 DR. BERMAN: I'd like to once again place
21 the questions before the panel.

22 CHAIRPERSON TRACY: I'm sorry. Did the

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1 sponsor want to wrap something up at this point or
2 would you prefer to wait until after the questions?
3 Now? After. Okay.

4 Any other questions? I'm sorry. I'm
5 jumping the gun here. Any other questions from the
6 panel members?

7 Dr. Krucoff.

8 DR. KRUCOFF: I just have one quick
9 clarification question about the last observation
10 analysis, and I want to make sure I'm understanding
11 this properly. Patients who withdrew from the
12 protocol were patients who had reintervention, which
13 looks about 20 to 22 percent of the total population.

14 Am I right in assuming that because they
15 probably had a reintervention for recurrent angina or
16 whatever, that that would be their last observations?
17 In other words, that 20 percent of the population
18 distributed over the two groups would be positive
19 endpoints or SAEs, depending on how you would
20 characterize the angina, but they would be positive
21 last observations or bad last observations; is that
22 correct?

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1 DR. WHITLOW: Well, their last
2 observations, in general, were very negative. I'm not
3 sure what you meant by positive. I mean, their last
4 observations were that they were very limited, and
5 then they were carried over, yes.

6 You know, if they had surgery or they had
7 angioplasty and their angina was relieved, they
8 weren't counted as a plus for the study. They were
9 counted as their last observation, which was negative.

10 DR. KRUCOFF: Okay. Because in one letter
11 of clarification from Eclipse, it sort of indicates
12 that these patients might actually, if included in the
13 analysis, be helpful to the nontreatment group, which
14 implied to me that their last observation would be
15 favorable rather than nonfavorable, where my
16 understanding of the last observation carried forward
17 strategy for patients who withdrew or underwent an
18 intervention for recurring symptoms would be that the
19 last observation would be their exit point, which
20 would be a bad one, a negative one.

21 DR. WHITLOW: And that is correct.

22 DR. KRUCOFF: That's correct. Okay.

1 CHAIRPERSON TRACY: Okay.

2 DR. WITTES: But that's not necessarily
3 true though, right? I mean, it's only -- the other
4 alternative analysis that you mentioned, which was to
5 assign them a negative value --

6 DR. WHITLOW: Yes.

7 DR. WITTES: You said that that didn't
8 change the results, but you didn't say how much it
9 didn't change the results.

10 DR. WHITLOW: Yeah, there were still
11 significant differences. The statistical significance
12 was not changed by that, assuming the worst.

13 DR. WITTES: But was the magnitude of the
14 effect change and how much was the magnitude of the
15 effect?

16 DR. WHITLOW: Certainly the magnitude of
17 effect was decreased when you assigned them such a
18 negative score, but it didn't change the statistical
19 significance.

20 I mean, it was. There were 20-some
21 percent that withdrew or had reintervention. If you
22 assigned them all an exercise time of zero, which

1 would be the worst way to analyze them, it decreased
2 the magnitude of the effect, but still even despite
3 that, there was a significant improvement in exercise
4 time and in angina score.

5 DR. LASKEY: By p value.

6 DR. WHITLOW: The p value units, yes.
7 Still significant, right.

8 DR. LASKEY: But the effect size, can you
9 just share with us what happened to the effect size?

10 DR. WHITLOW: I can, I think.

11 Okay. Angina improvement two classes went
12 down from the 41 percent that you saw down to eight
13 percent, and eight percent -- no. I'm sorry. Okay.
14 It went from 40 to 41 percent? Yeah, because most of
15 the patients were already failures. That's the reason
16 it didn't change that much.

17 DR. WITTES: And the eight percent changed
18 to what? So it used to be 42 versus eight, and now
19 it's 40?

20 DR. WHITLOW: Forty versus eight, yeah.
21 I mean, as we stated, their negative results were
22 already entered into the trial. Imputing more

1 negative results didn't matter.

2 CHAIRPERSON TRACY: Are there other
3 questions from the panel?

4 (No response.)

5 CHAIRPERSON TRACY: And as long as you are
6 there, I would ask you if you have any comments that
7 you'd like to make, go ahead and please.

8 DR. WHITLOW: Yeah. We've talked about an
9 awful lot of different things today, as we should
10 have, but I think that it's important just to focus on
11 a couple of things now as you're going to discuss
12 whether or not to approve this option.

13 What we've proposed to you is another
14 option for treating medically refractory patients with
15 severe angina who can't be otherwise revascularized.
16 There is a surgical option that was approved, and that
17 surgical option has a finite risk that is greater than
18 the alternative that we're offering today.

19 This procedure, without a doubt, has a
20 risk, and when you're instrumenting patients with this
21 kind of angina and this kind of heart disease, there
22 is a risk associated. I think we've defined what that

1 risk is reasonably well, and we believe that in these
2 patients who really want to have something done
3 because they're so limited, they want to have
4 something done to accept the risk, that this is a much
5 better alternative, less risky alternative than what
6 is approved, and that is TMR.

7 I think the other thing that we have done
8 over the last six months is Dr. Nordrehaug's data
9 addresses very nicely the sham effect, the sham
10 placebo effect, and shows without a doubt a lot of the
11 mechanism of improvement is not placebo, and I think
12 that that has been clearly shown by his study.

13 We can't offer you a lot of other data
14 about mechanisms, but we can say that the sham placebo
15 effect is not the most important effect in
16 contributing to the patient's angina relief.

17 And I just wanted to summarize a few
18 things before we end, and I appreciate your attention.
19 I know it's been a long afternoon.

20 DR. KLOCKE: Pat, in terms of the last
21 things you said, I want to be sure you understand.
22 That's true for the six month, but the three month in

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1 the BELIEF study is still a negative. It's a
2 nonstatistical positive difference, and as I
3 understand it, your best guess for that is that
4 somehow however this works it takes longer than three
5 months.

6 DR. WHITLOW: That's correct.

7 DR. KLOCKE: Okay. Thank you.

8 CHAIRPERSON TRACY: Okay. Thank you.

9 All right. Back to the questions posed by
10 the FDA.

11 DR. BERMAN: Okay. The FDA would like to
12 once again place before the Panel the questions which
13 we have asked you to consider and please consider
14 these in the light of the discussion that you've
15 engaged in this afternoon.

16 As background for Question 1, Tables 3 to
17 5 in the FDA clinical review, which is in Tab 3, pages
18 7 and 8 of the clinical review, list the adverse
19 events associated with PACIFIC. Table 18 of the same
20 clinical review lists the adverse events associated
21 with BELIEF.

22 Note that PACIFIC by design had a 12-month

1 follow-up and BELIEF by design had a six-month follow-
2 up.

3 Question 1(a): the total of serious
4 arrhythmias, heart failure, myocardial infarction,
5 thromboembolic events, and deaths in the PACIFIC study
6 was higher for the treated patients than for the
7 control patients. In the BELIEF study, there was only
8 one such adverse event in the treated patients.

9 Please discuss and consider the
10 implications of these findings for the assessment of
11 safety for this device system when used as indicated.

12 CHAIRPERSON TRACY: Okay.

13 DR. BERMAN: Do you want to do them one at
14 a time?

15 CHAIRPERSON TRACY: Why don't we? We'll
16 go over them one at a time, and I'll just take a stab
17 at starting by saying that part of the problem I'm
18 having with this is the lack of power to the look at
19 any of these individual endpoints, and I'm finding
20 that I find like many other people have reflected here
21 on the panel that if we had higher numbers of
22 patients, we might be able to make more definitive

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1 statements about some of these adverse events.

2 So the implications in terms of safety,
3 I'm not particularly reassured by BELIEF that that
4 adds much in terms of the safety information compared
5 to PACIFIC.

6 I find myself in a quandary in terms of
7 determining whether we've demonstrated safety for many
8 of these endpoints, and I can't bring it past this.

9 Anybody else?

10 DR. KLOCKE: One other thing I wondered
11 about and wanted to comment is if the learning curve
12 is steep, and BELIEF had the benefit of a particularly
13 experienced unified group that had mounted the
14 learning curve more completely than was possible even
15 with the 11 excellent studies, excellent institutions
16 they had in PACIFIC.

17 DR. DOMANSKI: I wonder whether the
18 learning curve really is that all steep though for
19 this procedure. I'm concerned that that doesn't
20 necessarily explain, although I think one ought to be
21 expert in doing the interventional procedures. This
22 one doesn't have some of these done.

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1 I don't think -- I haven't done them, but
2 I've seen some of them done. I'm not impressed that
3 it's inaccessible to somebody doing interventional
4 cardiology, frankly. So I guess I'm not sure I'd walk
5 away with that as the answer.

6 CHAIRPERSON TRACY: Dr. Pina.

7 DR. PINA: You're looking at the patient
8 characteristics at baseline, and the greater number of
9 diabetics who by and far have more vascular disease.
10 I don't have any coronary arteriography data, but my
11 sense is that the PACIFIC population is sicker, maybe
12 not by chest pain symptoms, but by burden of disease
13 with the inclusion of more diabetics.

14 And so, again, my sense, my gut sense is
15 that they are going to have more complications because
16 they have more disease entity to begin with, and
17 that's how in my mind I look at the differences in the
18 adverse events, and I would expect a sicker population
19 to have more adverse events. I don't know if that
20 helps.

21 CHAIRPERSON TRACY: Does that help us at
22 all in terms of the safety in PACIFIC?

1 Dr. Wittes, Dr. Borer?

2 DR. WITTES: Yeah, I actually don't
3 understand why everybody is so worried about the power
4 for safety. I mean, it seems to me I see a two and a
5 half-fold excess risk of serious cardiac events, and
6 it seems to me it doesn't matter what the power was a
7 priori. Those are the data.

8 And it's hardly surprising that we can't
9 identify which particular event is more significant
10 than, you know, what's a significant specific event.
11 If you think about when you do a cardiovascular trial
12 and you use a composite endpoint, you use a composite
13 endpoint because you say we think of it all in some
14 kind of a continuum, and you can't look at -- we don't
15 have enough power for individual events.

16 So I don't understand. I guess I don't
17 understand the concern of the rest of the committee
18 about the lack of power to identify whether there's an
19 excess of individual cardiac events.

20 DR. DOMANSKI: Well, I don't know if
21 there's a cosmic explanation, but I was the one that
22 was so worried about power, and the reason I was

1 worried about it was because there seemed to be a real
2 trend in a setting where the numbers were small enough
3 so that you wouldn't expect to see anything, and we're
4 seeing it.

5 And so I was concerned the power is very
6 low.

7 CHAIRPERSON TRACY: Dr. Borer.

8 DR. BORER: Yeah, I must say I agree
9 completely with Janet. You know, the numbers are the
10 numbers, and if you look at the individual adverse
11 events, forgetting about the angina issue which we
12 discussed before, virtually all of them go the same
13 way. I mean, there's a tremendous amount of internal
14 consistency there.

15 And just as Ileana was pointing out, you
16 know, the BELIEF population seemed to be perhaps less
17 sick. The study was shorter. It was smaller, and
18 there was less evidence of benefit in BELIEF than the
19 putative evidence of benefit in PACIFIC, methodology
20 differences notwithstanding.

21 So you know, the lack of an apparent
22 signal that I can find in BELIEF just doesn't negate

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1 for me the concern that's raised for me about the
2 PACIFIC study. I think that you have to conclude that
3 there's a risk here.

4 We may not know the magnitude of it, but
5 there's a risk, and the risk is important events that
6 happen not peri-procedure, but later for whatever
7 reason, and I don't want to start speculating about
8 the reasons, but you know, they seem to happen and
9 happen consistently.

10 DR. KAPTCHUK: I want to disagree and then
11 finally agree with the last two comments.

12 The reason the power is a question in my
13 mind is that you want to eliminate the possibility of
14 chance, and if it's a small number, it could be chance
15 finding that you get a little bit of adverse -- let me
16 finish and then tell me if I'm wrong -- and the reason
17 I want to contradict myself and agree with you is that
18 all of the little differences all point to one
19 direction, which is actually not likely due to chance,
20 that is, that even though it's not statistical, if
21 it's any one of those little readings, the fact that
22 they all point in one direction would very unlikely be

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1 chance.

2 So I agree that there's some problem with
3 safety issues.

4 DR. WITTES: Yeah, it seems to me the
5 problem with power is the problem as Mike describes.
6 If you see something, a small difference with a p
7 value isn't quite significant. You say, well, maybe
8 there's a power issue, but here the number that
9 matters is 37 versus 14, which is the summation of all
10 the people, not all the events that have these.

11 CHAIRPERSON TRACY: Just as a comment on
12 that adverse events, I was tempted to want to remove,
13 and I did sort of on my own pencil and paper, remove
14 the arrhythmic problems because they do seem to be
15 related to site of energy delivery and sort of things
16 that you could expect if you thought about it a little
17 bit.

18 But even if you removed the arrhythmic
19 events there still is a discrepancy between the two.

20 DR. BORER: Yeah, I must say I did the
21 same thing when I did my analyses before coming here,
22 and I found the same as you did.

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1 MR. DILLARD: No, I think that was very
2 helpful, and I think what came out at the end was --
3 and the only difference that I heard perhaps during
4 the discussion was from Dr. Laskey about how to handle
5 those hospitalizations due to recurrence of angina.

6 But it sounds like you guys have worked
7 out fairly reasonable consensus, and I think I
8 understand that.

9 Thank you.

10 CHAIRPERSON TRACY: Okay.

11 DR. BERMAN: Okay. As part of Question 1
12 we have Question 1(b). We ask that you please discuss
13 the clinical importance of the adverse events observed
14 in these patients.

15 CHAIRPERSON TRACY: I think we've kind of
16 addressed this in the answer to the Part 1(a). We
17 think that the group in BELIEF was probably a little
18 less sick, and that might be the difference there, but
19 that we are very concerned about the adverse events in
20 PACIFIC.

21 DR. BERMAN: Thank you.

22 DR. KRUCOFF: I'd just add in the overall

1 scope that I think when we have an invasive procedure
2 whose mechanism is unknown that there is an even
3 higher level of obligation we have to patients when
4 we're comparing it to medical therapy to insure
5 safety, and I think that that is a part of this mix as
6 we come towards this consensus.

7 DR. BERMAN: Thank you.

8 Question 2: the primary effectiveness
9 endpoint in both studies was an improvement in angina
10 as measured by the Canadian Cardiovascular Society
11 angina score. The co-primary endpoint in PACIFIC was
12 an improvement in exercise time, and a secondary
13 endpoint in both PACIFIC and BELIEF was an improvement
14 in the Seattle angina questionnaire score.

15 Question 2(a): in PACIFIC the CCSAS
16 improvement was assessed by the investigators.
17 Although some patients had a blinded assessment, all
18 of the CCSAS measurements in BELIEF were blinded.
19 Please discuss the possible impact of investigator
20 bias on the evaluation of improvement in the angina
21 score.

22 CHAIRPERSON TRACY: Well, I think you've

1 heard a lot of discussion about our concern that there
2 might have been bias to some extent that is overcome
3 in the BELIEF study, but since we're talking about an
4 efficacy at treatment of angina, it does still remain
5 an important issue that I don't think we can
6 completely be solid in saying that there isn't room
7 for bias to be influencing decisions here.

8 Any other members of the panel care to
9 make comments on this questions?

10 DR. LASKEY: Just to take some particular
11 importance with subject of endpoints, I mean, if there
12 were objective corroboration it would be somewhat
13 mitigating, but there aren't any.

14 DR. BORER: Yeah. Number one, I think
15 that the potential for bias certainly in PACIFIC for
16 bias affecting the quantitative results is great, but
17 probably not completely as we see from BELIEF.

18 My concern though is determining what the
19 true magnitude of reduction in the perception of this
20 abnormal sensation is. Forget about the exercise test
21 for a moment, and you know, the reasoning that Fran
22 went through a little earlier, I think, is key here.

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1 I think that this method reduces the perception of
2 chest pain, but I don't know how much, and that's a
3 little problem when you do a risk-benefit assessment.

4 So I think the true magnitude of reduction
5 in the symptom is relatively modest, but real when you
6 put it all together just the way Fran did.

7 DR. KAPTCHUK: I just want to say that I
8 think that the BELIEF study is a really good study,
9 that it's very rare to see a device controlled that
10 well in a randomized control trial, and this is a
11 collecting device trials. That's one of the nicest
12 trials I've seen in a long time.

13 In terms of detection bias, I think there
14 was no detection bias or as little as one can get in
15 a randomized control trial, but I do think that
16 there's a question, and it has to do with the fact
17 that the other outcomes didn't match the primary
18 outcome, and that's really bizarre from my
19 perspective.

20 And I would have to say that there's
21 something that needs to be paid attention to, but in
22 terms of the angina primary outcome, it's a really

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1 well controlled for both placebo and bias.

2 CHAIRPERSON TRACY: Yes, I think that
3 there's some concern there as you can see from the
4 panel, varying from the question of bias versus mixing
5 the endpoints of something more concrete versus
6 something more subjective.

7 DR. BERMAN: Okay. Dr. Kaptchuk's
8 comments kind of preview Question 2(b).

9 The percent of patients meeting the
10 criteria for improvement in CCSAS, SAD and ETT are all
11 significantly greater for treated and for control
12 patients in PACIFIC. In BELIEF treated patients out
13 performed the controls for angina, but not for SAQ or
14 ETT. Please discuss that mismatch.

15 DR. WITTES: I thought maybe SAQ couldn't
16 be translated into Norwegian.

17 (Laughter.)

18 CHAIRPERSON TRACY: I'm not sure that --
19 I think that there is a mismatch there. I'm not sure
20 how we can reconcile it.

21 DR. KLOCKE: I agree, and I don't want to
22 overstate it. On the other hand, I do believe that

1 it's harder for me to ascribe -- to focus on the
2 change in exercise test treatment in PACIFIC in which
3 it was unblinded when I'm confronted with the BELIEF
4 one. So I personally would give the BELIEF one higher
5 emphasis.

6 CHAIRPERSON TRACY: Mitch.

7 DR. KRUCOFF: I actually happen to agree
8 entirely, although I think it's worth recognizing that
9 BELIEF was a substantially smaller patient population,
10 but the role of blinding and unblinding patients and
11 their performance on the treadmill is such a primary
12 one that I also find it impossible to ignore the
13 BELIEF lack of exercise test improvement in blinded
14 patients.

15 It makes it even fuzzier then to
16 understand if we take Pat's sort of summary earlier
17 that belief clearly shows that not all of the effect
18 that's beneficial is placebo effect. We're still left
19 with what to me with the treadmills especially is a
20 very fuzzy attempt to say, well, what isn't or how
21 much isn't placebo effect when the functional data,
22 the exercise treadmill, are going in the other

1 direction.

2 CHAIRPERSON TRACY: Okay.

3 DR. BERMAN: Thank you.

4 DR. KAPTCHUK: Could I just say -- I
5 really just want to say that one of the things is I
6 looked at lots of acupuncture trials, which has a
7 similarity to the intervention. You know, you're
8 needling someplace. You're not sure exactly why, and
9 you get an outcome, and you get a lot of positive
10 trials, and you get a lot of negative trials.

11 And it's really hard to know what to do
12 with contradictory results, and I just want to say
13 this is a similar conundrum. It's a contradictory
14 result, and I have not seen a good explanation.

15 DR. BERMAN: Thank you.

16 Two (c) --

17 MR. DILLARD: Mike, let me ask you one
18 clarification. Would it be fair to say that the
19 overall sense of this particular panel is that based
20 on the two studies that the angina results are pretty
21 strong and that then the other information causes a
22 little bit of fuzziness to the angina scores, but

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1 nonetheless, would it be the sense of this panel that
2 the angina scores are real based on these two studies?

3 CHAIRPERSON TRACY: I think that I'm not
4 sure I'd use the word "strong," but I think there is
5 consensus that there is some anginal improvement here,
6 but --

7 DR. KRUCOFF: Present, the results are
8 present.

9 CHAIRPERSON TRACY: Right. Well, I'd go
10 a little farther than present, but I think that the
11 discrepancies are a little bit difficult to reconcile.

12 DR. LASKEY: The choice of this endpoint,
13 is this not what happens when you have fuzzy
14 endpoints? I mean, that's part of the -- at least one
15 part of the conundrum. When you have fuzzy endpoints
16 and soft endpoints, it's hard to get clear-cut
17 results, and CCSAS is just a fuzzy, vague, ordinal
18 endpoint. It's hard to get your arms around.

19 It's not what we would have chosen to do
20 anti-anginal assessment. I mean, there are other
21 rigorously verified and validated in the pharmacologic
22 literature ways of looking at angina relief.

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1 DR. KAPTCHUK: Is this not a good
2 endpoint? Please forgive my ignorance.

3 DR. KRUCOFF: I would argue one that I
4 have no trouble with CCSAS. I think it's the
5 unblinded use or the use of CCSAS in patients who were
6 unblinded to therapy that makes the PACIFIC data
7 softer, and then the BELIEF data helps show something,
8 but I don't mind the endpoint for angina.

9 CHAIRPERSON TRACY: Right. I think no
10 matter how a trial would be constructed, what you're
11 looking at is symptom relief. So somewhere or another
12 symptoms have to play in there. The beauty of belief
13 is that you have a sham procedure versus the real
14 thing, and I think that therefore, I do believe that
15 there is anginal relief.

16 Plus, from PACIFIC even the independent
17 assessment of anginal score does show some benefit.
18 So I think there is benefit, but there are the other
19 issues.

20 Dr. Borer.

21 DR. BORER: You know, this is a very
22 difficult area. As a way of taking a history from

1 someone, I don't have any trouble with CCSAS, but it's
2 hard for me to give it as high a bounce as time
3 walking on a treadmill until you develop angina while
4 somebody is watching you.

5 And so I believe -- I believe because I
6 think the data are sufficiently compelling so that I
7 should believe -- that there was a reduction in the
8 perception of spontaneously reported events. I
9 believe that.

10 I don't know the magnitude, as I said
11 before, but the importance of that is hard for me to
12 judge when I look at a very -- and I would echo what
13 Ted said -- I mean, a very well performed trial,
14 BELIEF, where there was no evidence of improvement in
15 exercise tolerance. In fact, nominally no
16 significance attached. Things went the wrong way.

17 So it's hard for me to interpret the
18 positive results in analysis of CCSAS.

19 DR. WITTES: May I make a suggestion?
20 Because I find this really puzzling, too, Both the
21 CCSAS, both the exercise tolerance and this SAQ, it
22 may be worth -- and what we know with exercise

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1 tolerance is it has this huge tale, and it's very
2 variable, and, yes, we're looking at the medians, but
3 it may be worth looking at the trivariate outcome just
4 to explore when is an improvement in CCSAS.

5 Do you see an improvement in exercise
6 tolerance? Do you see an improvement in SAQ to get
7 some sort of internal consistency of the data from the
8 belief trial?

9 CHAIRPERSON TRACY: Okay. All right.

10 DR. BERMAN: Okay. This is a continuation
11 of Question 2. This is 2(c). The Canadian
12 Cardiovascular Society anginal score and the Seattle
13 angina questionnaire both assess aspects of angina.
14 In PACIFIC, a higher percentage of the treated
15 patients as compared to controls showed improvement in
16 both CCSAS and SAQ.

17 In BELIEF this was true for CCSAS, but not
18 for SAQ. We ask that you please discuss, again, this
19 apparent mismatch.

20 CHAIRPERSON TRACY: I think we've
21 essentially been addressing that with the comments
22 from Parts A and B. I'm not sure that there's

1 anything more specific to say about that.

2 DR. KAPTCHUK: I can say one thing more.
3 I'm trying to scratch my memory. Horowitz of Yale
4 wrote an article on contradictory trials in
5 cardiovascular. He took 90 trials. I forgot what
6 particular cardiovascular indication it was. Please
7 forgive me. It was published in Archives in about
8 1992, and you get contradictory results in double
9 blind control trials, and that happens.

10 And his explanation was heterogeneity of
11 the population that you took into the trial.
12 The cutoff points are variable and what have you, but
13 this happens, and it's unpleasant.

14 CHAIRPERSON TRACY: It's unpleasant, and
15 it's rendered even more unpleasant because we have two
16 different sort of components, too, what's being
17 presented today.

18 DR. BERMAN: Thank you.

19 Okay. Question 3: patients in both
20 PACIFIC and BELIEF had severe refractory angina.
21 However, some patients in the control group in each
22 study met the criterion for improvement in angina.

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1 Please comment on this improvement in the control
2 patients as it relates to the effectiveness of PMR as
3 a treatment of angina.

4 CHAIRPERSON TRACY: I think the answer to
5 that is that coronary disease isn't static so that
6 things change over time, and maybe the piece of
7 myocardium that was causing pain at day one isn't
8 causing pain at six months. But I don't think that
9 there's anything inconsistent about seeing a change in
10 the control group as time goes by. I don't think that
11 that affects what the outcomes are in either BELIEF of
12 PACIFIC in terms of believability.

13 I do think it's interesting. Of course,
14 it was the entry requirement in PACIFIC that they all
15 be Class III or Class IV, but it is interesting how
16 many people drifted into the Stage 1/2 at the follow-
17 up point. But I think this just happens.

18 DR. KRUCOFF: Go ahead.

19 DR. PINA: Even the older anginal trials
20 had improvements with the placebo group. So it's
21 pretty common, and I think if you look at trials
22 across the board, and I know this is true in the heart

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1 failure trials, once a patient is entered into a trial
2 and they have a nurse that's taking care of them,
3 that's watching them, people that are calling them,
4 they tend to improve and we've seen even improvements
5 in survival in those modes that you wouldn't expect in
6 the populations. So I'm not surprised at all.

7 DR. KRUCOFF: I agree. Waxing and waning
8 is the nature of the disease. Some of that waning may
9 be because the cells that cause pain die. It's not
10 always a good natural history, but clearly it does
11 implicate that if you're going to do an invasive
12 procedure on some patients today, they may not need it
13 if you had just waited three or six months.

14 The placebo effect has repeatedly been
15 shown to be operative in this patient population, and
16 I think at the end of the day what this does is
17 emphasize that in the absence of knowing what
18 mechanism this device has, the obligation becomes to
19 demonstrate with robust data what its safety and
20 efficacy really are.

21 DR. WITTES: There's also regression to
22 the mean that we mustn't forget. I mean, the very

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1 fact that the independent assessors measured some
2 people as ones and twos suggest that there was areas
3 in -- just measurement areas in assessing the threes
4 and fours, and that would reflect itself in regression
5 to the mean later on.

6 DR. KAPTCHUK: Can I say something as a
7 historian? And please forgive me. I know history
8 doesn't count sometimes, but one of the very first
9 randomized control trials in American history and
10 world history was Harry Gold's trial that was
11 published in 1937, which was an angina trial which has
12 dramatic, dramatic placebo effect, and in fact, he
13 developed the methodology of double blind, randomized
14 control trials in that trial.

15 In 1950, his second trial, large trial was
16 on angina, and he actually invented the word "double
17 blind" in that trial. And in fact, angina with pain
18 has been the two areas where you get these incredible
19 placebo effects that you need blinding and what have
20 you.

21 DR. BORER: A Cornell physician, I'll
22 point out.

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1 DR. KAPTCHUK: That's right. I should
2 have said that.

3 (Laughter.)

4 DR. KRUCOFF: Well, not just history. I
5 mean, the direct TMR study was a beautiful double
6 blinded TMR study where one cohort improved two
7 functional classes, but it was the placebo cohort.

8 DR. BERMAN: Thank you.

9 Question 4: there were three statistical
10 analyses provided for PACIFIC, the last observation
11 carried forward, all survivors and all survivors
12 without reintervention. Please comment on the
13 inclusion or exclusion of patients who received
14 reinterventions, and should those patients be counted
15 as failures of PMR?

16 CHAIRPERSON TRACY: This one goes right to
17 Dr. Wittes.

18 DR. WITTES: I would count them as
19 failures of PMR. I don't like last value carried
20 forward. But in this case it doesn't make any
21 difference.

22 We should hear from other people, too.

1 CHAIRPERSON TRACY: Any other comments?

2 (No response.)

3 DR. BERMAN: Okay. Question 5: please
4 discuss whether the data in this PMA supplement
5 provides reasonable assurance of effectiveness for
6 this device in the patient population study.

7 CHAIRPERSON TRACY: I think you've heard,
8 sort of, the reserved, yes, there is improvement in
9 angina, but we have to harken back to other concerns
10 about the safety of the device.

11 So I think there is at least belief that
12 there is some -- there is improvement in angina.

13 Dr. Borer.

14 DR. BORER: Yeah, I'd just like to suggest
15 a slight modification that, again, we're looking at
16 angina, a symptom, in two different ways here, one
17 with a questionnaire, and CCSAS is a questionnaire
18 just the way SAQ is. We're looking at it by taking a
19 history, and then we're looking at it by trying to
20 stimulate it on a treadmill, you know, and albeit an
21 artificial situation where the time walked on a
22 treadmill can't be directly extrapolated to what

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1 people do in their every day life.

2 It's two different ways of looking at
3 angina. And the one way has some objectification in
4 that you're watching and you can measure something,
5 you know, time to angina, whatever. The softer of
6 those two, I would suggest, is the history taking
7 part.

8 I think that the history taking part
9 consistently showed that the therapy did something and
10 actually reduced angina, but, you know, that's not
11 true; I don't think that's true of the treadmill
12 exercise stimulating angina and watching part.

13 So while I think that something happened
14 here, the importance of what happened is what I'm
15 trying to grapple with, and that's a problem, and I
16 think that just needs to be noted.

17 And I agree with Ted, of course, you know.
18 You look at trials. If you look at ten angina trials,
19 some things turn out positive in one trial, not in
20 another trial.

21 Something else you measured turned out
22 positive in the second trail, not in the first, you

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1 know. There's a lot of variability when you're
2 dealing with a symptom as the endpoint in a trial, but
3 that's what we've got, you know, and so we're left
4 with this problem.

5 CHAIRPERSON TRACY: Not having a
6 mechanistic understanding of what exactly goes on here
7 makes it more difficult to interpret. I guess, many
8 of these people, or some people went on to have
9 symptoms of heart failure, whether it was diastolic or
10 systolic. So there's a lot of other things that could
11 have potentially affected exercise tolerance.

12 That aspect of efficacy is pretty much
13 unknown. Anginal reduction, I think, there is data
14 for that, at least a piece of data for that.

15 DR. BERMAN: Thank you.

16 Question 6: FDA is required to evaluate
17 the device labeling to determine whether it properly
18 indicates which patients are appropriate for
19 treatment, whether it identifies potential adverse
20 events with the use of the device, and whether it
21 explains how the product should be used to maximize
22 benefits and minimize adverse events. If you

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1 recommend approval for this PMA supplement, please
2 address the following labeling questions.

3 Okay. This is copied from the Panel
4 pack, Tab 2, page 2. This is the sponsor's suggested
5 indication for use.

6 The eclipse PMR system is indicated for
7 use in percutaneous myocardial revascularization.
8 Procedures to decrease angina and increase exercise
9 tolerance in patients with chronic angina, CCSAS 304,
10 which is refractory to medical treatment and secondary
11 to objectively demonstrated coronary artery disease
12 and with the region of the myocardium with reversible
13 ischemia not amenable to direct coronary artery
14 revascularization.

15 That's what they want to say.

16 Six A: the indications portion of the
17 labeling that I just read to you states that this
18 device is indicated to increase exercise tolerance.
19 Please comment on whether the information presented
20 today provides adequate justification for this claim.

21 CHAIRPERSON TRACY: Jim.

22 MR. DILLARD: Jim Dillard.

1 Just a quick clarification because I think
2 we can take these issues, not necessarily thinking
3 whether or not you're going to recommend approvability
4 or not approvability. I think you can talk through
5 the issues and talk about where there may be problems
6 or difficulties, and that doesn't necessarily have to
7 shape your vote, just in case anybody was
8 uncomfortable.

9 DR. FERGUSON: Well, I'm uncomfortable
10 with including that wording. I'm definitely
11 uncomfortable with including the wording about
12 increasing exercise tolerance. I don't think they've
13 demonstrated that.

14 CHAIRPERSON TRACY: I think that would
15 probably be what the majority of people would have
16 some concerns about that on the Panel.

17 DR. BERMAN: Thank you.

18 Six (b): please provide any other
19 recommendations or comments regarding the indication
20 statement and/or any other aspect of the labeling for
21 this device.

22 CHAIRPERSON TRACY: I would just add the

1 -- I don't know if this is part of the labeling or
2 part of the warnings or part of the training or
3 something -- but I think that it might be reasonable
4 to think about temporary pacing and people
5 particularly if you're going to be working on the
6 septum.

7 And I guess as an electrophysiologist, I
8 see needing a permanent pacemaker as not the end of
9 the world. If I had a treatment that clearly was very
10 beneficial to a patient, but I told them that there
11 was at least a small chance that they'd require a
12 permanent pacemaker, that would not totally deter me
13 from recommending that that procedure be done.

14 But in terms of the actual performance of
15 the procedure, I'd consider a temporary pacer during
16 the procedure.

17 DR. KLOCKE: For me at least, Jeff has
18 summarized the issue about angina, and I could imagine
19 it's a minority, but I'd be more comfortable if it
20 said it's known to reduce the perception of angina.

21 CHAIRPERSON TRACY: That's a good point.
22 Mitch.

1 DR. KRUCOFF: Yeah, I agree. It's symptom
2 relief at most or perception of angina. I think
3 wording that suggests that this improves the
4 physiology in the setting the ischemic heart disease
5 is beyond the data and should not appear there.

6 The other thing I'm concerned about is as
7 indications go, there are a lot of technical features
8 to the patients who are involved here, including their
9 wall thickness, and I really wonder if some of those
10 from a safety perspective should be in the indication
11 statement.

12 DR. BERMAN: There will be in the labeling
13 a warning section and a caution section where wall
14 thickness would go. I mean it's in there now.

15 CHAIRPERSON TRACY: Mike.

16 DR. DOMANSKI: Yeah. I don't mean to get
17 into the minutia of this, but angina is a perception
18 of pain. So I'm not sure what it means to talk about
19 the perception of a perception. I'm nervous about
20 that language.

21 DR. KLOCKE: That point's well taken. I'm
22 not sure what the right phrasing is, but it would

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1 certainly influence my own thinking about whether I'd
2 be willing to recommend it or not.

3 DR. DOMANSKI: In other words, I think,
4 may I -- if I can say it, I think what you're
5 concerned about is that it may reduce the pain that
6 the patient feels without changing the underlying
7 physiology that holds them at risk for an adverse
8 event, I mean, like an MI or something. Is that a
9 fair statement?

10 DR. KLOCKE: I think it changes maybe I
11 should say the perception of anginal like pain, or
12 something like that. I'm not trying to wordsmith, but
13 I am concerned that in terms of -- again, I really
14 think that Jeff has summarized it well, and I
15 recognize that there is benefit, as Bill and other
16 people pointed out, there clearly is benefit in terms
17 of reducing that perception that is real and helpful.

18 At the same time, I think at least I would
19 be comfortable for those recommending it, I think they
20 ought to understand it in those terms.

21 DR. FERGUSON: Pardon my simplification.
22 My simple mind I should say, maybe. But what's the

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1 matter with saying what they have to decrease angina.
2 I mean, that's -- the reason I take issue is the
3 obscuration of the purpose, and this ought to be
4 fairly clear in the statement of what the purpose is.

5 DR. KLOCKE: The point is well taken. I'm
6 not sure that most physicians reading the label would
7 think it through and make that distinction although
8 the people here would but -- well, anyway, maybe I'm
9 a minority.

10 DR. KRUCOFF: Well, I'm on that side. I
11 think that if you just say reduce angina, there's an
12 implication likely to be read that you're improving
13 the physiology that leads to that. And if you say
14 symptomatic relief from angina or something that that
15 needs to be clear, that what the data show us is a
16 reduction of the symptoms without really knowing
17 what's happening.

18 DR. DOMANSKI: Well, angina is pain
19 though. It's not physiology.

20 CHAIRPERSON TRACY: Right. I think that
21 type of specific wording issue could be worked out.
22 That information is going to -- would be in the

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1 labeling, what the actual results of the studies were.

2 So any other points?

3 DR. BORER: Yeah, you asked about other
4 things in the label. I agree the wordsmithing can be
5 done by the FDA, but the Table 1 that's in the label
6 does include angina. It says angina, although as we
7 heard, this was really supposed to be angina
8 sufficiently severe to cause hospitalization in the
9 SAE table, and the result is that at the bottom it
10 looks like everything's all even.

11 Now, there may have been a prior agreement
12 between the FDA and the sponsor that mandates that
13 this is the way those data should be presented. So,
14 you know, I don't know anything about that, but in
15 view of the discussions we've had, it seems to me that
16 it may be a little misleading if somebody's going to
17 make a -- if somebody's going to try to -- a physician
18 or patient is going to try to define a risk to benefit
19 relationship if the data are presented that way, as
20 opposed to putting the reduction in angina data
21 altogether and putting all the other stuff together,
22 the AE's.

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1 DR. DILLARD: Jim Dillard.

2 There's no pre-agreement on any of this
3 labeling. I think what we have now is a data set, and
4 I think what we need to understand is how to most
5 appropriately get the data and the information in the
6 hands of the people who need to understand it, and
7 that being the patients and the clinicians.

8 CHAIRPERSON TRACY: So I think that's
9 probably a good point, that the data should be
10 separated with emphasis on the -- this is angina that
11 requires rehospitalization. So that would need to be
12 clarified if nothing else in that one table.

13 DR. WITTES: But that there also be a line
14 of patients with -- sorry. That there could be a line
15 that specifically says patients with cardiovascular
16 events excluding angina, that that line be there.

17 CHAIRPERSON TRACY: Or a different table.

18 DR. WITTES: Or a different table.

19 CHAIRPERSON TRACY: Okay.

20 DR. BERMAN: Okay. Question 7: please
21 identify and discuss the items that you believe should
22 be continued in a physician's training program for

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1 this device.

2 DR. PINA: I'll take an initial stab at
3 this. Other than the step-by-step of teaching
4 physicians how to use the device, I think it needs to
5 be said clearly about anginal improvement without
6 knowledge of the underlying mechanisms, and not fully
7 supported by exercise training, by exercise testing,
8 and that this should be reserved for patients with
9 coronary disease who are inoperable and, in fact, have
10 failed standard medical therapy, maximized.

11 I think all those caveats have got to be
12 in there.

13 CHAIRPERSON TRACY: Plus, I think the sum
14 of the technical experience from some of the
15 experienced operators is captured in the didactic
16 portion. I thought that wherever it went, the program
17 that the sponsor presented as a potential training
18 looked pretty reasonable to me.

19 DR. FERGUSON: Yeah, I agree with that.

20 DR. BERMAN: In the material presented
21 today?

22 CHAIRPERSON TRACY: In their initial

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1 presentation that's somewhere in here. Okay.

2 DR. BERMAN: This is Question 8. This is
3 the last question. This is looking towards the
4 future.

5 Eight (a): is additional clinical follow-
6 up of the PMA cohort needed to evaluate the long-term
7 effects of PMR?

8 CHAIRPERSON TRACY: Yes.

9 DR. BERMAN: Thank you.

10 (Laughter.)

11 DR. BERMAN: This will be in the
12 transcript.

13 Eight (b): please discuss the possible
14 use of PMR in conjunction with other modalities, and
15 would additional clinical trials be appropriate?

16 DR. FERGUSON: I'd like to speak to that.
17 I think that I'm not sure of the mechanism, but at
18 least until we have a fair body of follow-up data that
19 the instrument be restricted in its use to the pure
20 form, just like were outlined by the Eclipse people.

21 And the reason I say that is that, I mean,
22 we can do no worse service to Eclipse, nor can they do

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1 it to themselves, as to put this into somebody's hands
2 who's going to zap a few holes while they're doing
3 some other things, coronary stent and so on.

4 I feel very strongly about that.

5 DR. LASKEY: Could you help us? What
6 other modalities are you -- what's being swept under
7 the rug here?

8 DR. BERMAN: PCI.

9 DR. LASKEY: But these patients are not
10 candidates for revascularization by any means.

11 DR. KRUCOFF: That's not entirely true,
12 Warren. For instance, patients who have a
13 revascularizable lesion combined with a non-
14 revascularizable lesion or a lesion with a high risk
15 of restenosis. There are a lot of modalities --

16 DR. LASKEY: I see.

17 DR. KRUCOFF: -- that have already at
18 least partially been studied

19 CHAIRPERSON TRACY: Right, and I think you
20 would almost at that point be mimicking TMR where
21 there might be revascularization plus laser. I think
22 we wouldn't have enough data to support combining

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