

1 modalities at this point.

2 DR. BERMAN: Thank you.

3 (Laughter.)

4 CHAIRPERSON TRACY: Okay. I don't know
5 who dinged the gong there, but that didn't mean that
6 we had to stop.

7 (Laughter.)

8 CHAIRPERSON TRACY: I'd like to ask the
9 sponsor if they had any additional comments that
10 they'd like to make.

11 DR. WHITLOW: Yeah, there were some
12 questions about consistency of the data in terms of
13 angina relief and other parameters that we measured.
14 There are two slides that I think could help clarify
15 that if you'd allow us to show them.

16 Both are from the PACIFIC study. One is
17 ETT change by Canadian classification change, and the
18 other is the Seattle angina questionnaire change by
19 CCSAS change. If you wouldn't mind, we can show those
20 two slides.

21 CHAIRPERSON TRACY: Yeah, that's fine.

22 DR. WHITLOW: Okay. Well, the data are

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1 pretty striking. I mean, there's a relationship that
2 is linear between the proof --

3 MR. DILLARD: You need to speak into the
4 microphone for the transcriptionist.

5 Thanks.

6 CHAIRPERSON TRACY: Well, it's too small
7 to hold up and have you see, I guess. I guess you
8 don't have that on Power Point. Okay.

9 DR. WHITLOW: They took the computers
10 down.

11 CHAIRPERSON TRACY: Oh, dear. Okay. The
12 first is ETT change by angular change, baseline to 12
13 months, and help me.

14 DR. WITTES: Well, what it shows briefly
15 is that there's a strong association between the two.
16 What would be nice to see is the scatter because I
17 think the problem that we're facing is that if you
18 look at this, you see this nice trend, suggesting that
19 what you see in one variable overall you ought to be
20 seeing in the other variable, and we're not.

21 And so one explanation is that there's a
22 tremendous amount of scatter masked by the means, and

1 that's what we should be seeing.

2 DR. WHITLOW: Well, in this study, this is
3 PACIFIC. They do correlate, and the scatter is not
4 that great. In the BELIEF trial --

5 DR. WITTES: Oh, it's BELIEF, right.

6 DR. WHITLOW: This is the PACIFIC trial,
7 and they do correlate.

8 DR. WITTES: Okay. It's the BELIEF one
9 that's the problem, right?

10 DR. WHITLOW: Yes. I mean, that's what
11 you seem to be concerned about, and we believe it's a
12 matter of power, but that is not what you believe, and
13 I mean, that's your prerogative, and the difference in
14 the test, the way the test was run.

15 CHAIRPERSON TRACY: Any other issues?

16 (No response.)

17 CHAIRPERSON TRACY: Okay. Did the FDA
18 have any additional questions or comments?

19 MR. DILLARD: No, not at this time. Thank
20 you.

21 CHAIRPERSON TRACY: Okay. Either the
22 industry or consumer?

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1 MR. MORTON: Just a quick clarification.
2 Dr. Berman, on Question 8(b), the issue of additional
3 clinical trials, I'm not sure I understand who would
4 be responsible for those trials.

5 I know there's interest in seeing some
6 other studies done with other modalities, but --

7 MR. DILLARD: And let me see if I can
8 interpret what the response was from the Panel, which
9 was you didn't give us a real strong recommendation
10 one way or the other for clinical trials. I think
11 what I heard was that there is certainly no data for
12 combining modalities at this point, and I think we're
13 faced with what we're faced with every time with a new
14 technology when we do a clinical trial that's very
15 focused in a patient population, the expandability of
16 those results into other patient populations.

17 And certainly we draw a pretty fine line
18 at FDA in terms of labeling the product, and we would
19 restrict the labeling to much more closely mimic what
20 the clinical data told us, but the clinical practice,
21 I think, is the area where certainly our experience
22 has told us that we need to start proactively thinking

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1 about what do we do next.

2 And I think that we're going to start
3 adding a question like this much more frequently in
4 panel discussions because we need to think about next
5 steps.

6 And so I know we kind of sprung it on you
7 this time, but I'm just giving you a heads up that
8 we're going to keep springing it on you until we get
9 some good perhaps discussion about is there a need for
10 subsequent clinical trials; do these just sort of
11 evolve through clinical practice; do we think about
12 prospective registries to look at other patient
13 populations; and what are some of the best ways to get
14 at the information that's going to be most appropriate
15 for you in your clinical practice, and I think we all
16 need to start thinking about how do we continue to
17 further the science in new medical devices, and we
18 don't have the answer.

19 DR. KRUCOFF: So, Jim, the question though
20 is for trials other than what would be considered for
21 approval.

22 MR. DILLARD: Correct, but subsequent

1 approvals and/or subsequent clinical usages with other
2 modalities in this case.

3 CHAIRPERSON TRACY: Okay. Megan.

4 MS. MOYNAHAN: These are the panel
5 recommendation options for PMAs.

6 The medical device amendments to the
7 Federal Food, Drug, and Cosmetic Act, as amended by
8 the Safe Medical Devices Act of 1990, allows the FDA
9 to obtain a recommendation from an expert advisory
10 panel on designated medical device PMAs that are filed
11 with the agency.

12 The PMA must stand on its own merits, and
13 your recommendation must be supported by safety and
14 effectiveness data in the application or by applicable
15 publicly available information.

16 Safety is defined in the act as reasonable
17 assurance based on valid scientific evidence that the
18 probable benefits to health under conditions on
19 intended use outweigh any probable risks.

20 Effectiveness is defined as reasonable
21 assurance that in a significant portion of the
22 population the use of the device for its intended uses

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1 and conditions of use when labeled will provide
2 clinically significant results.

3 The recommendation options for the vote
4 are as follows:

5 One, approval if there are no conditions
6 attached;

7 Two, approvable with conditions. The
8 Panel may recommend that the PMA be found approvable
9 subject to specific conditions, such as physician or
10 patient education, labeling changes, or a further
11 analysis of existing data.

12 Prior to voting, all of the conditions
13 should be discussed by the panel.

14 Three, not approvable. The Panel may
15 recommend that the PMA is not approvable if the data
16 do not provide a reasonable assurance that the device
17 is safe or if a reasonable assurance has not been
18 given that the device is effective under the
19 conditions of use prescribed, recommended or suggested
20 in the proposed labeling.

21 Following the voting, the chair will ask
22 each Panel member to present a brief statement

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1 outlining the reasons for their vote.

2 CHAIRPERSON TRACY: All right. At this
3 point I'd like to ask someone from the Panel to put
4 forth a motion regarding this application.

5 Dr. Laskey.

6 DR. LASKEY: I hereby put forth the motion
7 to--

8 CHAIRPERSON TRACY: To what? What is your
9 motion?

10 DR. LASKEY: Well, just remind me of the
11 methodology here.

12 CHAIRPERSON TRACY: At this point we're
13 asking for a motion whether, given what Ms. Moynahan
14 just read to us, whether it's approvable, approvable
15 with conditions, or not approvable.

16 MS. MOYNAHAN: Not approvable, and if it's
17 -- I'll just remind the Panel that if it's approvable
18 with conditions, we'll go through each condition
19 separately.

20 DR. LASKEY: All right. Well, so in other
21 words, I would move for a specific one, two, or three.

22 CHAIRPERSON TRACY: Yes.

1 MR. LASKEY: All right. I think that what
2 we've heard today is certainly a noble effort to
3 grapple with a very difficult problem. As somebody
4 who has also dealt with this for 25 years now, the
5 combination of desperate patients and enthusiastic
6 physicians generally winds up one of two ways: a
7 disaster or a short-term benefit.

8 And I am struck by the rate of adverse
9 events in the PACIFIC trial. I can't look away from
10 it. It has nothing to do with power. It just has to
11 do with raw numbers.

12 That, in conjunction with the lack of a
13 substantial benefit that I can feel comfortable
14 quantifying, would lead me to propose that we do not
15 approve this PMA.

16 DR. DOMANSKI: Second.

17 CHAIRPERSON TRACY: All right. Since
18 there is no conditions to discuss or outline here, I
19 believe we'll just take the vote.

20 MS. MOYNAHAN: Yeah, when you take the
21 vote individually ask each Panel member to explain how
22 the sponsor would be able to move the application into

1 an approvable form

2 CHAIRPERSON TRACY: And state what your
3 individual vote would be.

4 DR. DOMANSKI: I don't think it's
5 approvable now, but I think that the way to -- oh, I'm
6 sorry. I thought you were pointing to me.

7 CHAIRPERSON TRACY: Do you want a raise of
8 hands for the vote?

9 Jim, do you want a raise of hands for
10 votes? All right.

11 All in favor of -- all who feel that this
12 is not approvable, please indicate so.

13 (Show of hands.)

14 MS. MOYNAHAN: Seven.

15 CHAIRPERSON TRACY: Those who disagree
16 with the motion that this is not approvable, please
17 indicate so.

18 MS. MOYNAHAN: Two.

19 CHAIRPERSON TRACY: All right. Now we'll
20 go around the table and please hear what your
21 individual votes are.

22 DR. DOMANSKI: I think the concern about

1 safety remains, you know, extant, and I think that
2 that could be removed by further study or sustained,
3 and it may be that the thing really is more dangerous,
4 and if it is, you'll know it. But I think there
5 probably needs to be more data collection that makes
6 that clear, and if it were, then I'd say it is
7 approvable because I do think it appears to reduce the
8 symptoms of angina.

9 We've certainly seen that in patients, but
10 the safety issue is not demonstrated.

11 CHAIRPERSON TRACY: Dr. Krucoff.

12 DR. KRUCOFF: I also think it's not
13 approvable in its current form because the safety and
14 efficacy issues to me are simply unresolvable in the
15 data set that was available to us today.

16 I think that increased patient numbers and
17 follow-up, some sort of measure or determination of
18 functional element, as well as symptomatic
19 improvement, and a more robust approach to safety
20 would bring us back to the table.

21 I think what is clear to me from the
22 investigators collected on behalf of the instrument

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1 today and from at least the overall sense that angina
2 is reduced is that the device is doing something, that
3 it may offer a nonsurgical approach to patients who
4 are in desperate straits, but that it remains in my
5 mind imperative until our unless we understood the
6 mechanism to have robust, objective, and functional
7 data about who you would really recommend this
8 procedure to and at what possible cost in terms of
9 their safety.

10 CHAIRPERSON TRACY: Dr. Klocke.

11 DR. KLOCKE: I think the terms of how it
12 might be improved either by resolving the safety
13 issue, as Mike has pointed out, our improving the
14 efficacy, as Mitch has pointed out, and those are the
15 two issues, and I think if that information were
16 available, I would certainly favor it being looked at
17 further, looked at again.

18 CHAIRPERSON TRACY: Dr. Pina.

19 DR. PINA: I would echo my colleagues'
20 suggestions. I would like to see the objective
21 evidence. We have had anginal trials for years, and
22 there are objective points that could be brought out

1 that would consistently support the anginal
2 improvement. I think if I had seen it in the second
3 trial I would feel better about it.

4 But I also think that disease severity --
5 and I hate to go back to it -- but I think that
6 disease severity is important, and therefore, honing
7 in on the patient population that is, in fact, sicker,
8 that has a greater burden of disease, perhaps that
9 diabetic group which we know don't do well, honing in
10 on that population may really be a very important part
11 of this.

12 CHAIRPERSON TRACY: Dr. Ferguson.

13 DR. FERGUSON: Well, I was going to
14 approach this in a little different fashion. I was
15 thinking that there's no question about the efficacy.
16 They've proved that from whatever reason or however it
17 works, and we've been through this with other
18 instruments and so on in the past.

19 I think our rejection of the PMA at the
20 moment is based on pretty thin data that we have
21 contrived. Now, that may be all right to do, but I
22 was going to approach it by saying I would approve it,

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1 but put very, very stringent rules and regulations on
2 how data, you know, was collected in the future, but
3 that's just my personal feeling.

4 CHAIRPERSON TRACY: Anything additional,
5 Dr. Laskey?

6 DR. LASKEY: Well, sine everyone is
7 qualifying it, none of us feel good about turning this
8 down because we've all taken care of these patients,
9 but I think that in addition to the objective
10 verification of the primary endpoint, it needs to be
11 realized that one-year follow-up for symptoms is
12 inadequate in the study of coronary disease. It just
13 needs to go on for longer, and it's quite possible
14 that the beneficial trends seen in this trial will not
15 persist at 18 months or 24 months.

16 So certainly longer follow-up is required
17 for these symptomatic endpoints.

18 CHAIRPERSON TRACY: Dr. Wittes.

19 DR. WITTES: Yeah, I just echo what
20 everybody else has said. I'm not convinced by the
21 balance of safety and efficacy, and I think that some
22 more concerted estimate to get an estimate of what the

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1 magnitude of efficacy would be is, and again, I echo
2 the follow-up data, asking for follow-up data to see
3 what kind of long-term safety profile there is.

4 CHAIRPERSON TRACY: Dr. Borer.

5 DR. BORER: Yeah, this is very difficult,
6 I think. I think there's a probably real, but
7 possibly modest and certainly inconsistent from the
8 data we've seen effect on a symptom, angina, and a
9 pure risk, the magnitude of which also isn't well
10 defined, without evidence of a pharmacologic effect
11 that could mitigate the risk like an anti-ischemic
12 effect.

13 So I think that what's needed here are
14 more data from a well designed trial, more studies
15 like BELIEF, which would enhance our acceptance of the
16 consistency of the anti-anginal effect with both ways
17 of looking at it, exercise tolerance and spontaneously
18 reported symptoms, and that would also provide us with
19 some evidence of a pharmacology effect.

20 I said pharmacologic effect. That's
21 wrong, isn't it? This is devices.

22 Some evidence of an effect, a

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1 pathophysiologically modifying effect that might help
2 to explain why the putative benefit occurs so that we
3 can feel more comfortable about the risk to benefit
4 relationship.

5 And, too, believe that we need longer
6 follow-up. I think, however, I would recommend that
7 the FDA request the sponsor to obtain further follow-
8 up if it's possible to do in the populations they've
9 already established because the burden of establishing
10 a new population and following that population for a
11 year seems excessive.

12 So I think there are populations more data
13 can be obtained from, and while the additional data on
14 consistency are obtained.

15 CHAIRPERSON TRACY: Dr. Kaptchuk.

16 DR. KAPTCHUK: I primarily voted against
17 the motion because I would have voted against any
18 majority vote because I wanted to abstain, but I
19 didn't know if I was allowed, and the reason I wanted
20 to abstain is it's really hard to make a judgment, and
21 I guess when you can't make a judgment clearly,
22 conservatively you should not make the judgment. That

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1 means a negative one.

2 But I want to argue one point that I think
3 that wasn't taken into consideration, which was that
4 I'm concerned that this TMR procedure is on the market
5 and iso ut there, and I don't know the evidence for
6 that. I have not read the material.

7 But I did notice their chart on the wall
8 where they showed across different trials the efficacy
9 comparison, and it would have been nice if that was
10 aggregated in a meta analytic way, but my guess is
11 that there's things on the market that are much worse,
12 both pharmacological and surgical.

13 But I was told that I'm not allowed to
14 consider data that wasn't presented, but actually
15 there was some data presented about other trials.

16 So I feel that this is a really hard call,
17 and my most important consideration was that I think
18 it was a really good attempt at putting into the
19 market and some really good trial efforts, and I just
20 wanted to say that I wanted to vote and say that it's
21 not clear. So I wanted to go against the majority.

22 MR. DILLARD: Jim Dillard.

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1 I just wanted to make a comment on that.
2 I think the issue is not that you can't consider other
3 information that already is in the clinical literature
4 and the majority of what they presented to you is
5 stuff that's already in the clinical literature, which
6 is certainly something that can be considered in your
7 deliberation, as well as in your thought process of
8 what a recommendation might be.

9 So I think where it gets a little bit more
10 difficult for us is if the sponsor present something
11 that isn't currently available and neither you nor the
12 FDA has seen that information. It gets problematic in
13 terms of the interpretation as well as the
14 recommendation.

15 But I think in this case much of that
16 information is already in the literature.

17 CHAIRPERSON TRACY: The only other comment
18 I'd like to make is that I wouldn't like to see the
19 sponsor saddled with being the one who has to show why
20 laser revascularization works. That, I think, is
21 beyond the scope of any type of study like this, and
22 I don't think that would be reasonable.

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1 And I also think that regardless of what
2 type of study we have, there's going to be some
3 internal discrepancy in the studies. This BELIEF was
4 much better designed, I think, than PACIFIC, or
5 PACIFIC would have been better designed had it not had
6 the two phases within it.

7 So I think just going forward having
8 apples to compare with apples would be useful.

9 Any comments from the industry rep.?

10 MR. MORTON: Yes, I agreed with Dr. Borer
11 regarding the issue of the desire for more than 12
12 months' follow-up. I encourage the agency to, number
13 one, be consistent with similar studies and similar
14 devices in the follow-up that has been required there.

15 And also if there is a way to look at the
16 cohort or somehow get that information that you desire
17 without putting the burden on the sponsor, I'd
18 encourage that.

19 CHAIRPERSON TRACY: Any additional
20 comments from the audience?

21 (No response.)

22 CHAIRPERSON TRACY: If not, then we'll

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close the open public session for today.

(Whereupon, at 5:27 p.m., the Panel meeting was adjourned.)

CERTIFICATE

This is to certify that the foregoing transcript in the
matter of: Circulatory System Devices Panel of the
 Medical Devices Advisory Committee

Before: DHHS/FDA/CDRH

Date: July 9, 2001.

Place: Gaithersburg, MD

represents the full and complete proceedings of the
aforementioned matter, as reported and reduced to
typewriting.


