

**U.S. DEPARTMENT OF HEALTH AND HUMAN  
SERVICES**

**FOOD AND DRUG ADMINISTRATION**

**CARDIOVASCULAR AND RENAL DRUGS  
ADVISORY COMMITTEE**

**85TH MEETING**

Thursday  
July 9, 1998

4015

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JUL 21

19:36

The Advisory Committee met in the Main Auditorium in the Natcher Building, National Institutes of Health, Bethesda, Maryland at 9:00 a.m., Dr. Milton Packer, M.D., Chairperson, presiding.

PRESENT:

MILTON PACKER, M.D., Chairperson  
ROBERT CALIFF, M.D., Committee Member  
JOHN DIMARCO, M.D., Committee Member  
THOMAS GRABOYS, M.D., Committee Member  
CINDY GRINES, M.D., Committee Member  
MARVIN KONSTAM, M.D., Committee Member  
JOANN LINDENFELD, M.D., Committee Member  
LEMUEL MOYE, M.D., Ph.D., Committee Member  
ILEANA PINA, M.D., Committee Member  
UDHO THADANI, M.D., FRCP, Committee Member  
ALAN HIRSCH, M.D., Guest Expert  
ROBERT TEMPLE, M.D., Guest Expert  
JOAN C. STANDAERT, Executive Secretary

This transcript has not been edited or corrected, except where relevant for the deletion of materials not releasable under the Freedom of Information Act. Accordingly, the Food and Drug Administration makes no representation as to its accuracy.

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**AGENDA**

Opening Remarks

Dr. Milton Packer.. . . . . 3

Ms. Joan Standaert . . . . . 3

**Sponsor's** Presentation - NDA 20-863 **Pletal** oral  
Otsuka America Pharmaceutical, Inc.

Dr. EduardoAbrao . . . . . 6

Dr. **Donald Cilla** . . . . . 11

Dr. William Hiatt . . . . . 35

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Committee Discussion and Recommendations . . . . . 324

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

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8:58 a.m.

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CHAIRPERSON PACKER: I'd like to bring the 85th meeting of the Cardiovascular and Renal Drugs Advisory Committee to order. I will ask Joan Standaert to read the conflict of interest statement for this morning's meeting. Joan?

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MS. STANDAERT: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting with the following exception.

In accordance with 18 U.S.C. 208B3, a full waiver has been granted to Dr. Marvin Konstam, which permits him to participate in all official matters concerning Pletal. A copy of the waiver statement may

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be obtained by submitting a written request to the Agency's Freedom of Information Office, Room **12A30** of the Parklawn Building.

In addition, Dr. Joan Lindenfeld's employer, the University of Colorado Health Science Center, is **involved** in unrelated studies sponsored by Otsuka America Pharmaceutical Incorporated. Although this interest does not constitute a financial interest in the particular matter within the meaning of 18 **U.S.C.** 208, it could create the appearance of a conflict. However, it has been determined, notwithstanding this interest, that it is in the Agency's best interest to have Dr. **Lindenfeld** participate in the committee's discussions concerning **Pletol**. In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to FDA's invited guests, Dr. Alan Hirsch has reported interests which we believe

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1 should be made public to allow the participants to  
2 objectively evaluate his comments. Dr. Hirsch would  
3 like to disclose that he is the Chair of the  
4 Peripheral Arterial Disease Primary Care Education  
5 Initiative of the Society for Vascular Medicine and  
6 Biology, which is sponsored by an unrestricted  
7 educational grant from Otsuka America. In addition,  
8 Dr. Hirsch participated as a principal investigator  
9 and a scientific advisor on **cilostazol**. Further, Dr.  
10 Hirsch also participated as a principal investigator  
11 in the Minnesota Regional PAD Screening Program  
12 sponsored by Hoechst Marion Roussel.

13 With respect to all other participants, we  
14 ask in the interest of fairness that they address any  
15 current or previous financial involvement with any  
16 firm whose products they may wish to comment upon.  
17 That concludes the conflict of interest statement for  
18 July 9, 1998.

19 CHAIRPERSON PACKER: Thank you, Joan. Let  
20 me just remind the members of the committee that the  
21 auditorium here is equipped with some certain  
22 advantages and disadvantages. One of the advantages

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1 is that we all have our individual microphones, which  
2 doesn't always occur, but these microphones have  
3 activation buttons. So please push the button if you  
4 would like to speak. Otherwise, no one will be able  
5 to hear you. So just a small technical issue for this  
6 morning's meeting.

7 We have reserved time for any public  
8 comment. **Is** there any public comment? There being no  
9 public comment, we will proceed with the presentation  
10 and topic for this morning. The drug being reviewed  
11 this morning is cilostazol. The indication is for  
12 intermittent **claudication**. The sponsor is Otsuka  
13 America. The sponsor can proceed with its  
14 presentation for this morning.

15 DR. ABRAO : Mr. Chairman and FDA  
16 officials, ladies and gentlemen, and members of the  
17 Advisory Committee for the Division of **Cardio** Renal  
18 Drug Products. My name is Eduardo Abrao. I am the  
19 Vice President for Regulatory and Medical Affairs for  
20 Otsuka America Pharmaceuticals.

21 We are pleased to be here today to present  
22 and discuss **Pletol**. Pletol goes by the generic name

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1 of' **cilostazol**. Cilostazol is a dihydal qinolinon  
2 derivative with a molecular weight of 369.47. This  
3 compound is a phosphodiesterase inhibitor. Its  
4 pharmacological profile includes anti-platelet  
5 activity, **anti-thrombotic** activity, **vasodilation**, and  
6 inhibition of vascular smooth muscle cell  
7 proliferation. In addition, **cilostazol** decreases  
8 triglycerides and increases HDL cholesterol levels.

9 The indication for **cilostazol** in this NDA  
10 is for the improvement of functional capacity in  
11 patients with intermittent claudication. **Cilostazol**  
12 has been subjected to a global clinical development  
13 program since the early 1980's for other indications  
14 in addition to intermittent claudication such as  
15 **ischemic symptoms, ulcer pain, and cold sensation in**  
16 chronic arterial occlusion. It was initially approved  
17 for marketing in Japan in 1988. Subsequently approved  
18 and marketed in other Asian countries as well as in  
19 Latin America. In all these countries, the  
20 recommended dosage for **cilostazol** is 100 mg twice  
21 daily.

22 In the United States, Otsuka America

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1       Pharmaceutical filed an IND for **cilostazol** in November  
2       of 1990. In September of 1997, we filed our NDA. In  
3       January of this year, we submitted our 120-day safety  
4       update. And on June 1, we submitted amendments to  
5       include data from the United States and the United  
6       Kingdom in toxic filing comparative files.

7                 The basis for approval in this submission  
8       is supported by eight adequate and well-controlled  
9       studies. In these studies, the efficacy of **cilostazol**  
10       was demonstrated through the improvement in walking  
11       distance, quality of life, and patient's functional  
12       status. **Cilostazol** has shown additional beneficial  
13       effects by increasing the levels of HDL cholesterol  
14       and decreasing the levels of triglycerides.

15                Our safety data submitted in this NDA  
16       includes 2,702 patients. 1,374 patients of these  
17       patients received **cilostazol** and only two were lost to  
18       follow-up. Our total safety data base also includes  
19       experience with more than 850,000 patients that were  
20       prescribed **cilostazol**. In this data base, common  
21       adverse events were observed such as headache and  
22       diarrhea. Due to the nature of this patient

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1 population , cardiovascular events will be discussed in  
2 detail during today's presentation. However, the  
3 treatment with **cilostazol** had no effect on the overall  
4 mortality rate.

5 Our first speaker today will be Dr. Donald  
6 **Cilla**. Dr. Cilla will present an overview of the  
7 pharmacology of **cilostazol**. To provide a background  
8 and discussion of current therapies for intermittent  
9 **claudication**, the following speaker will be Dr.  
10 William **Hiatt**. Dr. Hiatt is a professor of vascular  
11 medicine at the University of Colorado at Denver.  
12 Following Dr. Hiatt's presentation will be Dr. William  
13 Forbes. **Dr.** Forbes will discuss the clinical  
14 development program and the efficacy of **cilostazol**.  
15 Next, Dr. Gary Ingenito will review the safety data  
16 from our total safety data base. Our last speaker  
17 will be Dr. Jeffrey Borer, the Gladys and Roland  
18 Harriman Professor of Cardiovascular Medicine, Cornell  
19 University Medical College. Dr. Borer will conclude  
20 by providing the benefit/risk analysis supporting the  
21 approval of **cilostazol**. And finally, we have present  
22 here today other experts that are available for

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1 additional reference if it is necessary. I thank you  
2 for your attention and at this time I would like to  
3 invite Dr. **Cilla** to give his presentation.

4 CHAIRPERSON PACKER: Before we do that,  
5 Ray, let me just ask, the sponsor has submitted new  
6 studies to the Agency and to the Division on June 1.  
7 Have those studies been reviewed? Are those reviews  
8 -- or are our deliberations today dependent on  
9 subsequent review by the Division?

10 DR. LIPICKY: I don't know. I will have  
11 to ask the question. Do you know, Dr. Karkowski?

12 DR. KARKOWSKI: We have looked at the  
13 efficacy of the review, and I think there will be some  
14 changes based on reanalysis, but not substantial in  
15 nature. So I think that you could -- we have pretty  
16 much in agreement come to most of the main --

17 CHAIRPERSON PACKER: And you are prepared  
18 to discuss the analysis that you have done -- the  
19 reviews **you** have done on those studies?

20 DR. KARKOWSKI: Correct.

21 CHAIRPERSON PACKER: Okay. Terrific.

22 DR. LIPICKY: If that study is really

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1 critical to your decision making.

2 CHAIRPERSON PACKER: Okay.

3 DR. LIPICKY: I know you did not receive  
4 a copy of the review yet.

5 CHAIRPERSON PACKER : Okay. Could the  
6 sponsor identify which studies were submitted on June  
7 **1?**

8 DR. FORBES : Bill Forbes. Yes, study  
9 96202 was a U.S. comparator trial of **cilostazol** 100 mg  
10 vs. **Trental**. And study 94301, which was performed in  
11 the United Kingdom.

1 DR. TEMPLE: Don't we have -- 1 thought  
2 the statistical review of those studies was included  
3 in the package. It was included in mine, right? So  
4 you have **at** least the statistical review of those  
5 studies.

6 DR. KARKOWSKI: The medical review is  
7 there. The statistical review is there. And they  
8 have been incorporated into the thought process of the  
9 global review.

10 DR. TEMPLE: Okay.

11 CHAIRPERSON PACKER: Does that mean that  
12 the only thing that is missing is review of safety or  
13 has that been completed as well?

14 DR. KARKOWSKI: The review of safety is  
15 there except there are some discrepancies that are  
16 minor in nature that we are trying to clear up and  
17 some details as to the safety. So it is pretty much  
18 a complete review.

19 CHAIRPERSON PACKER : Okay. The reviews  
20 that we have received, both from yourself and Dr.  
21 Rodin, indicate that there are analyses which are  
22 either ongoing or have been requested. And that is

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1 still the status of those questions at the present  
2 time?

3 DR. KARKOWSKI : We have received an  
4 analysis of the helter yesterday. We have questions  
5 with respect to a couple of data bases that were used  
6 that I don't think are going to substantially change  
7 the conclusions.

8 CHAIRPERSON PACKER: Okay. Thank you.

9 DR. CILLA: With the permission of the  
10 Chair, I **will** go ahead and continue. My name is Don  
11 **Cilla**, and I am from the Clinical Pharmacology  
12 Department at OAPI. This morning I will be presenting  
13 a brief overview of the pharmacologic effects of  
14 **cilostazol** as observed in both animal and human  
15 studies.

16 The precise mechanism by which **cilostazol**  
17 improves physical mobility is not fully understood.  
18 However, the broad spectrum of pharmacologic effects  
19 may work together to bring about symptomatic relief.  
20 **Cilostazol** is first an anti-platelet/anti-thrombotic  
21 agent. **Cilostazol** inhibits platelet activation, which  
22 in turn prevents the accumulation of platelets and the

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1 release of prothrombotic proliferative inflammatory  
2 and vasoactive substances. In addition, **cilostazol** is  
3 a vaso-relaxant. These properties may contribute to  
4 improved peripheral blood flow.

5 Through enhancing the effects of  
6 lipoprotein **lipase**, **cilostazol** has a beneficial effect  
7 on the lipid profile in intermittent **claudicants**.  
8 These are patients who commonly have dyslipidemia.  
9 The likely mechanism of many of these effects is  
10 through increased cyclic AMP levels as a result of  
11 phosphodiesterase inhibition, specifically PDE3  
12 inhibition. As with other drugs of this class,  
13 **cilostazol** has some associated cardiac and hemodynamic  
14 effects which I will discuss shortly.

15 We propose that **cilostazol** be administered  
16 either **50** or 100 mg bid orally. These dosages are  
17 associated with plasma concentrations of approximately  
18 **3.6 micromolar**. The majority of **cilostazol** plasma  
19 concentrations were within the range of **1.8** to **4.8**  
20 micromolar. However, rare patients had values as high  
21 as **10 micromolar**. I provide the concentrations in  
22 **micromolar** measurements to allow you to place the data

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1 from the **preclinical** pharmacology studies into  
2 perspective.

3 Approximately 95 to 98 percent of  
4 **cilostazol** is bound to plasma proteins. **Cilostazol** is  
5 predominantly cleared **renally** and the metabolism of  
6 **cilostazol** is primarily through the cytochrome P450  
7 384 system. In vitro testing has established that  
8 **cilostazol** does not inhibit cytochrome P450 enzymes in  
9 clinically relevant concentrations. These topics will  
10 be addressed later today within the safety  
11 presentation.

12 In patients and healthy volunteers,  
13 **cilostazol** doses of 100 mg bid consistently inhibited  
14 secretion of platelet-derived mediators. In addition,  
15 **cilostazol** inhibited platelet aggregation induced by  
16 thrombin, collagen, ADP, and arachidonic acid.  
17 **Cilostazol's** effects were observed rapidly following  
18 a single dose and have been prolonged up to 24 hours  
19 in some studies. These effects on platelets are  
20 thought to result from decreased intracellular  
21 calcium. This comes as a result of increased cyclic  
22 AMP levels which stabilize the platelet and prevent

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activation and aggregation. These effects are enhanced by the addition of  $PGE_1$ .  $PGE_1$ , as we know, stimulates adenylate cyclase, which further increases cyclic AMP levels.

Cilostazol inhibits thrombus formation in the mouse pulmonary emboli model in a dose-related fashion. Anti-thrombotic activity has also been observed in the Foltz model. Significant reductions in cyclic flow variations were observed at one to two hours post interduodenal dose. Plasma concentrations in both of these models were well below those observed clinically.

Cilostazol also produces vasodilation and increases blood flow in dog models. Cilostazol dilated human subcutaneous resistance arteries in concentrations achieved clinically. In patients with intermittent claudication, doses of 100 mg bid were associated with improvements in blood flow following exercise. All of these effects may be mediated by decreased intracellular calcium as a result of increased cyclic AMP concentrations. This ultimately leads to vasorelaxation in vascular smooth muscle

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1 cells.

2                   **Cilostazol** also inhibits vascular smooth  
3 muscle cell proliferation in a concentration-dependent  
4 fashion. These effects were observed over the  
5 concentration range of 1:30 micromolar. Other **PDE<sub>3</sub>**  
6 specific inhibitors such as amrinone and non-specific  
7 inhibitors such as IBMX have limited effects in this  
8 model. Evidence of these effects were also noted in  
9 clinical trials of restenosis following percutaneous  
10 coronary interventions. In separate studies involving  
11 stenting and atherectomy procedures, there was a trend  
12 towards improvement in the rate of restenosis.

13                   **Cilostazol** has a beneficial effect on  
14 lipids. This appears to be the result of enhancing  
15 lipoprotein lipase activity. This facilitates the  
16 removal of triglycerides and increases HDL cholesterol  
17 levels. These effects are observed in rat diabetic  
18 models and in patients with intermittent **claudication**,  
19 particularly those patients who have hyperlipidemia.  
20 In these patients, reductions in triglycerides of 20  
21 to 25 percent and increases in HDL cholesterol of 10  
22 percent are observed. While there were not

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1 significant changes in LDL cholesterol levels, the  
2 ratio of APO-A1 to APO-B changed in a favorable  
3 fashion.

4 Like other drugs which inhibit PDE<sub>3</sub>,  
5 **cilostazol** exhibits similar trends in cardiovascular  
6 hemodynamics in isolated organ and **whole animal**  
7 models. These effects include increased heart rate,  
8 coronary blood flow, contractility, and others that I  
9 have listed on the slide. They are likely due to  
10 elevated intracellular cyclic AMP and cardiac myocytes  
11 and coronary vascular smooth muscle cells.

12 With the original NDA submission, OAPIdid  
13 not know the effects of **cilostazol** on cyclic AMP  
14 levels in cardiac myocytes. Additional experiments  
15 have been conducted to determine these levels and how  
16 the findings relate to other PDE<sub>3</sub> specific inhibitors.  
17 These results are now available. They were provided  
18 to the FDA this past week. And with the permission of  
19 the Chair, we would like to display these results  
20 today.

21 In the experiment depicted in the graph on  
22 the left, human platelets were obtained from healthy

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1 volunteers, platelet-rich plasma prepared, and the  
2 cells exposed to increasing concentrations of both  
3 **cilostazol** and **milrinone**. As you can see, the cyclic  
4 AMP levels increased from control in a **concentration-**  
5 **dependent** fashion for both drugs, **cilostazol** in the  
6 green **and milrinone** in the red. There were no  
7 significant differences between the two.

8 In the experiment depicted on the right,  
9 cyclic AMP levels were measured in rabbit ventricular  
10 myocytes following exposure to **cilostazol** and  
11 **milrinone**. **Cilostazol** had minimal effects on cyclic  
12 AMP up to concentrations of about 30 **micromolar**, while  
13 the cyclic AMP elevating effect of **milrinone** was far  
14 more potent.

15 And additional study to compare the  
16 cardiovascular effects of **cilostazol** and **milrinone** was  
17 conducted. This graph displayed shows that **cilostazol**  
18 and **milrinone** and similar effects on increasing  
19 coronary blood flow in an isolated heart model. These  
20 effects were concentration-dependent over a range of  
21 concentrations up to 30 **micromolar**. Heart rates in  
22 this **model** did not significantly increase in either

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1 the **cilostazol** or the **milrinone** groups.

2 Also in this model, the maximum  
3 contractility increased in a concentration-dependent  
4 fashion for both drugs. However, the effect for  
5 **milrinone** was much stronger. These effects were  
6 statistically significantly greater for **milrinone** than  
7 **cilostazol** at concentrations of 10 **micromolar** and  
8 above. This parallels the cyclic AMP changes observed  
9 in the rabbit myocytes.

10 In summary, **cilostazol** has many  
11 pharmacologic features which may contribute to its  
12 positive effect on the symptomatic relief of  
13 **claudication**. Many of these effects are likely to be  
14 due to cyclic AMP elevations in various tissues. That  
15 is the end of this presentation.

16 CHAIRPERSON PACKER: We will open this up  
17 for discussion and begin with our primary reviewer,  
18 Dr. **Lindenfeld**. JoAnn?

19 DR. LINDENFELD: In relation to comparison  
20 to **milrinone**, do you have any comparisons to any of  
21 the **other** PDE<sub>3</sub> inhibitors in any of these same  
22 preparations?

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1 DR. CILLA: No. We don't have amrinone or  
2 other PDE<sub>3</sub> inhibitors in these models at this time.  
3 These studies were literally conducted with in the  
4 last two to three weeks.

5 DR. LINDENFELD: And this is a clinical  
6 question, in all of the data, cilostazol increases  
7 heart rate both by EKG and helter. Can you give us  
8 some idea of how that relates to clinical studies of  
9 the other PDE<sub>3</sub>? Although I know they are different  
10 diseases, are these heart rate increases different or  
11 what -- or similar?

12 DR. CILLA: Can you help me understand the  
13 question?

14 DR. LINDENFELD: Sure. Can you relate in  
15 other studies of PDE<sub>3</sub> inhibitors heart rate increases?  
16 Does it increase more or less? I know they are  
17 different patient populations, but there is a  
18 substantial dose-related increase here.

19 DR. CILLA: Yes. Well, we see a modest  
20 increase in heart rate in the cilostazol clinical  
21 studies. And probably what I would do is ask if you  
22 could refer that question later to the clinical people

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1 that come up and have conducted our studies. They may  
2 have some **better** comparisons than I have available  
3 from the **preclinical** literature.

4 DR. LINDENFELD: And are we going to talk  
5 later about cytochrome inhibition? Is that going to  
6 come up later?

7 DR. CILLA: Yes. In fact, later today we  
8 will be discussing that.

9 DR. LINDENFELD: Okay. Go ahead, do you  
10 want to ask a question? Let's see -- improvement in  
11 the **ABIs**? That will come up later as well -- in the  
12 ankle **brachial** index?

13 DR. CILLA: I am having a hard time  
14 hearing you. I think it projects out.

15 DR. LINDENFELD: Improvement in the ankle  
16 **brachial** indexes? Are you going to show some more  
17 data on that later? You just referred to that.

18 DR. CILLA: Yes, that will be displayed  
19 later.

20 DR. LINDENFELD: Okay. And the lipid  
21 values too? In our brochure, one of the primary  
22 endpoints of one of the studies was an HDL, but the

1 data wasn't presented. Will that be presented later?

2 DR. CILLA: That will be presented later  
3 as well.

4 DR. LINDENFELD: I think that is my  
5 questions. Or one other question -- again, this **may**  
6 come later. But you referred to a trend to  
7 improvements in coronary stenting, but in our packet  
8 the data wasn't considered **evaluatable** or wasn't  
9 evaluated., is that correct? I can't remember who  
10 reviewed that. But the coronary stenting data was  
11 not --

12 DR. CILLA: These are publications which  
13 have recently come out in the American Heart Journal.  
14 Small numbers of subjects. There were statistically  
15 significant changes in 70 patients. However, because  
16 of the **sample** size, we really only indicated that  
17 there was a trend. And it seemed to be in a similar  
18 direction of what we saw in the **preclinical** models.

19 DR. LINDENFELD: Okay.

20 CHAIRPERSON PACKER: Okay. We will go  
21 through the many other members. Let me just ask each  
22 member to make sure that the question they are going

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1 to ask is not going to be the specific focus of a  
2 presentation later on, because otherwise it will be a  
3 little bit reiterative. So with that in mind, we will  
4 just go down the line. Ileana?

5 DR. PINA: As far as mechanisms go, you  
6 said that the drug inhibits vascular smooth muscle  
7 proliferation. Do you have any better elucidation of  
8 that mechanism?

9 DR. CILLA: We have looked specifically at  
10 models of thymidine uptake into human umbilical  
11 arteries and into rat aortic smooth muscle cells. And  
12 through that, we have seen a decrease in the amount of  
13 the substances coming up. With respect to the  
14 specific mechanism, no, we do not know that.

15 DR. PINA: So you don't know if it is a  
16 direct effect of the drug or is it an effect of the  
17 fact that you've caused vasodilation? Perhaps someone  
18 can comment on that. If that is going to be focused  
19 on later, I will wait.

20 DR. CILLA: I don't think it will be  
21 focused on later. My understanding from the models is  
22 that that would be a direct effect of the drug.

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1 DR. PINA: Okay.

2 CHAIRPERSON PACKER: It looks like the  
3 next person is Udho.

4 DR. THADANI: I think he might have partly  
5 answered the question. My major issue was the  
6 arm/ankle index. Are you going to show more data both  
7 at rest and exercise in patients with peripheral  
8 vascular disease or are you just going to remark --  
9 your comments are just going to be normal population?  
10 In patients with peripheral vascular disease --

11 DR. CILLA: Yes, there is a very extensive  
12 presentation later in patients with peripheral  
13 vascular disease.

14 DR. THADANI: The reason I am saying that  
15 is because looking at the review, the changes are kind  
16 of borderline. And yet, you are going to show some  
17 data?

18 DR. CILLA: Yes.

19 DR. THADANI: That is okay.

20 CHAIRPERSON PACKER: Tom?

21 DR. GRABOYS: Both your and the original  
22 introductory presentation underscore the benefits of

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1 the lipid changes. I assume this is inferential or  
2 assumptive. It is not based on outcomes data.

3 DR. CILLA: Oh, that is correct. We have  
4 observed lipid changes in clinical studies and we have  
5 **preclinical** results which support what we have  
6 observed clinically. But there are no long-term  
7 outcome data studies.

8 CHAIRPERSON PACKER: John?

9 DR. DIMARCO: Do you have any **preclinical**  
10 data on either electrocardiographic changes or  
11 **electrophysiologic** data in vitro?

12 DR. CILLA: NO, NO, we don't have that.

13 CHAIRPERSON PACKER: Marv?

14 DR. KONSTAM : Just going back to the  
15 comparisons that you have presented with regard to  
16 milrinone. Is there a way you can help us put this in  
17 perspective, **vis-a-vis** the achieved plasma  
18 concentrations in clinical trials with **milrinone**, for  
19 example?

20 DR. CILLA: Sure.

21 DR. KONSTAM: Versus this agent. And I  
22 guess, just let me -- where I **guess it gets more**

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1 complicated is that there are significant active  
2 metabolizes involved here. so that I don't know **how**  
3 -- how would we put this in perspective vis-a-vis the  
4 plasma concentrations?

5 DR. CILLA: Sure. The concentrations in  
6 the models that we were studying, there was a lot of  
7 effect for **cilostazol** in the 1 to 3 **micromolar** range  
8 and up to 10 **micromolar**, and that is pretty much the  
9 concentration range one would expect clinically. We  
10 don't expect concentrations any higher than that or  
11 any lower than that. With **amrinone**, the  
12 concentrations are probably also in the 1 to 3  
13 **micromolar** range when you adjust for the molecular  
14 weight.

15 DR. KONSTAM: But you showed **milrinone**.

16 DR. CILLA : I am sorry, with **milrinone**.  
17 I apologize.

18 DR. KONSTAM : Okay. But we think that  
19 there are a number of active metabolizes of this agent  
20 and so **hcw** do we put that in perspective?

21 DR. CILLA: Right now what we are doing  
22 with this particular data is to suggest that **PDE<sub>3</sub>**

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1 inhibitors are not all similar. That there may be  
2 some differences based upon different tissues. And  
3 that is all we are trying to accomplish with this. We  
4 have not studied the individual metabolizes in this  
5 particular model.

6 DR. LINDENFELD: In that same vein, do the  
7 other PDE<sub>3</sub> inhibitors have substantial metabolizes  
8 that are active? Just to try to compare these two.

9 DR. CILLA: I think that there are  
10 metabolizes. I do not know that they have the same  
11 activity that cilostazol does.

12 DR. LINDENFELD: Okay. So then we don't  
13 know if -- in the studies you have shown, just the  
14 dose itself without the metabolizes is comparable.

15 DR. CILLA: Right. These were in vitro  
16 studies. So we wouldn't see the effects of  
17 metabolizes of either milrinone or cilostazol.

18 CHAIRPERSON PACKER: Dr. Karkowski?

19 DR. KARKOWSKI: We received a study last  
20 week and Dr. Kerner just looked at it. It isn't in  
21 your package. There are a couple of points that  
22 probably should be made. Number one is that in the

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1 **milrinone** comparison study, the incubation time was  
2 very short. It was like 5 minutes. So that one has  
3 to assume that there is equivalent penetration into  
4 the **myocardium** during that short period of time for  
5 one to **make** sense out of the bath concentrations. The  
6 second point is that in none of the studies that were  
7 done that showed inotropic effect was the rabbit used  
8 as the model. So we don't know whether the rabbit is  
9 equivalently sensitive **cilostazol**. Those are two main  
10 critiques to the study.

11 CHAIRPERSON PACKER: All right. Using  
12 that as a follow-up, maybe I can ask why did you  
13 choose the rabbit? One is struck by the fact that you  
14 showed this slide which had a comparison of **milrinone**  
15 and **cilostazol**, and on the left is human tissue and on  
16 the right is rabbit tissue.

17 DR. CILLA: Yes.

18 CHAIRPERSON PACKER: Why did you choose  
19 the rabbit?

20 DR. CILLA: We selected the rabbit model  
21 because number one it is easily available. There are  
22 common preparations that are fairly standard in the

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1 cardiovascular industry. So we wanted to look at that  
2 particular model. We would always prefer to use human  
3 tissue for studies, and that is why we looked  
4 specifically at human platelet cyclic AMP levels as  
5 well .

6 CHAIRPERSON PACKER : The reason for asking  
7 is that one thing which is striking about  
8 phosphodiesterase inhibitors and their effects on the  
9 heart is that there are enormous species differences.  
10 If you give milrinone to human -- apply it to human  
11 **myocardium**, there is an **inotropic** effect. If you apply  
12 it to rat myocardium, there is no inotropic effect.  
13 And you use different phosphodiesterase inhibitors and  
14 you will get totally different results whether you are  
15 looking at guinea pig, rabbit, rat. So it is  
16 certainly possible that there are differences. I  
17 guess the question is are those differences  
18 reassuring.

19 DR. CILLA: We were specifically  
20 interested in comparing 2 PDE<sub>3</sub> inhibitors within a  
21 species. So if you look within a species, the  
22 comparison we felt was reasonable.

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1 CHAIRPERSON PACKER: I guess we should also  
2 remind ourselves that in the experience with  
3 **milrinone**, **milrinone** also has different effects in  
4 normal **myocardium** as compared to failing **myocardium**.  
5 And that is relevant because interestingly enough  
6 **milrinone** doesn't produce very much of an increase in  
7 **cyclic AMP** or very much of an inotropic effect in  
8 failing hearts, but does in normal hearts. And yet,  
9 it has an adverse effect in patients with failing  
10 hearts. So the fact that there is minimal increase in  
11 cyclic AMP, even if there were no comparator, or a  
12 minimal **inotropic** effect at a given concentration is  
13 not necessarily reassuring simply because that minimal  
14 inotropic effect and that minimal increase in cyclic  
15 AMP was produced by a drug which in the clinical  
16 setting was associated with an increase in  
17 cardiovascular risk.

18 DR. CILLA: I understand.

19 DR. LIPICKY: Can I just ask, isn't the  
20 data that you cited with respect to no changes in  
21 cyclic AMP and no positive inotropic effect from human  
22 myocardium 'taken at time of transplant?

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1           CHAIRPERSON PACKER: It is actually taken from  
2 two sources. One is -- correct, it is human  
3 **myocardium** at the time of transplant or at time of  
4 surgical procedure of some other type. But it is also  
5 taken in species that are responsive to **milrinone**  
6 where that species undergoes a procedure that creates  
7 an experimental model of heart failure.

8           DR. LIPICKY: Right, but it is very severe  
9 heart failure. That is, I mean it is sort of **end-**  
10 stage disease.

11           CHAIRPERSON PACKER: Yes, that is correct.  
12 Now the blunting --

13           DR. LIPICKY: And so that is at an extreme  
14 of **myocardial** function that you are citing.

15           CHAIRPERSON PACKER: Yes, the blunting of  
16 the **inotropic** effect and the blunting of the increase  
17 in **cyclic** AMP is dependent on the severity of  
18 **myocardial** dysfunction. You get a little bit of  
19 blunting in mild dysfunction and in severe dysfunction  
20 a lot of blunting. But of course in the clinical --

21           DR. LIPICKY: But you are surmising that.

22           CHAIRPERSON PACKER: No, that has been

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1 done.

2 DR. LIPICKY: I see. Okay.

3 CHAIRPERSON PACKER: Yes. But what is  
4 still interesting is the fact that the clinical trials  
5 with **milrinone**, the increase in mortality was in the  
6 most advanced, that is, the patient population that  
7 presumably had the least **inotropic** and cyclic AMP  
8 events.

9 DR. CILLA: If there are no further  
10 questions --

11 DR. LIPICKY: Well, I had one more  
12 question. I am still a little bit confused with  
13 respect to perspective. So if you just look at the  
14 data that were just being discussed on rabbit **myocytes**  
15 on **cyclic** AMP and contractility and you accept the  
16 fact that **micromolar** concentrations are things you  
17 should look at, and that the thing on the Y axis is  
18 important -- so I won't even ask whether that is true  
19 -- from what you are saying -- then **presumably my**  
20 interpretation would be that there is somewhere  
21 between a 3 to tenfold safety margin? Is that why you  
22 showed this data? That is, when cyclic AMP is

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1 affected or contractility is affected, that is not a  
2 good thing. And if it isn't affected, that is a good  
3 thing and that there is about a 3 to tenfold range of  
4 concentration difference that this data gives you a  
5 safety **margin** for?

6 DR. CILLA: Our purpose simply was to look  
7 at the difference in PDE<sub>3</sub> inhibitors. We feel that  
8 the safety of **cilostazol** really comes from our  
9 tremendous safety data base which will be discussed  
10 later.

11 DR. LIPICKY: Well, but it is with respect  
12 to the interpretation. So if that is the data, what  
13 am I supposed to interpret it? What does it mean? Is  
14 there an implication that I should take from it?

15 DR. CILLA: Yes. I think the implication  
16 is that PDE<sub>3</sub> inhibitors are not all the same. That  
17 you must **look** at the different tissues in which you  
18 are seeing the results to determine their various  
19 effects. For instance, we have more effects on  
20 **vasodilatation** than other PDE<sub>3</sub> specific inhibitors.  
21 I am probably not the person to answer your question  
22 on the safety margin.

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1 DR. CALIFF: I don't want to hammer on  
2 this too much, but I guess my interpretation of what  
3 you are asking is should your presentation in any way  
4 effect our deliberation on whether this drug is good  
5 or bad for people.

6 DR. CILLA: We feel that our safety and  
7 efficacy data stands on its own. And actually perhaps  
8 it --

9 DR. CALIFF: But not this data. This  
10 really shouldn't affect the way we think about whether  
11 this drug is good or bad for people. Is that what you  
12 are saying?

13 DR. CILLA: Right.

14 DR. CALIFF: Okay.

15 CHAIRPERSON PACKER: You really know how  
16 to hurt a guy, Rob. Okay, let's move forward.

17 DR. CILLA: I would like to next introduce  
18 Dr. Hiatt to discuss peripheral vascular disease.

19 DR. HIATT : Good morning. I am Bill  
20 Hiatt. I have been asked to provide an overview of  
21 the clinical aspects of peripheral arterial disease.  
22 My background is in vascular medicine at the

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1 University of Colorado Health Sciences Center. I  
2 practice vascular medicine. I do clinical research in  
3 vascular disease. And also I have been involved over  
4 the last 10 years or so trying to develop some  
5 clinical trial standards for assessing new  
6 **claudication** therapies. So in that context, I would  
7 like to give you just a very brief overview of this  
8 disorder.

9 Let me start with prevalence. These  
10 prevalence figures come from several epidemiologic  
11 trials where the use of the ankle brachial index, the  
12 ABI right there, is the objective measure of an  
13 occluded peripheral circulation. You can see with  
14 increasing age there is an increasing prevalence. So  
15 that over the age of 70, approximately 19 to 20  
16 percent of the population is affected with peripheral  
17 arterial disease. If you project those numbers out in  
18 terms of numbers of adults in those age groups, you  
19 will see about an 8 million prevalence figure for this  
20 disorder. So it is quite common.

21 Now let's look at the natural history of  
22 those patients who have peripheral arterial disease.

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1 This is selected from studies over the age of 55. And  
2 you will see as with most cardiovascular diseases that  
3 a good number are **asymptomatic**. So included in the  
4 previous prevalence figures were people with an  
5 abnormal **hemodynamic** measurement but no symptoms.  
6 About half the population has that. Of interest for  
7 your deliberation today is the group with intermittent  
8 claudication. That is about 40 percent of the  
9 population. And what we won't be talking about today  
10 is critical leg ischemia, which is the severe end,  
11 which is primarily a surgical consideration.

12 Now if you take the middle group, the  
13 patients with **claudication**, and look at their **five-**  
14 **year** outcomes, they are separated into two major  
15 categories. On the right addresses the cardiovascular  
16 morbidity and mortality. The mortality rate in this  
17 population is quite increased because of the  
18 associated coronary and **cerebrovascular** disease. So  
19 the mortality rate per year is around 4 to 5 percent,  
20 and therefore over 5 years is approximately 20 to 30  
21 percent. The vast majority of those deaths are  
22 cardiovascular in nature. Patients who survive have

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1 other non-fatal CV events like **myocardial** infarction  
2 and stroke.

3 Now on the other side is the natural  
4 history of the lower extremity. In those patients who  
5 have obviously not died, you have the following  
6 natural history. The vast majority of patients -- and  
7 this **has** been confirmed through a number of clinical  
8 studies -- have stable symptoms of **claudication**. So  
9 if they come to your clinic and they complain of a  
10 one-block **claudication** symptom and you do nothing,  
11 five years later they are going to have one-block  
12 **claudication** and be as disabled as they were in five  
13 years as when they first showed up. About 16 percent  
14 will worsen their **claudication** and become more severe.  
15 7 percent come to leg bypass surgery because they have  
16 crossed **the** threshold to critical leg ischemia or  
17 because they complain so much that they need to have  
18 an invasive procedure to treat their circulation, and  
19 only 4 percent come to amputation.

20 Now the clinical trial data you are going  
21 to hear today really focuses on this component of the  
22 patients with peripheral arterial disease, the stable

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1 claudicator. The question has come up about the  
2 representation of the data you are going to hear  
3 versus the U.S. population. So what I have tried to  
4 do is use some of the data from the **cilostazol** data  
5 base you **are** going to hear about, 2700 patients, and  
6 compare that with what has been published with  
7 **clopidogrel**, the anti-platelet drug that was recently  
8 approved of which 6,400 patients had peripheral  
9 arterial disease. In this data base, the PAD  
10 patients, 40 percent were symptomatic with  
11 **claudication** and 60 percent had had previous bypass  
12 surgery. So they aren't exactly the same as just a  
13 purely **claudicating** population, but they **all** had PAD.  
14 And the **last** group comes from **claudication** literature,  
15 where you take all these studies here and look at the  
16 demographics of those patients on entry.

17 Now they are all fairly remarkably  
18 similar. The majority of them are male. The average  
19 age is mid-60's. The prevalence of diabetes is 15 to  
20 25 percent, a very common risk factor for this  
21 disorder. Cigarette smoking is universal. This is  
22 current and former smoking rates which are quite high.

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The prevalence of hypertension is around 50 percent. I might comment that most of these trials do not include patients with heart failure that is clinically obvious. So this excludes Class III and Class IV heart failure. And the baseline ankle **brachial** index, the measure of the disease, is fairly similar -- .64 for the **cilostazol**, on average .63 in the literature, and the entry criteria was less than or equal to .85 for the **clopidogrel**. I don't have the mean ABI number, but I think it is around the .6 range. So I think the population you are going to see today is fairly representative of what is in the literature.

Next I would like to address the clinical relevance or the clinical meaning of what **claudication** is. **Claudication** is defined as an ischemic syndrome in the **leg** that is brought on by exercise and relieved by rest. It is due to a supply/demand mismatch in skeletal muscle because of the occluded circulation. So these patients are limited by an ischemic pain syndrome. Now what that does to their daily activity is shown here. The normal maximal walking speed or the normal rate we walk at is around 3 miles per hour.

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1 Because of their **claudication**, these patients slow  
2 their walking pace considerably to 1 to 2 miles per  
3 hour, and perhaps more importantly they can't go very  
4 far. Now the **walking** distance that they will tell you  
5 when they come into the clinic may be as severe as  
6 half a block or just getting around the house may  
7 cause symptoms. Or the more mildly affected ones  
8 might have a four block limit. But they all have a  
9 limit and they can't exceed a certain distance before  
10 they have to stop and rest for the symptom to go away.

11 Now we have tried to define that symptom  
12 severity by something you will hear about in a minute,  
13 the walking impairment questionnaire, a disease  
14 specific instrument. And using that questionnaire and  
15 looking at the 2,000 patients enrolled into the data  
16 base you are going to hear about, you will see that  
17 about 30 percent of patients will report on entry that  
18 they have difficulty walking around their house. **Two-**  
19 thirds have difficulty walking half a block, which is  
20 about 150 feet or 48 meters. So this is a severe  
21 symptom. And lastly, when you actually test them in  
22 a laboratory on a treadmill, and we have had a **lot** of

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1 experience doing this, measuring oxygen uptake, the  
2 peak  $\text{VO}_2$  values for these patients are around 10 to 15  
3 ml per kilogram per minute, which is not unlike the  
4 peak  $\text{VO}_2$  for Class III heart failure. Different  
5 **pathophysiology** but very similar impairment in peak  
6 exercise performance. So the point here is that this  
7 is not a trivial symptom. This actually has  
8 significant ramifications to daily activity.

9 Now how do you assess the severity of  
10 vascular disease? Well, you have heard already that  
11 there is this ankle brachial index, the ABI, which is  
12 simply the ratio of the systolic blood pressure in the  
13 ankle to the systolic blood pressure in the arm. And  
14 when that ratio falls below 1, there is a significant  
15 pressure drop across the circulation and the lower the  
16 value, the more severe the **hemodynamic** state. Now a  
17 question has come up of is this analogous to something  
18 like an **ST** segment change? It is really not. This is  
19 a reflection of hemodynamics, pressure and perhaps  
20 related to flow. We don't have an easily measurable  
21 instrument like an ST segment in the leg to tell you  
22 when the muscle is ischemic that can be easily used in

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1 large population clinical trials.

2           There is also another key point about the  
3 ABI . The relationship to any change in the ABI with  
4 treatments and change in functional status is not  
5 good. **So, for** example, you can increase the ABI with  
6 a bypass operation or with **angioplasty**, but for the  
7 patient that doesn't necessarily directly relate to  
8 improved performance. We know from extensive studies  
9 at the University of Colorado that you can put  
10 patients in an exercise training program and have no  
11 effect on the ABI but a tremendous increase in  
12 exercise performance. So I know a question has come  
13 up about objective measures and the ABI. You are  
14 going to hear some data about the ABI. But I want to  
15 just emphasize the importance of the interpretation of  
16 any changes in ABI.

17           The second instrument is the Rose  
18 questionnaire. This is a questionnaire that really  
19 establishes diagnosis in epidemiologic studies. So if  
20 you are screening a population and you want to know if  
21 they have **claudication** symptoms -- comes on with  
22 exercise and goes away with rest and doesn't come on

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1 at rest and that kind of thing -- that is the Rose  
2 questionnaire. But it is not useful to assess changes  
3 in performance or changes with therapy. To do that,  
4 we need to focus on these last two things. Treadmill  
5 testing is what I would say is the primary objective  
6 measure of changes in exercise performance, whether  
7 you are testing a new drug, a new surgical therapy, or  
8 a new medical therapy. And related to that, and I  
9 think also extremely important, are assessing changes  
10 in quality of life. Because what we are really trying  
11 to do with claudication therapy is improve functional  
12 status and do something that helps patients on a day  
13 to day activity. We want to take that functional  
14 limitation that I described in the previous slide and  
15 make that better.

16 Now let me just mention a couple of key  
17 things **about** treadmill testing. It is an objective  
18 and reproducible endpoint. There are two things that  
19 are measured during the treadmill test which you are  
20 going to hear about this morning. When patients first  
21 begin walking on the treadmill, they have no symptom  
22 of **claudication**. And then at a certain time **or**

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1 distance into the test, they will begin to notice  
2 **claudication** pain and that is called the initial  
3 claudication distance. They continue walking with  
4 **claudication** pain until they reach an endpoint where  
5 they have severe **claudication** symptoms and they can't  
6 walk any farther and that is called the ACD, the  
7 absolute **claudication** distance. And that serves as  
8 the primary endpoint for these studies. And this is  
9 the most reproducible endpoint as well.

10 Now there are two ways that you can test  
11 these patients. Historically or traditionally, the  
12 constant workload test has been used in the United  
13 States and in Europe. This fixes the work at a  
14 constant rate and a constant grade, usually 12 percent  
15 grade at 2 miles per hour, and you just go as far as  
16 you can. Myself and others have advocated more  
17 recently the use of a graded test which starts at a  
18 lower workload than the constant test and gradually  
19 increases the work to reach the ACD. Both of these  
20 tests have been validated. Both of them are useful  
21 for clinical trials. Reproducibility might be  
22 slightly **better** here than here, but I think you are

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1 going to see data presented in the data set next that  
2 use both of these tests, and I feel both of these are  
3 effective at showing clinical benefit.

4           The other instruments that you are going  
5 to hear about are measures of quality of life or  
6 functional status. One that we are most all familiar  
7 with is the medical outcome study SF-36. This has  
8 been used across a wide range of populations, both to  
9 characterize and look at the effects of therapy. This  
10 has two major domains, the physical functioning domain  
11 and the **social** role functioning domain. It is **non-**  
12 **disease** specific. At the University of Colorado, we  
13 have developed this disease specific instrument, the  
14 walking impairment questionnaire, which is designed  
15 for **claudicants** to assess their ability to walk to  
16 find distances, speeds, and severity of symptoms.

17           Let me give you just some representative  
18 data at baseline to again emphasize the **clinical**  
19 impairment these patients have. These data are from  
20 the walking impairment questionnaire at baseline  
21 looking at the 800 or so patients in the Otsuka data  
22 base that had this questionnaire administered versus

1 age-matched control normal values. On the Y axis is  
2 the scale, where zero would be great difficulty  
3 walking any distance and 100 percent would be no  
4 difficulty walking five blocks. You can see that the  
5 age-matched healthy population has almost no  
6 impairment in walking five blocks, whereas patients  
7 with **claudication** have a marked impairment in that  
8 distance as well as other shorter distances. And  
9 similar results are shown for speed. Normal  
10 individuals in their 60's can walk rapidly with no  
11 problem and' patients with **claudication** cannot.

12 These are data from the SF-36, and they  
13 make several important points on this slide. Again,  
14 this axis would go from zero, can't do it, to **100**  
15 percent, no problem. And what we have here are now  
16 three different populations. The white bar is from  
17 the healthy, unaffected control population that is in  
18 the large SF-36 data base developed by John Ware, who  
19 is here in the audience. He also gave us data for  
20 congestive heart failure patients. And then these  
21 green bar data are again from the Otsuka data base at  
22 baseline in 800 individuals. You can see that the

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1 physical functioning scores are markedly impaired in  
2 both patients with congestive heart failure and in  
3 **claudication**, not unlike the peak  $V_{O_2}$  data, a marked  
4 **impairment** in that domain. But it is also important  
5 to emphasize that these patients are not impaired  
6 across the entire range of functions because their  
7 mental health and their social functioning scores are  
8 quite normal. so a therapy guided against treating  
9 **claudicants** would be designed to improve physical  
10 function but not to improve mental health.

11 Lastly, I would like to turn to what is  
12 available to treat **claudication**. And this list I am  
13 putting **up** here is really my own summary of what I  
14 think the treatments options are that we have right  
15 now, and I would like to just review those very  
16 briefly. Again, I have been advocating the use of  
17 supervised exercise for a long time. When studied in  
18 a rigorous setting where you use primarily **hospital-**  
19 **based** cardiac rehab type settings and you have trained  
20 nurses and technicians to put these patients through  
21 the **paces**, you show good effectiveness in terms of  
22 improving treadmill performance and quality of **life**

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1 using supervised exercise. The limitation, I think,  
2 with exercise is availability. Third-party payers  
3 aren't interested in paying for it despite its  
4 efficacy, and there are only half a dozen centers  
5 around the country that really do it right and have it  
6 available. In contrast, if you simply tell your  
7 patient to go home and exercise, and we have done this  
8 too **using** a randomized control trial format -- and not  
9 only asked them to exercise, but go home and have the  
10 nurse call you weekly and take a log and do all those  
11 things -- this does not improve treadmill performance  
12 and does not improve quality of life questionnaires.  
13 So simply advising the patient to exercise, which is  
14 cheap and easy, doesn't work. But doing a supervised  
15 program works very well.

16           Angioplasty is a procedure that is quite  
17 commonly used in this country to treat the lower  
18 extremity circulation. The population appropriate for  
19 **angioplasty** has been patients with critical leg  
20 **ischemia** as well as patients with **claudication**. Now  
21 I am going to display some of my **bias here this**  
22 morning, but if you look at the published literature

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1 on **angioplasty**, it is good at improving the ABI. But  
2 in terms of improving the functional status and  
3 quality of life, the data are not very convincing. So  
4 I think it is possibly effective and it also has a  
5 very low mortality rate but some morbidity and it is  
6 not very durable. You have to repeat the procedure to  
7 keep the circulation open. So from my point of view  
8 as a vascular internist and non-interventionalist, I  
9 don't think this is a very good option for patients  
10 with **claudication**.

11 In contrast, bypass surgery has been shown  
12 in rigorous randomized trials to be very effective at  
13 relieving the symptoms of **claudication**, but it too has  
14 a certain morbidity and mortality, and therefore most  
15 surgical centers don't do a lot of **claudication**  
16 surgery. It is the patients who continue to complain  
17 and who fail medical therapy that come down this  
18 route. At our center, we only do two or three  
19 **claudicants** a year in terms of a surgical option.

20 And then finally there is this one drug  
21 that is approved, pentoxifyline, which I think looking  
22 at the literature has perhaps minimal efficacy at best

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1 and no quality of life data. And I think clinically  
2 this is not an option for us today.

3 so to summarize this, this is what I would  
4 like to see in a claudication therapy. And I think we  
5 need a new **claudication** therapy. That treatment  
6 should be able to improve treadmill walking ability  
7 and improve physical functioning and quality of life  
8 scores. It should be effective in patients with  
9 **claudication** who have different co-morbidities taking  
10 different drugs, and across a certain spectrum of the  
11 **claudicating** population, the drug or treatment should  
12 be effective. I think it should be safe, but I think  
13 availability is an issue as well. Thank you very  
14 much.

15 CHAIRPERSON PACKER: We will begin the  
16 questions with JoAnn.

17 DR. LINDENFELD: Bill, you have told us  
18 that restoring blood flow with **angioplasty** and/or  
19 surgery **may** not always improve walking distance. Then  
20 how does this -- if part of the effect of this drug is  
21 to improve blood flow, then why would it do it with  
22 the drug and not with a more mechanical means?

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1 DR. HIATT : The question relates to a  
2 relationship between improvements in flow and  
3 improvements in performance. I think the answer is  
4 that the **relationship** is there with improvements in  
5 flow, but it is not real tight For example, the  
6 relationship between cardiac output and physical  
7 performance is not real tight either. The  
8 relationship between the **FEB-1** and function on the  
9 treadmill is not real tight, but you know as the **FEB-1**  
10 decreases, function falls off. The same thing is true  
11 here. And it is also true that when you bypass an  
12 artery and the blood flow goes up, the patient **walks**  
13 further. But the pathophysiology of **claudication** is  
14 not simply blood flow restriction. There are other  
15 things **occurring** in skeletal muscle. There is  
16 platelet activation. There is **endothelial** effects of  
17 hyperlipidemia. There is an accumulation of  
18 **vasocholase** in skeletal muscle. The higher the  
19 accumulation, the worse the performance. As the  
20 **vasocholase** level goes down, the performance gets  
21 better even with no change in flow.

22 So I think that we **shouldn't** just think

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1 about **claudication** as simply a blood flow problem, but  
2 actually a complicated series of events that occurs  
3 with flow restriction and then leads to a host of  
4 other events that can be modified and improve  
5 performance in the absence of a change in perfusion.  
6 Now you are going to see some data that shows the ABI  
7 gets a little bit better, but I wouldn't want to say  
8 to this committee that every new therapy that comes  
9 before you should have that criteria. There are lots  
10 of treatments that don't affect ABI that do make you  
11 perform better.

12 DR. LINDENFELD: So what would your  
13 evaluation be of the most important effect of this  
14 drug in improving claudication?

15 DR. HIATT: In terms of mechanism?

16 DR. LINDENFELD: Yes.

17 DR. HIATT: I wouldn't want to speculate  
18 on that because I honestly don't know.

19 DR. LINDENFELD: A second question. You  
20 showed us a nice slide about that the patients in  
21 these studies are very similar to other **claudication**  
22 studies in terms of smoking and diabetes and those

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1 kinds of things. But in fact these patients were not  
2 limited **by** angina by definition.

3 DR. HIATT: Correct.

4 DR. LINDENFELD: And had no heart failure  
5 and had to be able to be off virtually all  
6 vasodilators as I understand the protocol. I will  
7 have to ask later about ACE inhibitors. So in your  
8 view, wouldn't that make them a substantially lower  
9 risk of a high risk subgroup?

10 DR. HIATT: Well, I must -- yes, the  
11 demographic. -- when we talk about all populations  
12 studied for **claudication**, one of the key factors is  
13 they are limited by claudication on the treadmill and  
14 not by dyspnea or heart failure or angina. So by  
15 definition, the clinical severity of their  
16 cardiovascular disease and other systems is much less  
17 than the severity of their claudication. Now  
18 clinically what you are seeing here I think is typical  
19 of what we see in clinic in terms of who comes in the  
20 door. They aren't severely limited by heart failure.  
21 They have lots of histories of prior MIs, but they are  
22 not having active anginal symptoms. So honestly I

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1 think what you are going to see is typical of the  
2 population that we treat.

3 DR. LINDENFELD: Okay. And then in terms  
4 of both -- you talked about the constant load and  
5 graded load treadmills, could you tell us what to  
6 expect in those two types of protocols on just the  
7 placebo group? What kind of improvement we would  
8 expect to see in a 24-week trial?

9 DR. HIATT: The question relates to the  
10 placebo effects on the different treadmill protocols.  
11 A while ago I was sort of publishing things saying  
12 that the placebo response is extremely high on the  
13 constant workload and it is a bad test and all that.  
14 But then **when** you actually look at the data here, you  
15 are **going** to see that the placebo response is around  
16 10 percent for both tests. They seem to be -- I think  
17 what I learned in a conference we held in **Basle** last  
18 November **was** that if you really get your methods down  
19 right, they both seem to minimize placebo response.  
20 So perhaps a lot of the bad data with the constant  
21 load test related to people who weren't very good at  
22 doing the tests.

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1 DR. LINDENFELD: Okay.

2 DR. HIATT: I think that both tests for  
3 the data you are going to see today do demonstrate  
4 efficacy, and I think they both can be seen as  
5 comparable.

6 DR. LINDENFELD: And just a final question  
7 that you may or may not have an answer to. What  
8 effect does stopping smoking have on walking time over  
9 a 6-week or 12-week period?

10 DR. HIATT: Oh, good question. Smoking  
11 cessation doesn't change walking performance very much  
12 at all. So we hammer away at it, but it is not a huge  
13 covariate in terms of changing performance. It has  
14 been looked at and it is not unfortunately a very good  
15 way to relieve symptoms.

16 CHAIRPERSON PACKER: Udho?

17 DR. THADANI: I agree with you that the  
18 treadmill is a more objective testing. We have been  
19 doing it in angina for a long time. If you modify the  
20 protocol -- I think one of the reasons you modify is  
21 because if you have a constant speed, you have to wait  
22 forever in some patients and they don't qualify for

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1 your study. So you go on to greater steps because  
2 once you increase the incline, the workload is  
3 increasing and so they are going to fit your protocol.  
4 So what you are doing by modifying the protocol is you  
5 are picking up patients who are not as sick, perhaps.  
6 Because "you have to increase the incline or perhaps  
7 the speed, **as** we do in angina. So there are different  
8 ones, and you may not be able to lump them together.  
9 They are 'different studies, at least in my judgment.  
10 So that is one -- just a comment on that.

11 Now if I remember correctly, I was reading  
12 an editorial on intermittent claudication several  
13 years ago by a British surgeon, and he said I don't  
14 know why you are asking me. The main treatment for  
15 intermit-tent claudication is to keep walking, and he  
16 could have finished the editorial there. So how good  
17 the data is there that if you tell the patient to  
18 gradually keep on increasing your walk around the  
19 block, perhaps the studies of three months are not  
20 enough. Because there is data in the literature  
21 saying that if you keep walking -- the reason people  
22 improve maybe beyond six months or eight months is

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1 because the collateral flow increases. The patient  
2 presents with intermittent **claudication**. For the  
3 first three months, it might get worse and then they  
4 improve. so the short-term studies -- I don't know if  
5 the conclusions you have made from your different  
6 categories, are they based on three month studies or  
7 have you looked at one year, six months? What was  
8 your objectivity on the data?

9 DR. HIATT: Your first comment regards the  
10 different treadmill protocols. They are different.  
11 We think the graded test may be a little more  
12 physiologic. But in fact, when you **look** at the  
13 percent change over time between drug and placebo, the  
14 percent changes are about the same for the two tests.  
15 But the absolute walking time is about half -- 50  
16 percent less with the constant workload test because  
17 it starts at a higher workload.

18 Now the question you asked about  
19 recommending physical activity is an extremely  
20 important one. Because if that were effective, we  
21 could just do that, and it has been certainly  
22 recommended ever since we have treated claudication.

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1       What I tried to show in that slide are the results of  
2       work that we have done in our center and other  
3       studies, and there aren't many, where you actually  
4       take a population and recommend exercise and study  
5       their performance before and after you recommend that  
6       therapy and have a control group. And using those  
7       more rigorous measures, it doesn't work. And I think  
8       the reason it doesn't work is that patient's legs  
9       hurt. They go off on their own and walk out to the  
10      mailbox and it hurts and they come back home and sit  
11      down. When we bring them into the laboratory, we turn  
12      the treadmill on to a speed and grade that brings on  
13      **claudication** and we make them do that. And that is  
14      different. And there is a whole different host of  
15      variables that occur in a more formal setting than in  
16      a casual go home and exercise.

17                   DR. THADANI: And the other issue is the  
18      ankle **brachial** arm index. The data you showed applies  
19      to resting values or you have actually done it during  
20      exercise in patients? Because there might be  
21      dissociation when you dilate the patient. They are  
22      maximally dilated anyway. If you have got a severe

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1 stenosis of the femoral artery, I don't think you can  
2 do much more dilation. Have you looked at the data?  
3 Is the data you are showing dissociation? Is it rest  
4 versus exercise data or exercise versus exercise data?

5 DR. HIATT: Most of the ABI data is going  
6 to be **resting** data. For category --

7 DR. THADANI: Which may not be relevant.  
8 Because what you really want to know -- these patients  
9 are not limited at rest.

10 DR. HIATT: Right.

11 DR. THADANI: They stop because they are  
12 exercising. And I am sure there are ways to measure  
13 ankle/arm index during exercise. Do you have no data  
14 whatsoever?

15 DR. HIATT : Yes -- no. Well,  
16 specifically, the ABI was measured both at rest and  
17 after exercise. The ABI goes down with exercise. If  
18 you kind of look at the ischemic window, they do have  
19 data on that that suggest that here is less of an ABI  
20 perturbation with therapy.

21 DR. THADANI: And since the mechanism is  
22 not clear because of the dissociation, perhaps **all you**

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1 are doing is that whatever the drug is doing, actually  
2 there -- because you are doing repeated exercise  
3 testing over time, you are improving the training. As  
4 in heart failure, the muscle metabolism changes or  
5 whatever has no direct effect. But you are improving  
6 -- because if you look at the placebo data, I am sure  
7 that it will show that there is parental improvement  
8 and it is greater in the drug.

9 DR. HIATT: Right.

10 DR. THADANI: so probably training  
11 improves **by** some mechanism. I don't know.

12 DR. HIATT : You know, again, the whole  
13 issue of what is the mechanism of the effect and what  
14 effects no pathophysiology I think can get very  
15 complicated quickly, and I would not want to speculate  
16 too much. You said, for example, that exercise  
17 training improves collateral circulation? That is  
18 probably not true. Measured by flow or ABI, there is  
19 no real change in collateral flow or perfusion  
20 pressure. What happens with training appears to be  
21 alterations in gait and changes in skeletal muscle  
22 metabolism. So the point of my answer is let's not

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1 get too hung on specific pathways. I think the  
2 clinical data have to stand on their own. This is not  
3 a drug that is targeting one pathway that is going to  
4 change the pathophysiology of **claudication**. It is  
5 multi-factorial.

6 DR. THADANI: For my learning, how **long**  
7 are the studies regarding no collateral flow changes.  
8 Is it short-term studies or have you looked at six  
9 months or one year?

10 DR. HIATT: We have looked at six months  
11 of training.

12 CHAIRPERSON PACKER: Bob Temple and then  
13 Alan Hirsch.

14 DR. TEMPLE: You may want to say that this  
15 is going to be addressed later, but there were a fair  
16 number of exclusions, and I am interested in your view  
17 about whether the population that was studied is  
18 typical enough of the population that might be treated  
19 with respect to its comorbid conditions. For example,  
20 there were certain anti-platelet drugs that for better  
21 or worse -- only one is actually approved for this --  
22 that are meant to be used in people with peripheral

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1 vascular disease. Clopidogrel actually has that as  
2 part of its population and for all we know people are  
3 using ticlopedine because of the meta-analysis, et  
4 cetera. Also, a lot of people in this age group have  
5 one or another reason to be on a non-steroidal anti-  
6 inflammatory drug. I couldn't -- I don't know whether  
7 they were excluded from all trials, but they were  
8 excluded from a lot of trials. That seems like a  
9 potential problem. Similarly, people with varying  
10 degrees of heart failure were excluded. That is  
11 obviously a disease that a lot of these people are  
12 going to have. Obviously, if they can't exercise at  
13 all, you couldn't really include them, but not  
14 everybody with a little heart failure can't exercise  
15 at all, et cetera. Either you or perhaps later,  
16 someone needs to comment on whether the exclusions  
17 make it difficult to think exactly what the population  
18 studied is. And whether you are talking about a very  
19 small subset of the total number of people with  
20 peripheral vascular disease.

21 DR. HIATT: Well, I don't want to overstep  
22 my bounds. My goal is to just provide background

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1 information on the disorder. You are going to see  
2 some data that show drug effect, on and off beta  
3 blockade, different age ranges and different gender  
4 ranges, and those kinds of things. I think the  
5 exclusions, if you look at what has been published in  
6 other clinical trials, are much less than, for  
7 example, the Trental data base, where there were a lot  
8 more exclusions than occurred here. And certainly  
9 that might limit generalizability a bit, but to the  
10 best of my knowledge I think it is a representative  
11 population.

12 DR. TEMPLE: Can we -- specifically, what  
13 about the need for, perhaps, anti-platelet treatment  
14 for some of these people to prevent important  
15 consequences of having arterial sclerotic vascular  
16 disease? Is that important? I am asking you because  
17 you are the big picture guy. So this is a sort of big  
18 picture question.

19 DR. HIATT: Anti-platelet therapy -- this  
20 group is not really recommended aspirin for PAD.

21 DR. TEMPLE: No, not aspirin. I don't  
22 mean aspirin.

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1 DR. HIATT: Clopidogrel?

2 DR. TEMPLE: Yes.

3 DR. HIATT: I think **Clopidogrel** is an  
4 important. advance for PAD. Now whether that treats  
5 symptoms or: not, I don't know. But I think **anti-**  
6 platelet therapy is something that should be given to  
7 these patients.

8 DR. TEMPLE: Do you think an implication  
9 of the exclusions are that you don't know whether it  
10 is safe to use **clopidogrel** concomitantly? Because  
11 anything with an anti-platelet activity was excluded.  
12 That is why I am asking.

13 DR. HIATT: Well, that is a good question.  
14 I **don't** know if the risk of continuing on aspirin and  
15 adding **cilostazol** is an issue. Should **clopidogrel** and  
16 aspirin be combined? It does seem to increase the  
17 anti-platelet effects of both drugs and studies should  
18 be done to look at that. So I think the answer is  
19 these **patients** should have a background of **anti-**  
20 platelet therapy on board.

21 CHAIRPERSON PACKER: This is an important  
22 question because there is a new question to the

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1 committee that specifically relates to this issue. It  
2 relates to the issue of the exclusion of anti-platelet  
3 drugs in all the protocols -- every single one. If  
4 one has a drug like **clopidogrel**, which actually has a  
5 defined experience in peripheral arterial disease, and  
6 for whatever it is worth has a point estimate of  
7 showing more benefit in peripheral arterial disease  
8 than in **almost** any other subset of patients that were  
9 evaluated in their clinical data base, and  
10 consequently one could imagine that given the fact  
11 that that drug reduced major clinical effects, that  
12 one could suggest that there were a mandate to use  
13 that drug. I mean reducing major events is really  
14 important. And that mandate in particular exists for  
15 patients with peripheral arterial disease, in  
16 particular since perhaps the data in aspirin in that  
17 patient Copulation isn't really so strong. It is hard  
18 then to know what to do with a drug where every single  
19 trial excludes the use of a drug which would now be --  
20 or types of drugs that would now be considered to be  
21 mandated. How as a clinician would you deal with  
22 that?

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1 DR. HIATT: Your first argument, I totally  
2 agree with. I think that an anti-platelet therapy is  
3 a necessary form of therapy to reduce risk of major  
4 systemic events. My thinking is that at least at a  
5 minimum, I would use **cilostazol** with aspirin. But we  
6 might **need** more information in terms of their combined  
7 effects on anti-aggregative effects. Bill, do **you**  
8 have any answer to that?

9 DR. FORBES: Yes, if I could just clarify  
10 something. In the largest trial, 96202, we did allow  
11 aspirin in the dose of 81 mg per day. In the open  
12 label trial now for almost two years, we have allowed  
13 aspirin up to 325 mg. So I don't know if you are  
14 looking at it from an efficacy or safety point of  
15 view, but we have loosened that criteria. So there  
16 are two trials, an open label and a double blind.

17 CHAIRPERSON PACKER: I think we need to  
18 ask the question again, but the reason for asking it  
19 to Dr. Hiatt was more the -- as Bob would say, the big  
20 picture clinical perspective, and we need to get more  
21 into a data dependent perspective in a little while.  
22 But from your point of view, and I guess you have

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1 answered the question, given your approach to treating  
2 these patients, if both were available, you would use  
3 both together in the same patient population?

4 DR. HITT: I think life is more important  
5 than limb, and I would choose the anti-platelet drug  
6 as my first form of therapy because that has a risk  
7 reduction associated with it. My question in terms of  
8 symptom relief would be whether I could combine  
9 clopidogrel with cilostazol or aspirin with  
10 cilostazol.

11 CHAIRPERSON PACKER: Let's see, Ray?

12 DR. LIPICKY: Just two comments. First,  
13 this is a new question and you and the company have  
14 not seen that question before. So I apologize for  
15 that. Second, there is a component here where the  
16 trials that constitute the basis for evaluation today  
17 were completed before clopidogrel was, in fact, ever  
18 dreamed of as an indication for use. So there is a  
19 practical problem there.

20 CHAIRPERSON PACKER: Yes, I don't think  
21 that --

22 DR. LIPICKY: But that is okay. We don't

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1 need to discuss it now.

2 CHAIRPERSON PACKER: I think, Ray -- first  
3 of all, you would remind us that the world remains a  
4 moving target.

5 DR. LIPICKY: Yes.

6 CHAIRPERSON PACKER: Second is that my  
7 sense is that it is a generic concept of anti-platelet  
8 therapy **as** opposed to **clopidogrel**. **Clopidogrel** is  
9 just one example of an anti-platelet drug. But in  
10 general, all the protocols prohibited anti-platelet  
11 therapy -- all anti-platelet therapy.

12 DR. LIPICKY: Well, two had aspirin.

13 CHAIRPERSON PACKER: What is that?

14 DR. LIPICKY: Two had aspirin. Two had  
15 aspirin.

16 CHAIRPERSON PACKER: Yes. Okay, Alan?

17 DR. HIRSCH: Maybe one more quick question  
18 to go back a step and to bind the first presentation  
19 to yours, Dr. Hiatt, since you have the global PAD  
20 perspective. What is frustrating for me is never  
21 knowing **the** mechanism of action when I have potential  
22 efficacy data. And whereas I am interested in

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1 efficacy, I am always interested in mechanisms. So I  
2 want to come back one more time from your perspective  
3 and look at potential PDE mechanisms and **claudication**  
4 and ask **how** it relates to other PAD data you are aware  
5 of. so, **for** example, **cilostazol** or PDE<sub>3</sub> inhibitor  
6 might improve cardiac output or inotropy. Is there  
7 experience with other animal or human data that  
8 suggests that increased cardiac output and **supply** to  
9 the muscle improves walking distance?

10 DR. HIATT: I know of no data that looks  
11 at that. **It** is certainly a really good question.  
12 Because if there are subtle impairments in cardiac  
13 output and you have something that makes perfusion  
14 pressure go up, that might help limb perfusion.

15 DR. HIRSCH: The second mechanism by which  
16 these drugs might work as a **class** is improving  
17 vascular smooth muscle relaxation and delivery  
18 obviously from the vasodilatory effect.

19 DR. HIATT: Right.

20 DR. HIRSCH: The same question, obviously,  
21 is a data base to make sure the audience is aware  
22 regarding **vasodilators** in general in **claudication** and

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1 walking distance. The efficacy of **vasodilators** in  
2 general has been?

3 DR. HIATT: Not well shown.

4 DR. HIRSCH: **Microvascular** flow -- anti-  
5 platelet efficacy, I am sorry.

6 DR. HIATT: Well, yes. We all know that  
7 **vasodilators** as a class don't work, but this compound  
8 does do something to the hemodynamics. It improves  
9 the **ABI**. It improves limb blood flow in some small  
10 studies. Maybe that is part of it, but I don't know.

11 DR. HIRSCH: But continuing on to two more  
12 mechanisms. The anti-platelet effect presumably has  
13 a microvascular effect?

14 DR. HIATT: Correct.

15 DR. HIRSCH: Your comment about collateral  
16 blood flow and small vessel flow -- has there been  
17 data **from** other trials to suggest that that improves  
18 walking distance?

19 DR. HIATT: Yes. You are leading me on  
20 here.

21 DR. HIRSCH: I am leading you on.

22 DR. HIATT : **Ticlopedine** as an **anti-**

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1 platelet drug has been shown to have modest benefits  
2 on walking tolerance. So that could be a potential  
3 mechanism as well.

4 DR. HIRSCH: The reason I am leading us **is**  
5 because I think we will all be frustrated by not  
6 knowing mechanism and we will keep circling back as  
7 cardiologists. Skeletal muscle effects?

8 DR. HIATT: I don't know of any metabolic  
9 effects in terms of the **vasocholase** issue that I  
10 mentioned earlier.

11 DR. HIRSCH: Cyclic AMP mechanisms within  
12 the skeletal muscle to improve efficiency or inotropia  
13 of the skeletal muscle?

14 DR. HIATT: Yes, I just don't know.

15 DR. HIRSCH : I was leading you to --  
16 obviously, we have multiple mechanisms. The PAD  
17 literature is less robust and it is very difficult to  
18 discuss potential efficacy.

19 DR. HIATT: But I will concede absolutely  
20 -- the **pathophysiology** is complex and it is not simply  
21 **hemodynamics**. There are lots of other things that  
22 impair your performance as a claudicant.



1 DR. LINDENFELD: Bill, does aspirin  
2 improve **walking** distance?

3 DR. HIATT: No, not that I am aware of.

4 DR. LINDENFELD: Is there any data?

5 DR. HIATT: No. But **ticlopedine** does in  
6 a placebo controlled environment at least in three  
7 studies, but **really modestly**.

8 DR. LINDENFELD: Does **ticlopedine** have any  
9 other effects that would make us think that it --

10 DR. HIATT: No, not that I am aware of.

11 DR. LINDENFELD: Other than its **anti-**  
12 **platelet** effects?

13 DR. HIATT: Yes, I don't think so. If  
14 anybody else is smarter than me, they can answer.

15 DR. LINDENFELD: I wonder if aspirin  
16 improves walking distance then.

17 CHAIRPERSON PACKER: Alan, you -- I think  
18 appropriately and proactively -- identified our  
19 potential frustration with not knowing how this drug  
20 works. But I guess until you started speaking, I  
21 didn't know how frustrated I should be.

22 DR. HIRSCH: That is why I **am here**.

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1 Having been through the PDE wars before and not  
2 wanting to refight them particularly, I guess I am  
3 trying to separate the data base. What we know about,  
4 for example, failing versus non-failing skeletal  
5 muscle and **your** comment earlier, Milt, about failing  
6 versus **ncn-failing** heart muscle.

7 CHAIRPERSON PACKER: I understand.

8 DR. HIRSCH: We barely answered it for the  
9 heart and we are nowhere near answering it for the  
10 legs.

11 CHAIRPERSON PACKER: I've got it. Okay.  
12 Bob?

13 DR. TEMPLE : Well, not to anticipate a  
14 later discussion too much, but how frustrated should  
15 one be at not knowing the mechanism. And if you think  
16 it is **really** important to know the mechanism, could  
17 you just quickly explain why aspirin doesn't seem to  
18 do anything in peripheral vascular disease and  
19 **ticlopedine** and clopidogrel do? Just while we are at  
20 mechanism.

21 CHAIRPERSON PACKER: Well, I can actually  
22 try to preempt that. This committee has never been

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1 restrained in its enthusiasm or lack thereof for any  
2 particular drug based on any relationship to a  
3 knowledge base about mechanism. **And** to, in fact, take  
4 the step one step further, usually our assumptions  
5 about mechanisms which may or may not be available at  
6 the time a drug is approved may be wrong.

7 DR. TEMPLE: I think that was my point.

8 CHAIRPERSON PACKER: But that --

9 DR. HIRSCH: That was my point as well,  
10 Milt.

11 CHAIRPERSON PACKER: But that has not  
12 inhibited the process from going forward in a useful  
13 fashion.

14 DR. HIATT: And the clinical data stand on  
15 their own. I mean I think backing in the mechanism is  
16 probably more productive than going forward with the  
17 mechanis:n.

18 CHAIRPERSON PACKER: Lem?

19 DR. MOYE : Do you envision the  
20 pharmacologic treatment of stable claudicators now to  
21 improve their walking distance as long-term,therapy or  
22 short-term therapy?

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1 DR. HIATT : That is long-term therapy.  
2 Because the natural history over five years is no  
3 spontaneous amelioration of their symptoms. So if  
4 they were on **block claudicators** today, they remain  
5 that way. And what I tried to say is that their  
6 disability does not just go away. It is **quite severe**.  
7 So it is a long-term therapy.

8 DR. MOYE : Well, then why would you be  
9 satisfied with data that only demonstrates short-term  
10 efficacy?

11 DR. HIATT: I think that the standard of  
12 trying to address the issue of symptom relief and  
13 functional status could be answered over a short-term  
14 study, whereas mortality events may take three years.  
15 Now you are going to see data that shows continued  
16 improvement -- the slope of the line is going up at  
17 six months in some of these trials, and you will see  
18 that in a minute. My experience would be that with  
19 exercise training if we treat them for three months  
20 and continue an ad hoc program, the benefit stays  
21 there for several years. So I don't think we need  
22 two-year studies to prove that they have **symptom**

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1 relief at two years.

2 DR. MOYE: Well, that requires  
3 extrapolation and I think extrapolation is a dangerous  
4 business.

5 CHAIRPERSON PACKER: Ileana?

6 DR. PINA: Clinically speaking, the  
7 population that remains stable for five years at 75  
8 percent, how many of those people do you think have  
9 underlying left ventricular dysfunction that is  
10 clinically "silent"? That is my first question. And  
11 you equated the functional capacity of the **claudicant**  
12 to that of **the** heart failure population with  $VO_2$ 's of  
13 about 10 to 15. Do you mean maximum functional  
14 capacity with RER's clearly over 1.1 achieving  
15 ventilator threshold, et cetera? Or do you mean  
16 early limitations by symptoms, because that would make  
17 them very different. I mean, I think I know the  
18 answer, but I would like to hear yours.

19 DR. HIATT: That is an interesting  
20 question. If you take a heart failure patient to  $VO_2$   
21 max, or I would probably say more correctly peak  $VO_2$ ,  
22 the RER values are always very high -- 1.1 or 1.2.

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1 And if you look at the lactate response during  
2 exercise, it is quite brisk because there is a global  
3 **under-perfusion** and there is a very high lactate level  
4 and that is what drives the RER so high.  
5 Paradoxically, we have done a lot of exercise testing  
6 in **claudicants**, and when you go to maximum  
7 **claudication** pain, you are limited by a regional  
8 muscle zone and the RER values peak out at about .9.  
9 They never go over 1. And the peak lactate levels go  
10 from 1 millimolar at rest to 2 millimolar at peak  
11 exercise. There is no lactate threshold. And I think  
12 the systemic organism is below a lactate threshold  
13 level of exercise.

14 DR. PINA: So, in other words, comparably  
15 speaking, they are functionally limited, but that is  
16 not really their maximum point. They are quite  
17 different from the heart failure population in that  
18 sense.

19 DR. HIATT: Yes. How they are limited is  
20 quite different. Just the peak  $VO_2$  number happens to  
21 be the same. And the point is that that is not a  
22 trivial reduction in peak  $VO_2$ . I think that is a

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1 fairly significant reduction due to a very different  
2 mechanism.

3 DR. PINA: Except I think if you do local  
4 lactates from femoral venous flow in the lower  
5 extremities, you would pick up the lactic acid that  
6 you don't see systemically. What about my previous  
7 question about how many of those patients would have  
8 underlying left ventricular dysfunction that we should  
9 at all be concerned about if they are going to get a  
10 PDE inhibitor.

11 DR. HIATT: You bet. Let me answer that  
12 two ways. If you cap these people, these people being  
13 the ones who go to the Cleveland clinic to get their  
14 legs operated on, so it is a select subgroup, 90  
15 percent have significant coronary disease. So they  
16 all have coronary disease. How much have LV  
17 dysfunction has not been rigorously studied. So I  
18 have to back into the answer clinically. Clinically,  
19 you don't see Class III and IV heart failure in these  
20 patients. so it has got to be something that is less  
21 clinically significant than their claudication. And  
22 when I examine them and listen for S-3's and look for

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1 neck veins and rales and that kind of thing,  
2 **surprisingly** I think it is underrepresented in this  
3 population. That is my clinical impression.

4 CHAIRPERSON PACKER: Let me ask one  
5 question **because** although we are **getting** a very  
6 valuable education here, there still is a drug that  
7 needs to be evaluated.

8 DR. HIATT: We can keep going if you want.

9 CHAIRPERSON PACKER: I want to ask you  
10 about how this committee should define quality of life  
11 in these patients. Quality of life has become a buzz  
12 word, a buzz word which many sponsors are interested  
13 in having incorporated in their labeling because they  
14 believe it provides them with certain commercial  
15 advantages. But the question is what is a measurement  
16 of quality of life in a patient with intermittent  
17 **claudication**. The analogies that you have made with  
18 heart failure is actually **really, I think, not only**  
19 valid but very interesting. Because as in  
20 claudication, there is a discrepancy between  
21 hemodynamics and symptoms or exercise performance, and  
22 there may or may not be a relationship between

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1 exercise performance and quality of life. You have  
2 described three ways or three instruments of measuring  
3 functional effects of drugs. One is a formal exercise  
4 test. A similar kind of test exists in heart failure.  
5 TWO, you have described the SF-36, which is what might  
6 be called a standard quality of life questionnaire.  
7 And there are or may not be parallels in heart  
8 failure. The WIQ is what the focus of my question is.  
9 It sounds to me -- and I think you were actually  
10 instrumental in developing it, so you could speak  
11 directly to this -- that it is not a measure of  
12 quality of life.

13 DR. HIATT: Correct.

14 CHAIRPERSON PACKER: What it is is what is  
15 equivalent in heart failure to a symptom score. It is  
16 a direct question to a patient as to how much they can  
17 do, but it is not a measure of the impact of their  
18 symptoms on their lives. We conventionally refer to  
19 quality of life instruments as falling into the latter  
20 category and not the former category. Do you agree?

21 DR. HIATT : Yes. I have wrestled with  
22 this a lot, and I don't know the optimal way to define

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1 these issues in **claudicants**, but I think it is  
2 extremely important. Drug approval is not the issue  
3 here. It is patient care. And that is why I care  
4 about it. Because I am trying to do something to make  
5 that person walk further, and I am not sure what it is  
6 that is so disabling for them and I need to figure  
7 that out. You are absolutely correct. The WIQ is a  
8 disease-specific functional status, not a quality of  
9 life instrument. And I wrestled with whether the SF-  
10 36 is really functional status or quality of life.  
11 This quality stuff -- you are asking the wrong person  
12 when it gets too beyond my level of **hemodynamic**  
13 thinking. **But** I think it is extremely important. And  
14 I think you have to address quality of life in  
15 multiple ways and not just use one instrument, and use  
16 a variety of approaches. I agree with everything you  
17 said.

18 DR. HIRSCH: Can I give a comment to that?

19 CHAIRPERSON PACKER : Yes.

20 DR. HIRSCH : It is a wonderful time to  
21 look for paradoxes between our instruments. I think  
22 it is less of a worry than we probably think it is.

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1 There **is** unpublished data that will be coming out in  
2 the coming year to sort of suggest that for the  
3 **claudication** patient, their walking impairment does  
4 affect their quality of life and the SF-36 physical  
5 domain, the walking impairment question or distance  
6 score, are likely, whether it is vascular surgery,  
7 **angioplasty**, Dr. Hiatt, or a medication, are likely to  
8 change in parallel for this kind of PAD patient. That  
9 is speculation, but that is my belief.

10 CHAIRPERSON PACKER: Yes, Alan, they may  
11 be correlated, but I think there is a need for  
12 precision of describing what these measurements are.  
13 Marv?

14 DR. KONSTAM: You know, I am not a quality  
15 of life expert either, but I just have a certain way  
16 of thinking about this. My own view about it is you  
17 are making some artificial distinctions. I think that  
18 the game plan really is to improve quality of life.  
19 But I **am** not sure at all that the best way to measure  
20 quality of life is a quality of life instrument. I  
21 think all of the things that we are looking at are  
22 linked to the patient's quality of life. And I think

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the quality of life questionnaires are specific attempts to drag that out of the patient. But I am not sure they are the best way to really know whether or not the quality of life for the patient has improved or not. so I view functional status indicators as giving another look at the big question of quality of life rather than focusing on the questionnaire per se.

CHAIRPERSON PACKER: Oh, I agree with that. Except that one of the questions to this committee is going to require us to deal directly with issues related to what was found and what labeling might be appropriate. So the reason to bring this up was to specifically ask the person who developed the questionnaire how he viewed his own questionnaire.

DR. HIATT: Can I just add to that? Both of these questionnaires have been validated to the PAD population. They have been found to be reproducible. They don't change with placebo and they do change with drug therapy. And I think that the drug should improve treadmill performance and questionnaire functional status. One without the other to me is

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1 probably a little less relevant.

2 CHAIRPERSON PACKER: Bob?

3 DR. THADANI: I am going to ask you one  
4 question. Why did you apply for this --

5 CHAIRPERSON PACKER: No, Bob --

6 DR. THADANI: I think it is very relevant.  
7 Because here you are saying the 5-year intermittent  
8 **claudication** will not get worse, and yet you told us  
9 20 percent die.

10 DR. HIATT: Right.

11 DR. THADANI: And also 20 percent have MI  
12 and all that. So I think that is worse than a stable  
13 angina patient if you don't have triple vessel  
14 disease. There is only 2 percent mortality per year.  
15 So dealing with comorbid conditions which might be  
16 much more relevant than just a little bit of  
17 improvement in say walking distance. So I think we  
18 cannot dissociate the two processes. Because one of  
19 the possibilities is that your  $MBO_2$  is going up. Your  
20  $dP/dT$  in some other data base goes up. So if a  
21 patient had underlying coronary artery disease and he  
22 **can't** walk much because of claudication, and yet when

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1 he walks more it could have a detrimental effect over  
2 the long-term. So I think three month studies might  
3 be reassuring for exercise improvement, but it might  
4 have a negative effect on the eventual mortality or  
5 morbidity, and I think Milton will agree that there is  
6 a dissociation between exercise improvement and  
7 mortality in some of the heart failure studies. So I  
8 think that is an important issue to keep in mind. And  
9 I am sure it will come up again.

10 CHAIRPERSON PACKER: Yes. I think,  
11 though, that there has already been a -- I guess Dr.  
12 Hiatt has already made the point that his first and  
13 foremost priority in treating patients is to modify in  
14 a favorable way their long-term outcome.

15 DR. HIATT: You bet.

16 CHAIRPERSON PACKER: And that he would  
17 take priority over any short or intermediate change in  
18 symptoms. Bob?

19 DR. TEMPLE: We have been seeing a lot of  
20 attempts to measure quality of life. And if there is  
21 one thing that emerges repeatedly, it is easier to  
22 show effects on the measurements of symptoms of the

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1 impact of the disease that you are looking at most  
2 directly. So that you are likely to find an  
3 improvement on physical aspects related to  
4 claudication. Not too surprising. It is much more  
5 difficult to show that that makes your sex life better  
6 or your mental function better because, for obvious  
7 reasons, those are multifactorial. There is more than  
8 one reason. Claudication is only one of them. That  
9 you are not getting along at home or that you are not  
10 enjoying your work life. So that I guess we have seen  
11 this a lot, and I guess I want to agree with what you  
12 said. The expectation is that you will affect the  
13 thing you are affecting. If you are very lucky and if  
14 it is a major impact on the person's life, maybe  
15 sometimes you will show that the whole person's life  
16 improves. But that is sort of terrific if you can  
17 achieve it. And most of the material we have seen  
18 don't show that.

19 DR. HIATT : I totally agree with that.  
20 You are going to see changes in physical function.  
21 But let me just add that the mental health scores are  
22 normal. And the social role function scores are

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1 norms 1. So these people, their whole life isn't  
2 screwed up. It is just their ability to exercise and  
3 do those physical things.

4 CHAIRPERSON PACKER: Okay. Let's proceed  
5 to the next presentation.

6 DR. HIATT: Thank you. Dr. Bill Forbes is  
7 going to show you the efficacy data.

8 CHAIRPERSON PACKER: I am sorry, Rob, I  
9 didn't see you.

10 DR. CALIFF: I thought you were going down  
11 the line. I have three questions. I will try not to  
12 make this take too long. You focused in on the stable  
13 claudicators. What do you think the mortality rate is  
14 in that population? You said 20 percent over five  
15 years in the whole group. In an all-comers clinic  
16 population as a doctor would typically use a treatment  
17 like this.

18 DR. HIATT : I have tried to look at the  
19 mortality data and it does range quite a bit and the  
20 populations are somewhat heterogeneous. They all have  
21 PAD . But if you look at even an asymptomatic PAD in  
22 Creakey's data base, their mortality rates are

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1 increased significantly. That is at least 2 to 3  
2 percent per year. The **clopidogrel** data base gives us  
3 a really good estimate of mortality, and that is  
4 around 4 to 5 percent per year, of which some are  
5 **asymptomatic** because they have had bypasses and some  
6 have **claudication**. So there is a secular trend,  
7 though, **like** anything else in cardiovascular disease.  
8 You are going to see lower mortality rates here. So  
9 I think the answer is probably around -- ranging 2 to  
10 6 percent per year.

11 DR. CALIFF: One of the reasons I am  
12 having trouble synthesizing the concept that this  
13 would be a typical population that was in the trials  
14 is because it seems like the mortality that was in the  
15 trial data base is considerably lower than what would  
16 be seen in a practice setting from what you said.

17 DR. HIATT : Well, the other thing I **am**  
18 showing you from some of that mortality data that goes  
19 back 10 and 20 years. So like in coronary disease,  
20 there has been a secular trend in mortality to go  
21 down.

22 DR. CALIFF: The question is I am trying

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1 -- as the big picture guy, I am trying to get a sense  
2 for the kinds of improvement in treadmill time that  
3 are shown here. What do they really amount to?

4 DR. HIATT: If you convert the treadmill  
5 change over placebo, and you are going to hear that  
6 later too, it translates into uphill a block or so,  
7 and on level ground you can multiply that by two to  
8 three. So I think it is enough of a change in a  
9 treadmill performance to matter in terms of a  
10 patient's life.

11 DR. CALIFF: So you think it is a block?

12 DR. HIATT: It is a block. I mean, if you  
13 could only go a block and now you can go two, that is  
14 meaningful.

15 DR. CALIFF: The last question is probably  
16 the toughest. You probably don't have a complete  
17 answer, but I think it really probably is going to  
18 turn out to be the key question. For an extra block  
19 -- you see a lot of these patients and you have done  
20 studies. For an extra block of walking time, how much  
21 of an increase in potential risk of mortality do you  
22 think a typical claudicator would be willing to take?

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1 DR. HIATT : I think that the thing we  
2 don't really appreciate is the severity of their  
3 symptom. And I think a block matters. And they tell  
4 us that through a variety of instruments. So I think  
5 a treatment effect that doubles walking time on the  
6 treadmill. or even less than that, that improves  
7 quality of **life**, is clinically relevant. Now what is  
8 the cost of doing that? At least in this data base,  
9 you are not going to see an increase in mortality. So  
10 from what I can see, I don't see a huge risk to be  
11 worried about. But you are going to have to evaluate  
12 that for yourself.

13 DR. CALIFF : But hypothetically -- the  
14 hypothetical treatment for an extra block, would the  
15 typical patient be willing to accept a doubling in  
16 mortality?

17 DR. HIATT: It is a quality kind of thing,  
18 isn't it? I don't know. I haven't ask that question  
19 to my patients.

20 DR. CALIFF: Okay. Thanks.

21 CHAIRPERSON PACKER: Okay. Let's proceed  
22 to the next presentation.

1 DR. HIATT: Am I off the hook now? Dr.  
2 Bill Forbes.

3 CHAIRPERSON PACKER: Thank you.

4 DR. FORBES: Good morning. I am going to  
5 present t-he clinical development and clinical efficacy  
6 of **cilostazol**. I am a little sensitive to the  
7 Chairman's concerns regarding time, so I just want to  
8 point out to you that there is a 7-digit number over  
9 here in the lower left-hand corner. You may have seen  
10 it before. If you want to write that number down for  
11 purposes of reference. I have been told that if you  
12 give that number, we can get to the slide very  
13 quickly.

14 Otsuka has conducted 8 well-controlled  
15 clinical trials in patients with intermittent  
16 claudication. In addition to the phase 3 trials shown  
17 here, there were three small trials conducted in  
18 Germany and two small trials conducted in Japan in  
19 patients with intermittent claudication. Due to the  
20 limited size and exposure of these trials, I will not  
21 be spending time on them in my efficacy presentation.  
22 However, they will be addressed in the safety

1 presentation.

2 A total of 2,702 patients participated in  
3 phase 3. The specific aim of the development program  
4 was to establish the efficacy and safety of **cilostazol**  
5 compared not only to placebo, but to the marketed  
6 formulation of pentoxifyline. Since it was the  
7 marketed formulation that was used both in the UK  
8 trial and in the U.S. trial, I will be using the trade  
9 name of **Trental** and the generic name of **pentoxifyline**  
10 interchangeably.

11 Of the 2,702 patients randomized, 1,374  
12 took one dose of cilostazol, 355 took a dose, **400 mg**  
13 tid of **pentoxifyline**, and 973 were randomized to  
14 placebo.

15 The efficacy of **cilostazol** was assessed by  
16 the absolute **claudication** distance or ACD. The ACD is  
17 the maximal distance the patients can walk on a  
18 treadmill. And prior to each treadmill test, the  
19 patients were instructed -- and I quote -- "to walk to  
20 the point that normally makes you stop." Thus, this  
21 measurement is believed to be the most clinically  
22 relevant as Dr. Hiatt mentioned earlier.

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1           Secondary efficacy assessments collected  
2 during the clinical development program which support  
3 the improvements seen on maximal walking distance  
4 include the ICD or pain-free walking distance.  
5 Additionally, quality of life and a number of  
6 functional status questionnaires were also collected.  
7 The use of quality of life and functional status  
8 questionnaires focused on the characterization of a  
9 patient's ability to regain their normal physical  
10 activity.

11           Other efficacy assessments collected but  
12 not listed on this slide include the change in resting  
13 ankle **brachial** index and the rate of pressure recovery  
14 following maximal exercise.     Though I have not  
15 included it in my primary presentation -- I didn't  
16 realize it would be such an area of interest -- I do  
17 have some slides that I can refer to after the  
18 conclusion that I can bring up quickly.     Also, plasma  
19 lipids were assessed during the development.

20           Inclusion criteria during the course of  
21 development was primarily based on the following.  
22 Patients had to be greater than 40 years of age. A

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1 history **of** having peripheral arterial disease greater  
2 than six months. An ankle **brachial** index of less than  
3 .9. They **had** to have at least a 10 mm drop in ankle  
4 pressure following maximal exercise at one minute.  
5 And of course they had to have a stable treadmill  
6 performance during the screening period.

7           During the development program, the  
8 exclusion criteria underwent very few modifications.  
9 Of particular interest in defining the population are  
10 the following exclusion criteria. The presence of  
11 critical limb ischemia, uncontrolled blood pressure  
12 either treated or untreated, clinically significant  
13 bleeding within one year, history of unstable angina  
14 pectoris, **myocardial** infarct, **angioplasty** or CABG  
15 within 6 months. Also, symptomatic cardiac  
16 arrhythmias or unexplained **syncopal** episodes. And  
17 additionally, patients were excluded if during the  
18 screening period they presented with an exercise  
19 limiting condition other than **claudication**. Examples  
20 of this include congestive heart failure, angina  
21 pectoris, and arthritis.

22           The baseline demographics and medical

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1 histories were similar across trials. Within each of  
2 the 8 trials, they remained similar across the  
3 different treatment groups. We have pooled the  
4 populations from phase 3 so as to provide you with  
5 some idea of the baseline characteristics of patients  
6 recruited into the controlled clinical trials.  
7 Patients were primarily 65 years of age. They had a  
8 baseline ankle brachial index, as Dr. Hiatt mentioned  
9 earlier, of 0.64. 76 percent were male. 90 percent  
10 were Caucasian, and 92 percent were positive for a  
11 smoking history and only 8 percent never smoked. Just  
12 for your information, about 30 to 40 percent of the  
13 populations entered into the controlled clinical  
14 trials were current smokers.

15 The medical histories of the patients  
16 enrolled in the phase 3 clinical trials were  
17 characteristic of the population seen in the published  
18 literature for studies in patients with intermittent  
19 claudication. Namel, 60 percent were hypertensive, 25  
20 percent had diabetes, 22 percent were positive for at  
21 least having one previous myocardial infarction.  
22 Additionally as you may note, 5 percent of the

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1 population had congestive heart failure as part of  
2 their medical history. Now since they had to be  
3 limited **by** their **claudication**, although we didn't  
4 collect the information, we **believe** these are **class I**  
5 or II heart failure patients. This 5 percent is  
6 actually 125 patients.

7 As defined a priori in all protocols, the  
8 endpoint of ACD was analyzed using the change in  
9 meters walked expressed as a log. For comparison of  
10 study **groups**, the log values of treatment effects were  
11 converted into a ratio of geometric mean. Ratios  
12 greater than one are in favor of **cilostazol** and ratios  
13 less than one in favor of placebo. Additionally, if  
14 a patient withdrew from therapy early, their last  
15 treatment value was used for each subsequent data  
16 point. so it will be referred to as the **last**  
17 observation carried forward.

18 I would just like to mention a few things  
19 regarding the sensitivity of the statistical analysis  
20 just to clarify a few issues. The primary analysis  
21 used the statistical methods pre-specified in the  
22 protocols. Log transformation was used in an attempt

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1 to normalize the data. In addition to the log  
2 transformation, the raw data were also analyzed and  
3 confirmed the log transformation results.

4 The results were significant regardless of  
5 adjustment for multiplicity tests for the four largest  
6 trials **conducted** in the United States. An intent to  
7 treat analysis was used that did not exclude patients  
8 with post-baseline information.

9 In reference to the impact of drop-outs,  
10 in a post-hoc analysis, we carried forward baseline  
11 whenever a patient did not have a post-baseline  
12 assessment, that is, had zero treatment effect. The  
13 analysis including these patients had no impact on the  
14 overall conclusion of the analysis pre-specified in  
15 the protocol. We also assessed the impact of non-  
16 compliance, and this too did not impact.

17 To follow up on the protocol specified use  
18 of **LOCF**, it is a commonly used method to account for  
19 patients who withdraw from a study prior to scheduled  
20 study completion. However, if a patient withdraws  
21 prior to the first efficacy assessment **post-**  
22 randomization, they are not captured in this analysis.

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1 What we have done for you here is to list the number  
2 of patients by study and by treatment group for each  
3 of the clinical trials that were not included in the  
4 LOCF . I will draw your attention to two studies that  
5 I will **be** talking about, 92202 and 96202. In 92202,  
6 there were 4 placebo patients, 7 50 mg, and 8 100 mg  
7 patients. For the comparator trial, 96202, which is  
8 noted down here, there are 13 placebo patients, 22 100  
9 mg patients, and 20 patients on Trental. Overall, 6.6  
10 percent of the population failed to have a **post-**  
11 treadmill test -- post-baseline treadmill test.

12 We will focus on two trials to provide a  
13 better understanding of the efficacy of **cilostazol**.  
14 These two trials enrolled the largest number of  
15 patients and enrollment was for 24 weeks of therapy.  
16 Study 92202 provided dose response information **for**  
17 **cilostazol** 50 mg and 100 mg dosed twice daily. I will  
18 refer to these dosing regimens as **cilostazol** 50 and  
19 100. Study 96202 compared the efficacy of cilostazol  
20 100 mg, again dosed twice daily, to 400 mg three times  
21 daily of **Trental**. This dosing regimen of 400 mg three  
22 times daily is the maximal recommended dose in the

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1 package insert.

2 The primary endpoint for study 96202 was  
3 a change from baseline in the ACD for **cilostazol**  
4 compared to **Trental** after 24 weeks of treatment.  
5 Additional assessments included the change in maximal  
6 walking distance for **cilostazol** versus placebo and  
7 **pentoxifyline** versus placebo.

8 as you are well aware, a MET is a  
9 measurement of energy expenditure or work rate. One  
10 MET is the energy expenditure at rest and a work rate  
11 of 2.5 METS is equivalent to expending 2.5 times the  
12 amount of energy expended at rest. The treadmill test  
13 required that patients initially walk at 2 miles per  
14 hour at a zero percent grade. Every three minutes,  
15 the grade increased 3.5 percent while the speed was  
16 maintained at 2 miles per hour. The subjects were  
17 instructed to indicate when they initially felt leg  
18 pain and continue to walk to the point that they  
19 normally would stop. As Dr. Hiatt mentioned earlier,  
20 normal walking speed for this population is about 1 to  
21 2 miles per hour on level ground. This translates to  
22 about 2 to 2.5 METS, and as you will see, **cilostazol-**

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1 treated patients not only increased their walking  
2 distance, but accomplished this at a greater intensity  
3 than they normally walk.

4 This is the treatment effect for the  
5 primary analysis of **cilostazol** versus **Trental**. Since  
6 this is the first in a number of similar slides, I  
7 will spend a very short period of time describing it.  
8 The number of weeks is plotted along the X axis, and  
9 the ratio of the geometric mean along the Y. The  
10 white horizontal line is the line of equal effect, and  
11 these green bars are the 95 percent confidence  
12 intervals with a point estimate included.

13 **Cilostazol** was superior to **Trental** at 24  
14 weeks of therapy as noted right here, with a highly  
15 significant P value. The estimated treatment effect  
16 for each time point prior to the primary endpoint of  
17 week 24 was also examined. The superiority of  
18 treatment with **cilostazol** over treatment with **Trental**  
19 was seen at every time point.

20 The secondary comparison of maximal  
21 walking distance for **cilostazol**, again highlighted by  
22 the green bars versus placebo, was statistically

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1 significant starting at week 4 of therapy. Dr. Hiatt  
2 mentioned earlier that the slope of the line continues  
3 to increase as treatment continues. So I will just  
4 bring to your attention the fact that the estimated  
5 treatment effects continue to go up over time. And  
6 this is true whether you are looking at log ratios or  
7 a change in meters walked for the large clinical  
8 trials.

9 In this population for this trial, **Trental**  
10 did not demonstrate a difference from placebo. This  
11 is the change in maximal walking distance from  
12 baseline over the duration of treatment. The  
13 horizontal axis is the weeks on treatment and the  
14 vertical axis is the change in meters walked from  
15 baseline. The green line represents **cilostazol**, the  
16 red line **Trental**, and the white line placebo. As **you**  
17 can see, the **cilostazol** group began to separate from  
18 the other "two groups as early as week four and  
19 continued to separate for the duration of this study.  
20 While the **Trental** and placebo response were virtually  
21 identical. Again, this is using a conservative  
22 analysis of LOCF. If patients dropped out early in

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1 their treatment, their value was carried forward. In  
2 spite of this, you see the treatment effect increasing  
3 with the **cilostazol** treatment. At the end of the  
4 treatment period, the maximal walking distance in  
5 **cilostazol-treated** patients increased 113 meters while  
6 it increased 68 meters in placebo and Trental-treated  
7 patients. This represents a 66 percent greater  
8 improvement with **cilostazol** than the improvement seen  
9 with either Trental or placebo.

10 This slide emphasizes two points about the  
11 results of this trial. Not only did the **cilostazol-**  
12 **treated** patients walk farther than the **Trental** and  
13 placebo patients, but because they were able to walk  
14 farther, on average they walked into the next stage of  
15 the treadmill test. Thus, the maximal walking  
16 distance for the **cilostazol** group achieved an  
17 intensity equivalent to 4.5 METS. This intensity is  
18 29 percent greater than the intensity reached with  
19 treatment with Trental or placebo. I would like to  
20 make one additional point. At baseline, all three  
21 groups **are** walking at this stage. While the placebo  
22 and the **Trental** group remain here, the **cilostazol-**

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1 treated patients were able to move into the next  
2 stage.

3 In summary, for 96202, cilostazol 100 mg  
4 increased walking distance 66 percent more than  
5 treatment with Trental or placebo. This improvement  
6 in walking distance was clinically and statistically  
7 significant, and the effect of Trental on walking  
8 distance was virtually identical to that of placebo.

9 Protocol 92202 studied the dose effect for  
10 both 50 and 100 mg of cilostazol in comparison to  
11 placebo. In this protocol, the change from baseline  
12 for both ICD and ACD at week 24 of therapy were listed  
13 as primary endpoints.

14 In contrast, for the treadmill test used  
15 in the comparator trial 96202, 92202 required patients  
16 to walk at 2 miles per hour on a constant 12.5 percent  
17 grade. This treadmill test required that patients  
18 walk in an intensity equal to 6 METS or an intensity  
19 two to three times greater than their normal walking.  
20 And improvement under these conditions would  
21 underestimate the true improvement in distance seen  
22 under normal walking conditions.

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1                   For the change in maximal walking distance  
2                   at 24 weeks of therapy, treatment with **cilostazol** 100  
3                   **mg** as shown in green significantly increased the  
4                   maximal walking distance with a highly significant  
5                   corresponding P value. A comparison of 50 mg to  
6                   placebo as shown in blue also had a statistically  
7                   significant difference from placebo. As you can  
8                   observe, significant improvement is seen from week 4  
9                   for 100 **mg** and week 8 for 50 mg. The results for the  
10                  initial **claudication** distance are very similar to  
11                  these, and for the purposes of time, I have not  
12                  included them in my original talk.

13                  The ACD is presented as a change in meters  
14                  walked from baseline over the 24 weeks. The data  
15                  support the primary finding by demonstrating a 106  
16                  meter treatment effect of **cilostazol** 100 mg as shown  
17                  in green over placebo shown in white. Treatment with  
18                  **cilostazol** 100 mg provided 381 percent greater  
19                  improvement than that improvement seen with placebo.  
20                  And assuming that one city block is 80 meters,  
21                  patients taking **cilostazol** walked one and one-third  
22                  blocks farther than placebo-treated patients.

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1                   As Dr. Hiatt emphasized, in . this  
2 population two out of three patients perceive having  
3 difficulty walking one block on level ground. The 50  
4 mg dose as shown in blue was also efficacious.  
5 Patients randomized to this treatment outperformed the  
6 placebo treated patients at each time point. At 24  
7 weeks of treatment, the 50 mg group experienced a 151  
8 percent greater improvement than the improvement seen  
9 with treatment with placebo.

10                   In summary, for 92202, **cilostazol 100 mg**  
11 increased walking distance 381 percent more than  
12 placebo treatment. We believe this increase is  
13 clinically as well as highly statistically  
14 significant, and **cilostazol 50 mg** also increased  
15 walking distance approximately 151 percent greater  
16 than that seen with placebo.

17                   The ratio of the geometric means of  
18 **cilostazol 100** over placebo are presented for all 8  
19 phase 3 clinical trials. We have already presented  
20 information showing the efficacy of **cilostazol** for the  
21 first two trials, 96202 and 92202. The other six  
22 trials **are** included to emphasize the consistency of

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1 efficacy. The point estimate always favors treatment  
2 with **cilostazol** over placebo. While positive, the  
3 treatment effect for studies 94301 and 95201 did not  
4 demonstrate statistical superiority. And in an  
5 attempt to understand why, we did a number of post-hoc  
6 analyses. Admittedly, these analyses need to be  
7 interpreted cautiously.

8 For 94301, which was the comparator trial  
9 conducted in the UK, we had a number of patients that  
10 missed more than one dose prior to their treadmill  
11 test. When the analysis is restricted to those  
12 patients who were compliant, we see an estimated  
13 treatment effect similar to the treatment effects  
14 commonly seen in the other trials conducted in the  
15 United States.

16 On the other hand, for 95201, attempts to  
17 understand why statistical superiority did not occur  
18 in patients on 100 mg has not resulted in a reasonable  
19 explanation, and some have thought that perhaps it is  
20 just a play of chance.

21 Regardless of what we see with 94301 and  
22 95201, the point estimate is always in favor of

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1     **cilostazol**. The data demonstrate that **cilostazol** is  
2     superior to placebo in increasing the maximal walking  
3     distance.

4             Atruly effective therapy for intermittent  
5     **claudication** needs to be effective across a broad  
6     range of patients with different demographics and  
7     different comorbid conditions. To this end, we pooled  
8     post hoc to gain further insight into the response of  
9     subgroups. The primary reason for pooling was to  
10    determine if the results we see across trials is also  
11    consistent across patients with different baseline  
12    characteristics. Patients receiving **cilostazol** 100 mg  
13    walked significantly farther than patients receiving  
14    placebo regardless of age or smoking status. **While**  
15    women and non-Caucasians were not statistically  
16    superior to placebo, their point estimates strongly  
17    suggest improvement.

18            Additionally, patients receiving  
19    **cilostazol** 100 mg walked significantly farther than  
20    patient receiving placebo regardless of the  
21    concomitant use of beta or calcium channel blockers,  
22    the presence of diabetes, and the duration of their

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1 peripheral arterial disease upon screening.

2 I know there have been several  
3 conversations about the quality of life, short form  
4 36, already. This particular form was used in 6 of  
5 the U.S. clinical trials. It is a widely used general  
6 health questionnaire and consists of 8 **subscales** and  
7 two summary scales. Dr. Hiatt mentioned earlier that  
8 the mental and emotional component of quality of life  
9 is not drastically impaired. Because of this, we have  
10 focused on the physical aspects of the quality of  
11 life, and this is where **cilostazol** should **show** a  
12 benefit. The physical component scale relates  
13 directly to the patient's ability to function and to  
14 how patients feel physically. **Subscales that** are  
15 weighted most in scoring the physical summary include  
16 bodily pain, physical functioning, and role physical.

17 The quality of life data for the physical  
18 component scales is shown as the estimated treatment  
19 effect **and** demonstrates superiority for each of the  
20 scales reflecting the physical component. Bodily pain  
21 is a measure of the frequency of pain and the extent  
22 of pain associated with disability. Physical

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1 functioning assesses limitations in walking various  
2 distances, climbing stairs, and performing everyday  
3 physical activities. Role physical assesses problems  
4 in performing role activities, including  
5 accomplishments at work, household chores, or leisure  
6 activities. The physical summary combines physical  
7 **subscales** and scores them on a different metric, which  
8 is much smaller than the standard deviation which is  
9 used for these bodily pain, physical function, and  
10 role physical. Standard deviation is one-fourth to  
11 on-half as large as the standard deviation used for  
12 these **subscales**. Thus, each point on the scale is  
13 much more meaningful. One way to interpret this  
14 summary **is** in relation to age. After age 50, on  
15 average we decline one point per year. Thus, a two to  
16 three point improvement we see with **cilostazol**  
17 treatment is like turning the clock back from 65 to  
18 age 62. The quality of life data is supportive and  
19 consistent with primary outcome data and provide  
20 evidence that improvements seen on the treadmill carry  
21 over to everyday activity.

22 In addition to the physical dimensions of

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1 quality of life, we collected the mental component to  
2 address quality of life comprehensively. The result  
3 indicates that treatment with **cilostazol** has no  
4 deleterious effect on the mental aspects of these  
5 patients.

6 In conclusion, **cilostazol** consistently  
7 increased maximal walking distance compared to  
8 placebo. The increases were sufficiently large as to  
9 be clinically relevant. **Cilostazol** improved walking  
10 distance regardless of baseline conditions or presence  
11 of certain medications. And patients treated with  
12 **cilostazol** reported an improvement in the physical  
13 component of their quality of life. That is my  
14 conclusion.

15 CHAIRPERSON PACKER: Again, we will begin  
16 with our primary reviewer. Again, the focus of the  
17 questions will be on efficacy. Anyone with questions  
18 about safety, they should reserve them to the next  
19 presentation.

20 DR. FORBES : Excuse me, would you still  
21 like to start with the ABI -- the ankle **brachial**  
22 index?

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1 CHAIRPERSON PACKER : I am sorry?

2 DR. FORBES : Would you like any data on  
3 the ankle **brachial** index?

4 CHAIRPERSON PACKER: Why don't we -- is  
5 that what remains in your presentation for efficacy?

6 DR. FORBES: I actually took it out of my  
7 primary presentation, but I know that there has been  
8 discussion revolving around it. So if there is any  
9 data that wants to be presented, I will be happy to  
10 call for it.

11 CHAIRPERSON PACKER: Why don't we do this.  
12 I think there is some interest in it based on some of  
13 the questions. But since the committee has already  
14 turned their chairs, why don't we hold that.

15 DR. FORBES: Sorry about that.

16 DR. LINDENFELD: There were a fair number  
17 of drop-outs in the study, more in the **cilostazol**  
18 groups than in the placebo. Can you tell me -- I know  
19 it might be hard in all of the pooled studies, but in  
20 either of your two pivotal studies, what the absolute  
21 **claudication** distance was in the dropouts versus the  
22 rest of the patients? What I am getting at here is

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1 did people drop out who had less walking distance and  
2 could that be one of the reasons for the gradual  
3 improvement ?

4 DR. FORBES : Yes. Can I have back-up  
5 slide 226, please? This is for protocol 96202, the  
6 comparator here in the United States. There were 55  
7 patients **that** were randomized, but they had no **post-**  
8 **baseline** treadmill test. These patients were not  
9 included in the original LOCF analysis, and you can  
10 see that their baseline ACD for placebo is 218,  
11 **cilostazol** 221, and we have a typo there. That is  
12 actually **Trental**, and **Trental** is equal to 176 meters  
13 at baseline. And as you can see, there is no  
14 statistically significant difference between these  
15 patients. Would you like to see 92202?

16 DR. LINDENFELD: If you have it there. Is  
17 **it** the same? There is no difference?

18 DR. FORBES: It is the same.

19 DR. LINDENFELD: Okay. That is good  
20 enough. I think that is good enough. Did I  
21 understand you correctly to say 30 to 40 percent of  
22 the patients in these studies were active smokers?

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1 DR. FORBES: That is correct.

2 DR. LINDENFELD: So that would be -- how  
3 would that compare to your standard? It sounds like  
4 that is substantially less than what we might see in  
5 a clinic population for active smokers.

6 DR. FORBES: As far as active smokers? I  
7 guess I would have to refer that to one of the  
8 clinical specialists. Dr. Hiatt, would you like to  
9 address that issue?

10 DR. HIATT: The published data would say  
11 that 90 percent are either current or former smokers,  
12 and the current smoking rates are typically 30 to 40  
13 percent in clinic populations. I think it is about --  
14 it is really higher in the U.S. population. There may  
15 be a secular trend there too.

16 DR. LINDENFELD: How many patients were on  
17 aspirin in 92202? That was the randomized and not the  
18 open label, as everyone is saying. I just want to  
19 know if the same numbers were on aspirin.

20 DR. FORBES: I have to get the answer for  
21 you. It will take just a minute.

22 DR. LINDENFELD: Or just an approximate

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1 percentage.

2 DR. FORBES: Do you want to go ahead with  
3 your other questions and then we can come back to this  
4 one?

5 DR. LINDENFELD: Well, I guess and then in  
6 the study in which there was open label aspirin, was  
7 there a difference?

8 DR. FORBES : If I am not mistaken, there  
9 were about 400 patients that took aspirin  
10 concomitantly, both in the open label and in the 96202  
11 that were on **cilostazol**. But we will check the number  
12 and make sure.

13 DR. LINDENFELD: Okay. And was there a  
14 difference in the placebo groups versus the **cilostazol**  
15 groups that were taking aspirin in the open label?

16 DR. FORBES: We did not look at that.

17 DR. LINDENFELD: Okay. And in the  
18 comparison to **pentoxifyline**, do you have any idea how  
19 many patients were excluded from the study because  
20 they were -- how many were screened and were on  
21 **pentoxifyline**, or could we even get an estimate of  
22 that?

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1 DR. FORBES : Yes. Actually, for all of  
2 our protocols, approximately 80 percent of the  
3 patients that were screened got randomized, which left  
4 20 percent of the patients being excluded. And in  
5 follow-up of that, about one-fifth were excluded  
6 because they had shortness of breath on the treadmill  
7 or they had angina on the treadmill. About one-fifth  
8 of the patients, so I am talking about 3 percent of  
9 the population total -- about another 3 or 4 percent  
10 of the population was excluded because their treadmill  
11 walking distance didn't fit between 1 and 10 minutes,  
12 which was the criteria at baseline. And then another  
13 about 3 or 4 percent of the population was excluded  
14 due to ankle brachial indexes that were greater than  
15 .9. Dr. Ingenito, I think, has an answer on your  
16 aspirin question.

17 DR. INGENITO: To answer your question,  
18 Dr. **Lindenfeld**, for the placebo patients there were --

19 CHAIRPERSON PACKER: Just get closer.

20 DR. INGENITO: There were 190 placebo  
21 patients who were taking aspirin and 783 who were not  
22 taking aspirin. For cilostazol, 201 patients were on

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1 aspirin and 1,170 were not.

2 DR. LINDENFELD: Okay. So about the same.

3 DR. FORBES : Gary, is that the 100 mg  
4 group or 'all cilostazol?

5 DR. INGENITO: That represents all  
6 cilostazol -- cilostazol total.

7 DR. LINDENFELD: Okay. And then the  
8 secondary endpoints here are confusing. Maybe you can  
9 -- there are quite a few secondary endpoints, and it  
10 said in the review that no **single** one reached  
11 statistical significance. Can you comment on that?  
12 In other words, of the large number of secondary  
13 endpoints in each individual study, our review says  
14 that **there** was no one that was actually individually  
15 statistically significant. It is also commented on  
16 that there was no prospective way to define how these  
17 were evaluated or how we would assess the statistical  
18 significance of all of these. Can you comment on  
19 that?

20 DR. FORBES: Well, I think it is correct  
21 to say that the secondary endpoints, there were a  
22 number **of** them listed in the protocol. I am a little

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1       unclear as to the statistical significance. We did  
2       not adjust for P values for secondary analyses. As  
3       far as the treadmill tests are concerned, many, many  
4       of the secondary analyses were positive, particularly  
5       for the large trials. When we look at lipids for  
6       93201, that was positive. And so I think -- I am not  
7       sure if they can clarify perhaps what the issue is a  
8       little bit.

9                   DR. LINDENFELD: Perhaps we can -- let me  
10       see if I can find -- we can go on and I can find it.

11                   CHAIRPERSON PACKER: Okay. While JoAnn is  
12       pursuing this, let me ask Lem to go forward next  
13       primarily on some of the statistical issues related to  
14       these trials. Lem?

15                   DR. MOYE: Well, Milton, I don't have any  
16       particular questions about the stat issues. I can  
17       comment on some of them, if you like.

18                   CHAIRPERSON PACKER: Okay.

19                   DR. MOYE: Okay. The question that the  
20       committee has been asked to address is the notion of  
21       a logarithmic transformation. I need to first preface  
22       my short comments by saying that that is a traditional

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1 and standard tool commonly applied to skew data. The  
2 perceived need for this tool is that the original data  
3 are not normally distributed. And not only are they  
4 not normally distributed, but they really don't have  
5 much of a central tendency. And the notion of taking  
6 the log transformation provides the central tendency  
7 and **perhaps** makes the inference from the P values more  
8 believable or more plausible.

9           There is a fly in the ointment, though,  
10 and that is why I think any primary analysis for log  
11 transform data really needs to be supplemented by the  
12 analysis on the original data untransformed. The  
13 sponsor has told us that they have done this and in  
14 fact the P values don't change. I am not surprised to  
15 hear **that** because the P values are very small anyway.  
16 But the reason for the wrinkle, I think, is that in  
17 some data sets, perhaps some pathologic data sets,  
18 some people have shown that a log transformation can  
19 sometimes mask the relationship between the endpoint  
20 and the main covariate of interest, number one. And  
21 also induce new relationships between this transformed  
22 endpoint and covariates. Again, it doesn't happen

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1 very often. It happens pathologically. But the fact  
2 that it is possible suggests that in pivotal studies  
3 the analysis needs to be performed on the  
4 untransformed **endpoint** as well. But that occurred  
5 here. The **P** values are all small. So I don't think  
6 a decision is going to rise or fall based on the log  
7 transform.

8 The notion of the last observation carried  
9 forward. Researchers in these very powerful repeated  
10 measure designs which harness the variability within  
11 the subject to get the best, most precise estimate of  
12 a point -- the most precise point estimates of  
13 efficacy are very efficient. But unfortunately, this  
14 requires researchers to attempt to capture follow-up  
15 information on every patient at every time point and  
16 of course this is impossible. What researchers then  
17 have to do is work with these incomplete data sets.  
18 The evolution of incomplete data set analysis has  
19 progressed very far in these past 15 or 20 years. The  
20 last observation carried forward is a very useful  
21 tool. It is an acceptable tool, and I don't think  
22 that the sponsor should be criticized for using that

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1 tool . Somebody else might suggest that perhaps  
2 something like generalized estimating equations would  
3 be useful here as well. I don't know if they were  
4 done. If they were, the answer probably wouldn't  
5 change very much because again the P values are very  
6 small.

7 CHAIRPERSON PACKER: Lem, while you still  
8 have the microphone, let me ask a question about last  
9 observation carried forward. Almost every data base  
10 we see with repeated measures has a -- I guess  
11 commonly uses a last observation carried forward  
12 approach, be it angina trials or hypertension trials  
13 or heart failure trials or whatever. And I guess one  
14 is comforted by the fact that it is so commonly used  
15 that it probably is okay. One could imagine, however,  
16 that there are two potential problems with the last  
17 observation carried forward approach. The first is  
18 what do you do with patients who don't have any **post-**  
19 **treatment** double blind measurement of the primary  
20 endpoint? And I guess there are ways of dealing with  
21 that, **but** that question of course is important because  
22 then the analysis is not done on all randomized

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1 patients. It is only done on patients who have a post  
2 randomization measurement. The second question that  
3 arises on the last observation carried forward  
4 approach is that it is possible that patients who are  
5 doing well in terms of their performance on the  
6 primary endpoint, but then turn sour during the course  
7 of the trial do not have another measurement of the  
8 endpoint, but they drop out. They clearly have not  
9 done well, but their last observation doesn't reflect  
10 the deterioration of their clinical status which  
11 occurred between scheduled visits. Therefore, some  
12 have suggested, and this has come up in various  
13 discussions within the agency, that the conclusions  
14 that are reached from a last observation carried  
15 forward method probably need to be tested by other  
16 analyses, perhaps more conservative analyses, in which  
17 patients who are doing badly and drop out are given,  
18 let's say, worst rank, and then the data would be  
19 analyzed using various non-parametric methods. Can  
20 you comment on both the first issue of patients who  
21 have dropped out of the analysis and therefore are not  
22 in an all-randomized patients analysis? And the

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1 second, whether you would favor doing something other  
2 than or in addition to a last observation carried  
3 forth analysis where patients who drop out are given  
4 worst rank?

5 DR. MOYE: Yes. The first problem that  
6 you mentioned involving no post-RZ measurement I think  
7 is very problematic. However, it is handled most  
8 clearly and most easily by assuming the worst possible  
9 outcome for those patients. And in fact, if I  
10 remember the stat review here, that was in fact  
11 carried out and they found that the findings for the  
12 primary endpoint did not change. That is not  
13 surprising because there were relatively few patients  
14 who had no post-RZ measurement.

15 The other possibility or the second  
16 issue that you raised, and that is that during the  
17 randomization period something happens to this patient  
18 perhaps related to therapy that causes them to drop  
19 out and not have any future observations is very  
20 problematic". It is very real and it is very  
21 problematic. As usual, a step out of this kind of  
22 problem is a step into another one. You know, we

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1 could argue or one could argue for an endpoint that  
2 was combined that looked at your last measurement of  
3 this repeated measures endpoint or some dichotomous  
4 clinical event. That is a **left** censored endpoint.  
5 There is really not very much been done statistically  
6 on that. I don't know that that kind of endpoint is  
7 an acceptable endpoint to have. And certainly to try  
8 to come up with that prospectively might send the  
9 wrong message to the investigator. It is as if you  
10 are saying to them it is okay if patients don't come  
11 back because we have a way to statistically correct  
12 for their absence. That is not the message you want  
13 to give investigators. so that is extremely  
14 problematic.

15 CHAIRPERSON PACKER: Lem, let me just --  
16 I guess I will just comment last on this. I am not  
17 certain, first of all, how many investigators read the  
18 statistical. analysis of their protocols, I am sorry to  
19 say.

20 DR. MOYE: I am speechless.

21 CHAIRPERSON PACKER: And so I am not  
22 certain that any would be truly influenced to be

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1 encouraged to drop out a patient simply because they  
2 would or would not be affecting the primary analysis  
3 the sponsor had intended. But I would like to ask or  
4 perhaps pursue the question that you just asked, which  
5 is I understand the -- I think this was in Dr.  
6 **Karkowski's** review, but we probably need to clarify  
7 this. Abe? You performed or maybe Dr. Rodin  
8 performed a worst rank analysis for these trials. I  
9 just want to understand, there is mention of that in  
10 one of the reviews. Lem just referred to it. Did the  
11 worst rank analysis assign worst rank to people with  
12 no post-treatment measurement or did it assign worst  
13 rank to people with no post-treatment measurement and  
14 people who dropped out during the trial?

15 DR. KARKOWSKI: We only did that for one  
16 study . Okay? So it isn't done uniformly throughout  
17 the whole data base. In fact, we did it even a little  
18 bit less -- what we did is we assigned the worse rank  
19 only to the treatment patients and we left the placebo  
20 patients as censored. That was our robustness test.  
21 Is that correct?

22 DR. JIN: We only assigned the worst rank

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1 to the patient with no post-baseline measurement.

2 CHAIRPERSON PACKER: But not to the  
3 patients who dropped out who had a post-randomization?

4 DR. JIN: No. I don't think you can do  
5 that. If you assign worst, they will **fail**. That is  
6 how it will fail.

7 CHAIRPERSON PACKER: I see. If you  
8 assigned the worst rank to the people who dropped out,  
9 the trial **would** fail?

10 DR. JIN: Yes, I think so. Which kind of  
11 worst rank are you assigning? Are you assigning zero  
12 or are **you** assigning 1? Then I think the penalty is  
13 too high. And also -- we also did an analysis for the  
14 kind of generalized model, like basically a kind of  
15 repeated measurement. This is another kind of the  
16 carry forward. You carry forward the slope instead of  
17 carrying forward the last observation. But all these  
18 measures are a shortfall. You assume that the  
19 information before the fail -- you can carry forward  
20 that information, which all the measures I don't think  
21 have a great advantage over each other. All has some  
22 shortfalls. So we don't impose that on the review.

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1 DR. MOYE: If I understood what you just  
2 said, you said another option would be to not just  
3 carry forward the last observation, but to make a  
4 prediction based on the trajectory.

5 DR. JIN: Yes.

6 DR. MOYE : But that regardless of what  
7 procedure you use, there is a --

8 DR. JIN: They are all the same  
9 conclusion. So the slope carried forward -- the  
10 result for slope carried forward are between the LOCF  
11 and the completer. So it is reasonable.

12 CHAIRPERSON PACKER: Let me just pursue  
13 this just one moment, but only because it comes up in  
14 our Q&A. I think it may be too much of a penalty to  
15 say that someone who drops out for any reason at all  
16 should **be** assigned worst rank, especially if that  
17 assignment is only made in the active treatment group  
18 versus the placebo group. But I think there is a  
19 considerable amount of logic to saying that patients  
20 who are dropping out because of worsening of their  
21 condition should be assigned worst rank, because you  
22 could get a very cleaned up data base by having a drug

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1       **which** allows patients to deteriorate but fails to  
2       measure that deterioration simply because that  
3       deterioration occurred between two scheduled visits.  
4       That seems like it sets us up for reaching the wrong  
5       conclusion.     Maybe not in this data base, but in  
6       general in terms of interpretation of trials and the  
7       utilization of last observation carried forward.    But  
8       the question that comes to the committee is not just  
9       specific to this study, but is a general question  
10      about the utility of last observation carried forward.  
11      Bob?

12                   DR. TEMPLE:   Well, as Lem said, as soon as  
13      you do one thing, you run into difficult problems.  If  
14      someone has an event that causes them to deteriorate  
15      between two observations, it isn't clear whether that  
16      has anything to do with whether the drug in this case  
17      is good **for** claudication.  It has something to do with  
18      whether there has been a bad event.  So it is probably  
19      more of **a** safety problem than an effectiveness problem  
20      if you really look at it.  And it goes without saying  
21      that all of the plans for doing this have to be  
22      prospective or they are highly suspect.  I guess the

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1 other observation I would make is that while it is an  
2 interesting test to only cream the patients on the  
3 treated group, that is only count them as the worst  
4 case, you get to do that only when the P values you  
5 are starting with are .001 or something like that. It  
6 is perfectly obvious that if you ever do that for a  
7 more marginal statistical result, it will never  
8 survive **it**. And treating data that way is another way  
9 of saying I don't want to use .05 anymore. I want to  
10 use .001 **as my** standard. Because the outcome of doing  
11 that is completely predictable. Every trial has  
12 dropouts. So it is a fairly big question to do that.  
13 It is an interesting test of robustness of an extreme  
14 sort, but it is not really a good alternative  
15 analysis.

16 CHAIRPERSON PACKER: Yes, Bob, **it** may be  
17 a particular stringent test of robustness, but in the  
18 area of heart failure, we regularly see **people**  
19 **enrolled** in trials, for example, of exercise tolerance  
20 and Udho sees trials of patients enrolled in angina  
21 trials and whatever, where patients are dropping out  
22 because **of** worsening of their underlying condition,

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1 like worsening heart failure. And frequently that  
2 occurs more commonly in active therapy than it does on  
3 placebo. And one can make the data base look really  
4 clean by saying that that is a safety issue. But it  
5 is not a safety issue, it is an efficacy issue.

6 DR. TEMPLE: That doesn't seem so clear,  
7 Milton. I mean, if the drug is really making people  
8 deteriorate rapidly and drop out, that ought to show  
9 up as more dropouts due to worsening disease.

10 CHAIRPERSON PACKER: You will see more  
11 dropouts and worsening disease, and if you are  
12 measuring the effect of the drug on the disease, that  
13 needs to be incorporated into an efficacy part of the  
14 equation as well as the safety part of the equation.

15 DR. TEMPLE: I think that is debatable.

16 DR. KONSTAM: Yes. I think this is much  
17 more of an issue in heart failure trials perhaps than  
18 in looking at claudication as an endpoint. Where in  
19 heart failure it is -- I mean there is a substantial  
20 likelihood that patients are dropping out because  
21 their heart failure is worse. Here I think it is a  
22 little bit -- and I think this is what Bob is saying

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1 -- it is a **little** bit more difficult to construe that  
2 they are dropping out from their next treadmill test  
3 because their **claudication** is worse. I think it is  
4 more of an issue in heart failure trials than it is  
5 here.

6 CHAIRPERSON PACKER: But it really is an  
7 issue in heart failure trials. I think that is the  
8 point that I want to make. Because we have seen drugs  
9 that improve exercise time but are associated with a  
10 three-fold increase in the risk of worsening heart  
11 failure. And it is clear that their exercise time is  
12 improving because the people aren't having an exercise  
13 test at the time that their heart failure is  
14 deteriorating. Udho?

15 DR. THADANI: I think even in angina  
16 **pectoris**, when you are doing trials, there are  
17 patients hospitalized with unstable angina say on the  
18 day of their exercise visit. so if you do carry  
19 forward analysis, that patient is really worse. He  
20 may not be able to walk on the treadmill because he is  
21 having resting pain. And theoretically, there might  
22 be patients with intermittent claudication who start

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1 getting resting claudication. And that could really  
2 have a potential problem in carry forward analysis.  
3 I think it might be real. If the plaque rupture plays  
4 a role in say coronary artery disease, does it play a  
5 role in intermittent claudication? I don't know. So  
6 I think it has to look at each patient. Obviously, if  
7 somebody had an accident, it is different. But if  
8 there is a disease associated deterioration, I think  
9 one should probably give them a worst score in order  
10 to address that issue.

11 Can I ask a question to you? You said  
12 that in one of the studies in which pentoxifyline was  
13 used, the UK study, it was negative -- there was more  
14 difference between your drug than pentoxifyline. And  
15 then you said one of the reasons you are not putting  
16 too much emphasis on it is because they might have  
17 missed the morning dose. Obviously, they took -- it  
18 is a bid drug. We know the trough effect is there,  
19 and in that sense the probability is based on the bid  
20 regimen because the trough beat the placebo. So they  
21 must have taken the night dose. Are there any other  
22 differences in the patient population that you are not

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1 able to show a difference between 100 mg and  
2 **pentoxifyline** in your study --

3 DR. FORBES: 94301?

4 DR. THADANI: Yes, 2194301 compared to  
5 2196201. Because I am having a hard time. I know one  
6 P value is 0006 and the other one is totally non-  
7 significant. Unless you are saying the UK patient  
8 population is different or the study design was  
9 different, which I find difficult.

10 DR. FORBES: The only subtle difference in  
11 the study design is that when patients stopped their  
12 study medication and came back for a termination  
13 visit, they were required to walk a treadmill. Which  
14 means that some of the patients were off study  
15 medications for more than two weeks. So that is why  
16 we tried to take a look at patients that had missed  
17 more than one dose.

18 DR. THADANI: How many patients had missed  
19 that long?

20 DR. FORBES : I would say that when we do  
21 it greater than 14 hours after the last dose, we lose  
22 about 50 percent of the population. So the analysis

1 that we came up with included about half the patients  
2 enrolled. And admittedly -- I mean, we understand  
3 that that has to be interpreted cautiously. I mean,  
4 that is our only explanation of what happened there  
5 relative to the U.S. trough. Which as you saw in your  
6 briefing packet, if you were to pool them, and I  
7 understand there are some problems with pooling -- but  
8 if you were to pool them, you will see that it is  
9 still significant.

10 DR. THADANI: Yes. I am just -- the other  
11 issue is when you log transform. I know it is a  
12 statistically valid way to get away with the noise in  
13 the baseline. The graphs you showed showed a very  
14 marked improvement -- you know you are talking about  
15 60 or 80 meters. And yet the statistics reveal if you  
16 look at the median values on -- the absolute values,  
17 most of the trials -- I don't know if you have seen it  
18 or not -- but in front of us show an improvement of 20  
19 meters rather than 60 or 70, with the exception of one  
20 trial. In pivotal trial 2192202, the 100 mg  
21 improvement in absolute median change is 25.5 meters  
22 rather than 60 or 80, which is far less than when you

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1 log transform it. And similarly, if you look at your  
2 other pivotal trial, **pentoxifyline** is 24 meters in  
3 absolute terms.

4 DR. FORBES : I think we would like to  
5 address this. First, if I could call for back-up  
6 slide M-32, please. Dr. Kazempour, would you like to  
7 -- Dr. Kazempour from our biostat department has  
8 looked at this for us, and I am going to ask him to  
9 comment on the median versus the mean.

10 DR. KAZEMPOUR: I agree that median is one  
11 of the methods that it is possible to use when there  
12 are some variation in the data, the way that we are  
13 using it **to** follow the robustness. But that is only  
14 a metric. If you are going to look at all the data  
15 and the distribution of them, you can look over there.  
16 We have the **Ogiba** curve. The one on the Y axis is  
17 cumulative percent and that 50 percent is the median.  
18 You can see. the median walking distance difference  
19 between placebo patients and **cilostazol** patients and  
20 the change with that. But when you go above that and  
21 look at the 75 percentile, for example, you see a  
22 large improvement. So median, although it is a good

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1 metric **to** use and log transform is another technique  
2 which is fairly similar to median, but I don't  
3 recommend **to** use median when the data variation is  
4 large and also **there** are dispersions in the variation.  
5 so the better technique is to look at **all** the  
6 population, like the one that we have up here.

7 DR. THADANI: I am not questioning the  
8 validity of the statistical analysis. But in real  
9 terms **for** a patient who takes the drug, he is not  
10 going to improve on a log basis. He is going to  
11 improve from baseline of X to post-treatment Y. You  
12 can make it a log or you can triple it. So the  
13 clinical validity or the statistical significance  
14 versus clinical benefit, that is how I am addressing  
15 the issue. I think one has to -- they are both going  
16 in the right direction. Don't take me wrong. But I  
17 think **the** values are much **lower** if You **look** at  
18 absolute terms. We have the same problem in angina  
19 trials too. So say if somebody improves by 10 seconds  
20 on a treadmill, in angina we have been doing time  
21 rather than meters. I think you could do the same  
22 there. So walking a quarter block more rather than

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1 when you log transform it, it transforms into one full  
2 block . That was my comment.

3 DR. KAZEMPOUR: Log may have a bad name,  
4 but basically it is nothing other than looking at the  
5 percentage or a similar percentage. Because basically  
6 log is transforming things in terms of multiplication,  
7 which is a form of percentage.

8 DR. FISHER: The issue we are talking  
9 about now has nothing to do with a log transformation.

10 CHAIRPERSON PACKER: Lloyd, just introduce  
11 yourself.

12 DR. FISHER: Lloyd Fisher. It has nothing  
13 to do with a log transform. It is whether you use the  
14 mean or the median for the raw data, number one. So  
15 that is kind of a red herring thrown in. And when you  
16 look at the curves, it is not that -- in fact, I was  
17 asked whether the mean or the median is correct, and  
18 I said, well, they give you different characteristics  
19 of the distribution. Neither is right or wrong. But  
20 what happens here you can see is there are a number of  
21 people who get a modest gain, and that goes all the  
22 way up to about 50 percent. But I don't think you can

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1 totally discount all the 40 percent who get a much,  
2 much **larger** gain in treadmill time. so you just have  
3 to look at the distribution. It is what it is. And  
4 if you have an ax to grind either way for the sponsor  
5 given that choice, you will take the mean because it  
6 is skewed and you will get a bigger number. And if  
7 you are very conservative, you will take the median.  
8 But I would suggest that the committee really wants to  
9 think about it this way when you **look** at Your  
10 risk/benefit ratio.

11 DR. THADANI: Lloyd, on that the changes  
12 differ because also it varies with baseline. Somebody  
13 walks 50 meters and he goes to 100, he has got 100  
14 percent improvement. If another guy walks 300 or say  
15 he walks 400 meters and he goes to only 435, it is  
16 going to be a much more percentage. So I think there  
17 is a lot of dichotomy between the baseline and the  
18 changes. It depends on how disabled you are in the  
19 beginning, and the percentage of improvement could be  
20 also misleading sometimes.

21 DR. FISHER: Oh, yes. You can investigate  
22 the relationship to the covariates. And as Rob

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1 suggested, assuming the end result of all of this is  
2 favorable, obviously the physician and the patient  
3 have to sit down and discuss the relative merits and  
4 balances that somebody might get. But usually I don't  
5 think you go that deeply into the different **covariate**  
6 effects **and** so on for a general presentation like  
7 this.

8 CHAIRPERSON PACKER: Ray?

9 DR. FISHER: Oh, just one other remark  
10 about the logarithm. The sponsor didn't mention it,  
11 but they also did the usual two-sample **Wilcoxon** test,  
12 which are non-parametric. So you get exactly the same  
13 P value whether you transform or not, and all of those  
14 things, of course, are also highly significant. So  
15 that is not really an issue here.

16 CHAIRPERSON PACKER: Maybe it would be  
17 important **to** emphasize that given the smallness of the  
18 P values across most of these studies, most of the  
19 discussion which is taking place here is a discussion  
20 on principles as opposed -- because if one applies a  
21 variety of methods, including some very conservative  
22 methods, do P values still hold? But I think it is

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1 important to discuss the principles. One, because we  
2 are being asked to discuss some of these principles  
3 generally in the questions. And two, it allows us to  
4 perhaps distinguish what we mean today from what we  
5 might mean in the future.

6 DR. FISHER: Yes, just one point not  
7 immediately related to this, but I was thinking when  
8 you were having your discussion about how to treat the  
9 people who drop out and so on. It is very, very  
10 important to look at mechanism. And the reason is if  
11 you think about it, if you are going to give a worst  
12 case to everybody who drops out, that would mean you  
13 would never approve a drug that had a tremendous  
14 benefit for a lot of people but also had a number of  
15 people who had bad adverse events and couldn't take  
16 it. Because that would go to the rear of the rank.  
17 And given your test statistics, it would be easy for  
18 me to construct -- in fact, I could do it with **real**  
19 drugs. It would be easy for me to find and construct  
20 examples **where** if you do that analysis, these drugs  
21 wouldn't **have** a prayer of being approved. So that is  
22 far too draconian. But I agree totally that if you

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1 look at why they do it, particularly in something like  
2 CHF, and **we** have been in a number of trials together  
3 and that is very important.

4 CHAIRPERSON PACKER: Bob , just because I  
5 know that you commented on this. Do you have any --  
6 the concept that is being proposed is that when there  
7 is a fair amount of dropout due to the underlying  
8 disease, worsening of the underlying disease, a last  
9 observation carried forward method, and particularly  
10 if those dropouts are not equally distributed between  
11 the treatment arms, one could get a very biased -- a  
12 big problem in bias. Therefore, the proposal is that  
13 a last observation carried forward may not be  
14 reasonable or may not be very good at reflecting the  
15 **true treatment** effect, and that one should in fact  
16 assign a worst rank to people dropping out because of  
17 the disease in an analysis where there are finite  
18 assessments made at prespecified visits.

19 DR. TEMPLE: I think that needs a lot of  
20 thinking. If someone in a heart failure trial has a  
21 heart attack between two visits, is that evidence that  
22 the drug doesn't improve heart failure anymore, or **is**

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1 it an event that you ought to take into account  
2 because maybe the drug is causing it. I am not saying  
3 that these events should be ignored, but I think it is  
4 mixing two separate things up. But that is something  
5 that needs a lot of discussion. I want to actually  
6 put in a plug for those cumulative distribution  
7 curves. For people who read other literature than  
8 cardiovascular, you will notice that in drugs for  
9 **Alzheimer's** disease, we regularly show them to try to  
10 give some idea not only of what the mean effect is,  
11 but what the range of effects is. Now in the case of  
12 drugs for **Alzheimer's**, the mean and the extremes are  
13 very close to each other. It turns out that there  
14 isn't anybody who benefits a lot. But this sort of is  
15 interesting because you could argue there is a group  
16 of people who seem to be benefiting quite a bit and  
17 it is informative to do that. You will never know  
18 that if **you** look at just medians. It is worth  
19 mentioning. Somebody said that the change from  
20 baseline might be interesting. You could plot the  
21 ratios at baseline to final just the same way and get  
22 some idea. of how much people improve as a percent of

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1 change and you could see that for the placebo group  
2 and the treatment group. So those are very nice kinds  
3 of distributions.

4 But I had a question too. The statistical  
5 review, I think Dr. Lin's, was critical of the quality  
6 of life material because it was not so clear that the  
7 planned analyses were prespecified. And if you make  
8 corrections for multiple possibilities, there are just  
9 dozens and dozens of them. So that none of the  
10 analyses survive that. And I just wondered if you had  
11 a response to that. You say -- as presented here, you  
12 just say well it is perfectly obviously that only the  
13 physical parts were going to improve. The other parts  
14 just didn't deteriorate and we are very grateful about  
15 that. But how much of this was prospective and how  
16 much was not. This is a very common problem in  
17 quality of life analyses. I don't know if you saw Dr.  
18 Lin's review or not, but what it does say is that --  
19 I think he was up to 30 or 40 different comparisons,  
20 and you do a Bonferroni and you don't have much left.  
21 So what do you have to say about all that?

22 DR. KAZEMPOUR: For quality of life and

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1 secondary endpoint, it is customary to not adjust for  
2 the P value. For all the quality of life that we  
3 presented, rather than looking at the P value, I  
4 **recommend** you to look at the efficacy found over there  
5 for every single one of them. Rather than looking at  
6 P value -- I know this committee in particular doesn't  
7 like that much surrogate marker. P value is a  
8 surrogate for repetition of trials. The way that we  
9 have in every single trial, always the point estimate  
10 goes in the right direction. That includes in the 8  
11 trials that we have and in almost all of the efficacy  
12 trials for the physical function, not the emotional.  
13 Not only the point estimate goes in the right  
14 direction, but the constant interval almost for **all** of  
15 them. I don't have -- you have them in your briefing  
16 packets. Almost all of them go in the right direction  
17 and in many cases they are statistically significant.  
18 So what I would ask the committee to look at is to  
19 look at the repetition. Leave alone the P value. P  
20 value is a good indicator and is a good surrogate, but  
21 rather than that, look at the repetition that we have  
22 and we have it quite often. In the primary efficacy

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1 and in the secondary efficacy and in the ABI, always  
2 they go in the right direction. Because of that,  
3 please look at that rather than the P value, which can  
4 be a good indicator. I know Dr. Ray Lipicky may not  
5 like surrogate.

6 CHAIRPERSON PACKER: Rob?

7 DR. CALIFF: I just want to put in a plug  
8 to agree with you on this. I really think we need an  
9 FDA guidance on prespecification. I reviewed a  
10 protocol yesterday that had three pages of  
11 **prespecified** endpoints because the sponsor wanted to  
12 be sure that if an analysis was ever done that they  
13 could say it was prespecified. So I think this  
14 concept of because you write it down as one of a host  
15 of things that is prespecified and therefore it is  
16 okay needs to be dispelled and there needs to be some  
17 guidance on it. But if you did a P value on the  
18 likelihood that all of those parameters would come out  
19 the same direction, you would have an incredibly small  
20 P value. So I support what you said about that.

21 DR. TEMPLE: Unfortunately, Rob, there is  
22 a guideline on that. It is an international

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1 guideline, ICH9 , and it really says you should  
2 prespecify. But I don't disagree. I was just trying  
3 to make some discussion.

4 DR. CALIFF: so just think of everything  
5 you might ask and write it down in the protocol and  
6 then it is okay?

7 DR. TEMPLE: Well basically it says that  
8 analysis that are prespecified are a lot more credible  
9 than ones that aren't. Now what we are being told  
10 here is you've got 8 trials and they all show the same  
11 thing. You've got to think that maybe that means  
12 something. I don't disagree with that. But I am just  
13 telling you that the last guideline written is very  
14 powerful on prespecifying your endpoints. Lem could  
15 have written it. It is very strong on that point.

16 DR. CALIFF: I am actually not disagreeing  
17 with the concept, but I think it needs to go one step  
18 further. Because if it is said that way, it just  
19 means let's write 30 pages of prespecified endpoints  
20 and then it is okay. That is what we are seeing now  
21 as a response to that guideline I guess.

22 DR. FORBES : Could I just make -- I want

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1 to add to something that Hiatt mentioned earlier.  
2 Since I have been on the project for a little while,  
3 the use of the WIQ and the **claudication** outcome  
4 measures and the SF-36 were meant to support the  
5 treadmill testing. And something that he said before  
6 is something that we have believed from the beginning.  
7 If you improve exercise testing on the treadmill but  
8 the patient doesn't tell you that you are doing that  
9 in their everyday living, how meaningful is that? And  
10 I think that is what these secondary endpoints tell  
11 you . I understand the difficulties of multiplicity.  
12 But if **ycu** look across the endpoints, do they tell you  
13 what the treadmill tests tell you, and I think the  
14 answer **to** that is yes.

15 CHAIRPERSON PACKER: The sponsor may  
16 notice that a lot of the discussion that is taking  
17 place now has little to do with the NDA.

18 DR. FORBES: It has to do with potential  
19 claims, **though**, Milton.

20 CHAIRPERSON PACKER: No, I -- let me just  
21 say that you shouldn't be offended by that because in  
22 fact a lot of the discussion is based on sort of

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1 general principles which may or may not be pertinent  
2 to this. **It** just so happens that this data base gives  
3 us an opportunity to talk about these things. Not  
4 that we actually needed this **opportunity to** talk about  
5 these things, but it does provide that.

6 DR. FORBES : Well, I apologize for the  
7 commercial segment then.

8 CHAIRPERSON PACKER: Okay. Wait a minute,  
9 Rob still has the floor.

10 DR. CALIFF : I just had a couple of  
11 questions that actually may have something to do with  
12 the NDA. These are all of the studies that have been  
13 done on this compound?

14 DR. FORBES : Again, I mentioned earlier  
15 that there were five small trials, three in Germany  
16 and two in Japan in the population of intermittent  
17 **claudication**. But there have been numerous studies  
18 **conducted** in other areas.

19 DR. CALIFF: So --but what we have in the  
20 application is all that you -- I mean, we have 8 or 10  
21 trials or whatever the number is. That is all of  
22 them.

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1 DR. FORBES: That is correct.

2 DR. CALIFF: I just wanted to be sure of  
3 that. And the quality of life data was all the  
4 quality of life data you collected within those  
5 trials?

6 DR. FORBES: Yes.

7 DR. CALIFF: Okay. The only other  
8 question I had is somewhat of a statistical question.  
9 Roughly what your data shows is a one block to a one  
10 and a third block improvement in sort of for the  
11 typical patient in ability to walk. The thing that  
12 surprised me a little bit is the confidence for a P  
13 value that small. The confidence intervals about that  
14 were fairly wide and the cumulative distribution  
15 function helps to get a picture of part of that. But  
16 I am trying to get just a common sense sort of  
17 translation of the statistics. One block plus or  
18 minus what? Because that has got to be balanced  
19 against any potential risk on the other side.

20 DR. KAZEMPOUR: The confidence interval  
21 that you saw were on log transform data.

22 DR. CALIFF: Okay.

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1 DR. KAZEMPOUR: And, therefore, it reduces  
2 the variability. The way that log works, as you know,  
3 is if ~~the~~ value is way, way up here, it brings it  
4 closer. So it penalizes the **cilostazol** arm in  
5 particular because those on **cilostazol**, all three of  
6 the patients, were walking further. But the  
7 variability, if you want to look at it, the **Ogiba**  
8 curve is the one that really gives you the best  
9 depiction of the distribution of the patient. And to  
10 give you plus or minus what -- if I give you a  
11 confidence interval for non-transform data, it may not  
12 mean that. much because the data are skewed and the  
13 data are not normalized. Using those techniques may  
14 not be correct. So purposefully we stayed away from  
15 giving you a confidence interval on the **walking**  
16 distance. But on the other hand, we gave you the  
17 whole distribution of them.

18 DR. CALIFF : Would you agree -- my  
19 interpretation of the cumulative distribution plot is  
20 that your typical patient gets a little bit less than  
21 what you have as your average, but that there are a  
22 fair number of patients who get a great deal more. In

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1 other words, if you look below the 60th percentile,  
2 the difference is fairly small. When you get above  
3 the 60th percentile, you have a pretty big difference.

4 DR. KAZEMPOUR: That is accurate. For  
5 example, in study 92202, those who were in the first  
6 core **trial**, they benefitted about 20 percent. In the  
7 second core trial, more than that. And in the third  
8 core trial, somewhere around 40 percent. You are  
9 accurate. Those who walked a smaller distance at  
10 baseline,' they improved a **smaller distance post-**  
11 **baseline.** That is accurate.

12 DR. CALIFF: Okay. I just had one  
13 editorial comment. I mean, I think for claudication  
14 studies, these were great studies and I thought the  
15 data were really well presented. The way that things  
16 were handled I thought was excellent. You also had  
17 the best. pictorial slide of the year, I think, with  
18 the **stairstep** and the little patients going different  
19 distances. It really gives you a visceral feeling for  
20 the difference in exercise tolerance.

21 CHAIRPERSON PACKER: Do you also like the  
22 comment about turning the clock back?

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1 DR. CALIFF : If I can get three years  
2 backwards, that would be tremendous.

3 CHAIRPERSON PACKER: Let me -- Rob, before  
4 you go, let me just ask a question. Again, this is a  
5 general question. Because of the internal consistency  
6 in the effects, for example, on physical domain in the  
7 SF-36, **if** one did 10 trials, they all went in the same  
8 direction. None of them were statistically  
9 significant in any of the trials. But if you pooled  
10 the data, they would be highly significant. Would  
11 that be -- for question number one, would that be  
12 persuasive **to** you? And second, if it were persuasive  
13 to you, what purpose would be served by ever  
14 calculating individual P values in the trial? Why not  
15 simply pool the data across all trials all the time  
16 and say that that is your primary way of analyzing the  
17 data in any NDA?

18 DR. CALIFF: Well -- and Lem is probably  
19 going to disagree with me here -- but I would argue  
20 that in any clinical research designed to help us  
21 treat patients, that the question you always want to  
22 answer is what is likely to happen to my next patient.

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1 And I would argue that your vest view, as long as the  
2 studies were done in a similar way, is actually to  
3 pool data and not segmenting the trials into  
4 individual trials. And I would be very persuaded by  
5 10 trials that each within themselves were  
6 insignificant, but where they all went in the same  
7 direction and the pool result was highly significant,  
8 as long as I knew it was really all the trials. And  
9 that is the problem. Very often you only get a small  
10 fraction 'of the studies that were done, the ones that  
11 look the best.

12 CHAIRPERSON PACKER: Lem, do you have a  
13 comment?

14 DR. MOYE : Yes. I am somewhat less  
15 enthusiastic than Rob is for the pooling option. If  
16 you have an individual experiment, the individual  
17 experiment should be itself designed to answer the  
18 question. That is why you spend a good deal of time  
19 and deliberation and intellectual horsepower in coming  
20 up with the effect size you want to determine. You  
21 worry about statistical errors, trying to cap those,  
22 and you execute that experiment, hoping to reach a

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1 conclusion about efficacy. I don't think an  
2 individual experiment -- I mean, to my knowledge, an  
3 individual experiment is not carried out hoping that  
4 it would be pooled with other experiments in the end  
5 which would reach the answer. I mean, if that is the  
6 case, then it really isn't an individual stand alone  
7 experiment by itself from my point of view.

8 CHAIRPERSON PACKER: Ray, you have had  
9 your hand up for a while. But before going --

10 DR. LIPICKY: It is a whole other topic.

11 CHAIRPERSON PACKER: Just before going  
12 forward, it is clear that of the two options, one  
13 advocated by Rob and the other one which would be  
14 advocated by Lem, that the agency would probably not  
15 be very enthusiastic --

16 DR. LIPICKY: Let me just say I have seen  
17 both work.

18 CHAIRPERSON PACKER: You have seen both  
19 work?

20 DR. LIPICKY: Yes.

21 CHAIRPERSON PACKER: Work meaning approval  
22 or that they tell the truth?

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1 DR. LIPICKY: Work both ways in making  
2 very important decisions, yes.

3 CHAIRPERSON PACKER: Okay.

4 DR. LIPICKY: And in the circumstances  
5 where both ways have worked, I think the decisions  
6 were quite reasonable.

7 CHAIRPERSON PACKER : Okay. Ray, go on to  
8 the next topic.

9 DR. TEMPLE: No. I have a comment on this  
10 one.

11 CHAIRPERSON PACKER : Bob?

12 DR. TEMPLE: There is a certain -- don't  
13 take this wrong -- bogus quality to the question. I  
14 mean, you don't sit down and plan a series of two  
15 small studies. You plan a series of studies that you  
16 think are going to do something or you plan a **multi-**  
17 center study, which is really just a bunch of studies  
18 you are planning to pool after all. Or you could even  
19 -- I can imagine this -- plan a series of very closely  
20 related studies that you would argue should be pooled  
21 for the analysis later. That is your plan. And there  
22 is no impediment really to doing that. You can do

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1 that. So then if they are all kind of going in the  
2 right direction, you work out. But if something  
3 happens where somehow all of the studies don't show  
4 anything, and it is almost hard to imagine how that is  
5 going to occur -- why would they all be just short of  
6 showing anything -- it makes you wonder whether  
7 something odd is going on. And I think that needs  
8 further **thought** also. The one time this does occur,  
9 of course, is when people have done large numbers of  
10 studies to look at, say, symptomatic treatment, and  
11 they don't have a lot of endpoints in them and now  
12 someone pools the whole bunch of data together and  
13 does a **meta-analysis** because now you have accumulated  
14 enough endpoints and then you are sort of forced to  
15 come to grips with that session. But in ordinary drug  
16 development studies of symptoms, that would be a very  
17 odd thing to occur -- 10 studies, none of which make  
18 it, but all of which lean would be really funny, and  
19 I don't think it happens.

20 DR. CALIFF : I actually think this is a  
21 very important point, and I agree totally as long as  
22 you phrase it studies of symptoms. Because the power

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1       **in** those studies is so incredibly high. But what we  
2       are seeing very commonly is clinical endpoint studies.  
3       And because of the slope of the power curve relative  
4       to the effect size, people are right on the margin in  
5       terms of what an affordable trial is. So it is not  
6       uncommon in those kinds of trials to have several that  
7       fall just short. Because the power for a smaller  
8       effect size would have cost another \$30 million or  
9       something.

10                   DR. TEMPLE: But then you should plan on  
11       -- you should think of them as a combined effort.

12                   DR. CALIFF: That is -- Yes, I agree with  
13       that.

14                   DR. HIRSCH : But until you know the  
15       treatment effect, you can't plan it ahead. So we for  
16       the first time have data to suggest what the treatment  
17       effect is in PAD. So a future trial can take that  
18       into account and be powered accordingly.

19                   DR. TEMPLE: Well, one of the things you  
20       are supposed to do while you are doing trials is to  
21       keep watching the results and plan to make the next  
22       one bigger if it needs to. It would be a funny

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1 outcome for all of them to be just short. You would  
2 have to wonder whether you had all the data or whether  
3 something funny was going on, I think anyway.

4 DR. LIPICKY: Just to throw a slightly  
5 deviate point of view in. It strikes me most of the  
6 time that people come and talk about the study they  
7 want to do, that they haven't the foggiest notion of  
8 what they are talking about nor what to expect. And  
9 yet they say this is my primary endpoint. I mean  
10 baloney. But if that is what you want it to be, fine.  
11 And so I see a lot of room for the notion of doing a  
12 bunch of studies, pool them, and figure out what you  
13 think the drug does, and then do another study to  
14 confirm that, in fact, that is what it really does.  
15 Because this business of prespecifying and picking  
16 primary endpoints is one of the biggest myths and  
17 follies that I think I know. And it is forced by this  
18 business of almost taste, that if I am scientific and  
19 rigorous, I must do things in some proscribed way. So  
20 I throw that out for what it is worth.

21 CHAIRPERSON PACKER: But it is interesting  
22 because the sponsors of NDAs do come to the table with

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1 certain preconceptions about what is expected and  
2 present data in a certain hierarchy. For example --  
3 and this is not a specific comment -- well, it is a  
4 specific comment to this presentation, but whatever.  
5 Had the **individual** trials showed a significant effect  
6 on the SF-36, that slide would have been shown.  
7 Instead, **the** pooled data was shown.

8 DR. LIPICKY: Yes.

9 CHAIRPERSON PACKER: Okay. Now one could  
10 take a position of defending that type of  
11 presentation, but in fact that would not have been the  
12 preferred presentation. That would not have been the  
13 presentation had the individual studies been  
14 significant.

15 DR. LIPICKY: I agree. I don't disagree.

16 DR. KARKOWSKI: Milton?

17 CHAIRPERSON PACKER: Go ahead.

18 DR. KARKOWSKI: I would like to point out  
19 that we are not sure whether **they** did a last  
20 observation carried forth analysis for the quality of  
21 life or whether they just censored all people who  
22 discontinued. So that one would be a little bit less

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1 comfortable with that outcome.

2 CHAIRPERSON PACKER: Maybe we should ask  
3 and we **could** find that out.

4 DR. FORBES : Yes, it was actually the  
5 observed population that was analyzed in the quality  
6 of life.

7 CHAIRPERSON PACKER: I will just ask then  
8 why did you not do last observation carried forward on  
9 the secondary endpoints, but you did on the primary?

10 DR. FORBES: Actually --

11 DR. KAZEMPOUR: I would like to clarify a  
12 couple of points. The quality of life was  
13 statistically significant in several individual  
14 trials. You have them in your briefing packets. We  
15 have shown them to you by individual trial as well as  
16 pooling them at the end. So you can see all of them  
17 at the same time. And several of them came out for  
18 the functional status that these related to the  
19 treatment are significantly significant. And in  
20 almost every single one of them, the point estimate is  
21 in the right direction. I do not advocate pooling  
22 data unless you have the primary endpoints set. There

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1 is no way we as sponsors can manpower the studies for  
2 all the secondary endpoints. And being a P value  
3 significant or not significant is a function of the N,  
4 the sample size. so that was the reason that we  
5 decided to show every single study and present them or  
6 pool **them** together so we can observe.

7 Coming up to the issue of the last  
8 observation carried forward for the secondary  
9 endpoints, again purposefully we decided to deal as  
10 the data that we have. For the primary endpoints, we  
11 did a lot of analysis -- the last observation carried  
12 forward, worst case scenario, carrying forward  
13 baseline for those patients for the primary endpoint.  
14 But for the secondary endpoints, we Purposefully  
15 decided not to. If we did it, the NDA, rather than  
16 being 200 volumes, would be 400 volumes. So for the  
17 secondary endpoints, we just dealt with the observed  
18 cases with no imputation whatsoever.

19 DR. FORBES: Can I just add to that? The  
20 quality of life in the 6 studies was really performed  
21 at the same time the treadmill tests were. It was  
22 administered via phone, but it was done at the same

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1 time point. So we do have that kind of information.  
2 We could do that type of analysis. But the  
3 information you have in front of you is observed. I  
4 will say from looking at it that I don't think the  
5 analysis would change much, but we haven't done it.

6 CHAIRPERSON PACKER : Let's see, we **will** <sup>^</sup>  
7 hold on a second. Ray, I think you had a different  
8 topic. Let's try that.

9 DR. LIPICKY: Yes, I did want to change  
10 the topic. But are you done now?

11 CHAIRPERSON PACKER : Does anyone have any  
12 -- Bob?

13 DR. THADANI: On the quality of life  
14 issue, I know the statistician is saying there is no  
15 difference. Which are we to believe now? Because i  
16 am looking on page 24. You said given the multiple  
17 questions related to the quality of life measurement,  
18 the patients' or physicians' assessment can be  
19 considered as statistically -- none of them could be  
20 considered. And yet you are showing that some of them  
21 are significant. So there are some differences  
22 between yours and his.

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1 CHAIRPERSON PACKER: Abe?

2 DR. KARKOWSKI: The P values you saw from  
3 the sponsor I don't believe were corrected for  
4 multiple secondary endpoints and multiple doses and  
5 multiple times of operation.

6 DR. LIPICKY: They don't need to be.

7 DR. CALIFF : Milton, we have a world's  
8 expert in quality of life, Dr. Ware, who is here. It  
9 would be interesting to get his perspective.

10 CHAIRPERSON PACKER: Well, before we do  
11 that, let me -- let's hold that for a second. Because  
12 it would be useful to sort of close one topic before  
13 we go on to the next one. Bob?

14 DR. TEMPLE : I think Ray said something  
15 very important. It is perfectly possible to do what  
16 Lou Shiner likes to call exploratory studies or  
17 learning studies and then in your subsequent studies  
18 confirm them. And there was plenty of opportunity to  
19 do that here. These studies weren't all done at the  
20 same time. One could perfectly well have said, okay,  
21 now I have the result and it looks like the physical  
22 component is the one that works and that is going to

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1 be my primary quality of life endpoint. And you could  
2 certainly do that. And then that way you satisfy both  
3 your basians and your frequentists and everybody is  
4 content. That is worth thinking of. There is really  
5 no impediment to doing what Ray said. And in an  
6 orderly development process where you learn from one  
7 study and then go on to the next, it is perfectly  
8 possible to do that. What we find, however -- not  
9 here particularly -- is that people do the multiple  
10 studies, don't pick an endpoint, look amid the data  
11 and find the thing that works and say, oh, I made it  
12 without wanting to do the confirmatory study. And in  
13 a couple of very conspicuous cases, when we have **said**,  
14 well, that is interesting but really you have to do a  
15 confirmatory study, what was completely obvious from  
16 the initial studies didn't turn out. So one has to be  
17 careful and one has to do the confirmatory study.  
18 That doesn't mean the data can't be overwhelming in  
19 some other way.

20 CHAIRPERSON PACKER: Why don't we do this.  
21 Let us, if we can -- I just want to make sure that  
22 members of the committee who have not had a chance to

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1 speak have a chance to do so. We will start with  
2 **Ileana** and we will work our way all the way down.  
3 **Ileana?**

4 DR. PINA: Yes. I have a different  
5 question. Is it all right to go to another topic?

6 CHAIRPERSON PACKER: Absolutely.

7 DR. PINA: But also with the same speaker.  
8 I realize that there may be scatter in the response of  
9 a particular patient or a particular group of  
10 patients, and some may respond a little bit and some  
11 may respond a lot. But if I had to make a comparison  
12 between **the** 50 mg dose and the 100 mg dose, some  
13 patients look like they responded to the 50 mg dose.  
14 How would **you** translate that into blocks walked,  
15 meters walked, feet walked? You can take a mean or  
16 you can take a median. Because one of the questions  
17 that we will be asked her is how efficacious was the  
18 50 mg **dose** and should some patients be started on the  
19 50 mg dose?

20 DR. FORBES: Sure. Let me try to address  
21 that in a number of ways. First of all, the 50 **mg**  
22 dose was tested in two different clinical trials. The

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1 first one I have already shown you. In the second on,  
2 it did not show superiority -- statistical superiority  
3 over placebo, although it was better than placebo.  
4 And in that particular trial, the 100 mg beat 50 mg.  
5 Now we believe the 100 mg is more efficacious than the  
6 50 mg dose, but I won't argue with you that the 50 mg  
7 dose does provide some symptomatic relief. The  
8 question is does it provide it to the degree that the  
9 100 mg dose does. And if you will allow me, I would  
10 like to pull up a back-up slide to show you a subgroup  
11 of patients from the 92202 study. Can you give me  
12 slide M-22, please?

13 This particular analysis is going to be  
14 titled completers. And I want to be very specific  
15 here and very clear. This group of completers  
16 performed the protocol as it was set out to be  
17 performed. It includes between 106 and 110 patients  
18 per treatment group. This was one of the -- when we  
19 first got this data, this was some of the information  
20 that I looked at to determine whether or not truly 100  
21 was different than 50. Now as I mentioned before, in  
22 the LOCF we carried forward patients that dropped out

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1 and it **is** a conservative analysis. But if you want to  
2 take a look at patients that survived the protocol as  
3 it was written, you will see that this is the 100 mg  
4 group, this is the 50 mg group, and this is the  
5 placebo. What we noticed in 94201 as well as 94202 is  
6 a little bit of a flattening here between week 16 and  
7 24. It is our belief that somewhere around 3 months,  
8 you probably get the maximal benefit with 50 mg twice  
9 daily. **As** you continue to take 100 mg, as you can see  
10 the slope of this line which Dr. Hiatt was referring  
11 to earlier, continues to rise. I don't know if this  
12 helps you **in** your deliberations.

13 CHAIRPERSON PACKER: I guess for the sake  
14 of trying to make sure that we finish this meeting on  
15 this calendar day, it would be important to say that  
16 there are lots of problems with the completers  
17 analysis, and therefore one needs to reach conclusions  
18 about **the** completers analysis with a great deal of  
19 caution.

20 DR. FORBES: Absolutely.

21 CHAIRPERSON PACKER: Ileana, anything  
22 else? Lem, any other questions? No? Alan?

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1 DR. HIRSCH: I will try to make it quick  
2 so that **we** can finish this on the same day we started.  
3 We looked at overall efficacy analysis and overall  
4 quality of life analysis, but I am still interested in  
5 the subgroups. You made the comment that this was a  
6 series of doses of a single drug that was responsive  
7 over different stratifications post hoc. So let me  
8 ask you about a clinically relevant PAD question. PAD  
9 is not a single disease. It is a spectrum of illness.  
10 You can't sort of say everything about PAD without  
11 stratifying a little bit. The most common  
12 stratification we use is the ABI, which as Dr. Hiatt  
13 said, doesn't correlate with walking particularly well  
14 but does correlate with adverse effects,  
15 cardiovascular events, and survival. So the question  
16 is, for **the** efficacy data, did you look at a less than  
17 or greater than either a diad .6 or .7 ABI, or did you  
18 look at a tertile score? In other words, is this  
19 drug, like with the pentoxifyline data, more or less  
20 effective in those with worsened limb profusion or  
21 greater limb profusion?

22 DR. FORBES: Let me ask Dr. Borte to come

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1 over or Dr. Kazempour, one or the other. Because they  
2 have been doing some of this analysis.

3 DR. HIRSCH : In other words,  
4 stratification of the disease itself, not a  
5 concomitant treatment would seem to be important.

6 DR. KAZEMPOUR: For ABI, we did not  
7 stratify. We do have the data, but we don't have them  
8 in terms of a slide that I can present. But we did  
9 find some correlation between ABI and walking  
10 distance, but we did not stratify them. The reason  
11 was that ABI is a continuous variable. When you start  
12 to cut it from .7, the next person is going to say how  
13 about .6. We did not do it by cutting it based on  
14 whatever criteria. But we do see a correlation -- a  
15 weak correlation. Because both of them, the walking  
16 distance as well as ABI, they are highly variable.

17 DR. HIRSCH: But I must say, like other  
18 cardiovascular drugs, blood pressure is a continuous  
19 variable, but we stratify them mild, moderate, and  
20 severe, and so is ejection fraction for systolic  
21 dysfunction. so making generic cutoffs is a  
22 reasonable thing in a disease of 10 million people.

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1 I would like to see the data.

2 A related question very quickly is you  
3 stratified based on beta blockers, use and non-use,  
4 calcium blockers, use and non-use. Again, I didn't  
5 hear the answer. What about aspirin use and non-use  
6 in those two trials? Have you got data?

7 DR. FORBES : Actually, we have not done  
8 that **analysis**. You are talking regarding efficacy of  
9 the concomitant?

10 DR. HIRSCH: Yes. Efficacy data based on  
11 concomitant inhibition of platelet function.

12 DR. FORBES : We could take a look at it  
13 and try to get back to you a little later today.

14 DR. HIRSCH: Thanks.

15 CHAIRPERSON PACKER: Udho?

16 DR. THADANI: I always have questions. In  
17 your trial 2195201, that is the only trial with the  
18 150 mg. And the P value -- that is the non-  
19 significant trial it seems like. In 2195201, the P  
20 value on 150 is about .04 and 100 mg did not beat the  
21 placebo .91. So is that enough to say that 150 won't  
22 be more effective than 100? Because you have **got only**

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1 one trial. I realize there are some difficulties.  
2 Because we are talking about dose response. 100 is  
3 better than 50, but would 150 be, one trial, would  
4 your confidence number work better?

5 DR. FORBES : Well, the treatment effect  
6 that we saw with the 150 as we looked across trials --  
7 and again, I realize you have to be cautious here.  
8 But as we looked across trials, it wasn't that much  
9 different than what we saw with 100 mg twice daily.  
10 Within that trial, you are absolutely right. 150 beat  
11 100 in that particular trial. So the question of  
12 whether **or** not you get additional benefit with 150 is  
13 possible, it doesn't appear from looking across our  
14 trials that you would get a great deal more benefit.  
15 I don't know if that answers your questions.

16 DR. THADANI: I think there is only one  
17 trial with 150, right?

18 DR. FORBES: That is correct.

19 DR. THADANI: So we really can't say much  
20 with just a kind of borderline P value.

21 DR. FORBES : That is correct.

22 DR. THADANI: so if you carry forward, I

1 don't know what will happen there. So we are limited  
2 with say 200 or 150. It might be more beneficial, but  
3 we have no way of knowing right?

4 DR. FORBES: That is correct.

5 DR. THADANI: In the same context, if you  
6 believe that 150 -- even if you don't know the  
7 mechanism of how the drug works, but presuming it  
8 improves the cardiac output or increases  
9 contractility, you would think that that dose would  
10 have shown more benefit. And yet on the ankle  
11 brachial ratios, I realize that there is a dichotomy.  
12 The FDA reviewer says he has not seen any studies  
13 which were analyzed with respect to ABI ratios and  
14 showed an increase in blood flow both at rest and  
15 during exercise. I know you did not show the data,  
16 but is there any evidence that it does anything to  
17 ABI?

18 DR. FORBES: Yes, there is.

19 DR. THADANI: I know you have been  
20 mentioning it, but I haven't seen it.

21 DR. FORBES : Do you want to see it or  
22 would you like me just to talk through the data.

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1 DR. THADANI: If you can, give the  
2 numbers. Because the table the FDA people gave me,  
3 the patients who improved the most in ABI ratios  
4 sometimes are the ones whose index is less than .5  
5 rather than the other way. And some of the placebo  
6 improved the same way. So it is hard to believe how  
7 it is changing by the drug effect or is it just a  
8 chance.

9 DR. FORBES : Okay. But you are  
10 specifically looking at resting ankle **brachial** and the  
11 changes that we see with it?

12 DR. THADANI: Yes.

13 DR. FORBES : Okay. We actually did a  
14 couple **of** things. The first was we measured the  
15 resting **ankle** brachial index. And not every trial is  
16 significant, but there are three trials, I believe,  
17 that are actually statistically significant showing  
18 the ABI increases with **cilostazol** treatment relative  
19 to placebo. Now the increases, you may say are they  
20 clinically relevant? The changes that we are seeing  
21 in an ankle brachial index -- I told you the baseline  
22 value **is** 0.64 -- we are seeing something around the

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1 magnitude of a .05 increase. So that is statistically  
2 measurable, and we have had debates about whether it  
3 is clinically meaningful. Additionally, what we have  
4 done is we have looked at pressure recoveries.  
5 Because as you know, the pressure drops in these  
6 patients after exercise or during exercise, and then  
7 afterwards you can measure it. So we measured it at  
8 1, 5, and 9 minutes after randomization, and what we  
9 found is that those pressure recoveries are quicker.  
10 So that is the extent of what we know about pressures  
11 around exercise and around the symptoms of  
12 **claudication cilostazol.**

13 CHAIRPERSON PACKER: Tom? Cindy?

14 DR. GRINES: I had a question about the  
15 treadmill testing. It seemed like many of the trials,  
16 the placebo group had longer treadmill times at  
17 baseline. And since your ultimate measurement is  
18 comparing the treatment treadmill duration to  
19 baseline, wouldn't that give the drug group an unfair  
20 advantage?

21 DR. FORBES: I think actually most of the  
22 treadmill baseline distances were within about 10 to

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1 15 meters at baseline. And you are right, there were  
2 some protocols where the placebos walked a little  
3 further. The statistics on that were obviously not  
4 significant, as I showed you a little bit about the  
5 patient that didn't have the post-baseline. But all  
6 the baseline with the post-baseline treadmill test,  
7 there was no difference between baselines for the  
8 treatment groups.

9 DR. GRINES : Was there any analysis  
10 performed to determine the change in exercise  
11 tolerance based on the baseline exercise duration?

12 DR. FORBES : I will refer that to our  
13 statistical department again.

14 DR. KAZEMPOUR: We did look at the  
15 baseline ACD walking distance to see if the  
16 randomization worked and they were balanced within a  
17 few meters. But none of them were statistically  
18 significant. But conducting a statistical analysis to  
19 see if the post-baseline walking distance was a  
20 function of baseline walking distance, yes, it was.  
21 And in three of the studies, we saw we call it  
22 treatment by baseline extractions. And when we looked

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1 at that treatment by baseline extractions, we found  
2 that that extraction, we statisticians use the term,  
3 is quantitative and not qualitative. Meaning those  
4 who walked a shorter distance at baseline had an  
5 improved smaller absolute value, and those who walked  
6 further distance at baseline, they improved a larger  
7 value. As I mentioned earlier for the 92202, for  
8 example, those who were in the first core trial of ACD  
9 baseline walking distance, they improved somewhere  
10 around 19 percent. And when you go to the third core  
11 trial, the improvement is somewhere around 30-some  
12 percent. So it is -- yes, walking distance **post-**  
13 baseline is a function of the baseline walking  
14 distance.

15 DR. GRINES: Okay.

16 DR. KAZEMPOUR: And all the analysis that  
17 you have seen were adjusted for baseline. Baseline  
18 was a covariate in the model.

19 DR. GRINES : Okay. I have another  
20 question about the changes in heart rate. It appears  
21 that there is a dose-dependent increase in heart rate  
22 that ranged between -- it looks like a sustained

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1 increase. And I wondered if you felt that --

2 CHAIRPERSON PACKER: Cindy, they may be  
3 talking **about** this in safety. Is that true?

4 DR. FORBES: Yes, actually.

5 CHAIRPERSON PACKER: Can you just hold  
6 that until -- any other questions? No, okay. John?

7 DR. DIMARCO: When I look at the curves  
8 for change in meters walked from baseline, it looks  
9 like it continues over time throughout the 24 weeks of  
10 the study. Is that correct?

11 DR. FORBES : That is correct.

12 DR. DIMARCO: Does it keep going up  
13 forever, do you know?

14 DR. FORBES: We don't know. We have not  
15 measured any time points in a double blind trial past  
16 24 weeks of therapy.

17 DR. DIMARCO: What happens if you stop  
18 drugs at 24 weeks?

19 DR. FORBES: We don't have data on that.  
20 We actually are trying to get some data right now from  
21 a center down in Texas. They did a withdrawal study.  
22 I don't have the analysis right now. We only have

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anecdotal information.

DR. DIMARCO: And why does it take six -- what is the mechanism for the continued increase? Is this a training effect? Is this --

DR. FORBES : Well, there has been some speculation that these patients are reconditioned. So as they are able to walk further, they realized that and over time they can start to condition themselves. Again, **all** speculative. We are not really sure what the net effect of that is or what the mechanism of that is. But we do see it and it is repetitive throughout the trials.

CHAIRPERSON PACKER: JoAnn? Marv?

DR. KONSTAM: I just have one question that relates to the comparison between **cilostazol** and pentoxifyline. You presented the data in detail from 96202 in which **cilostazol** won, but not the data from 94301, I guess, where I see that it doesn't seem that there is even a trend in that direction. So I wonder if you **could** comment on that.

DR. FORBES: Can I have back-up slide R-28, please? This is the absolute **claudication**

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1 distance in meters walked. And again, this is the  
2 last observation carried forward analysis. You can  
3 see the placebo response here again in red or pink, if  
4 you will, for Trental, and green for cilostazol.  
5 Again, other than to tell you that the only thing that  
6 we have really noticed here is that when we did our  
7 post hoc arbitrary analysis, we saw something a little  
8 different than this. But I will point out that this  
9 placebo effect that we see in this trial is a little  
10 greater than the other trials that we have conducted,  
11 but I am not sure that that would explain why we see  
12 differences. I don't know if there is any more  
13 information I can give you on 94301 other than what I  
14 have given.

15 CHAIRPERSON PACKER: Bob?

16 DR. FORBES: Do you have a specific  
17 question?

18 DR. KONSTAM: No. It is just that I don't  
19 get a clear take-home message looking at these two  
20 trials. I guess I am not sure whether Trental works or  
21 not based on the data that you have. I don't know, it  
22 is not critical to the question of cilostazol versus

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1 placebo, in which I think I am accepting of the  
2 directional change with all the multiplicity of  
3 trials. Here you have two very different results. So  
4 I don't have a take-home message frankly.

5 CHAIRPERSON PACKER: Are you talking about the  
6 comparison versus pentoxifyline?

7 DR. KONSTAM: Yes, just in terms of that  
8 question as to whether there is any evidence that it  
9 is better.

10 CHAIRPERSON PACKER: Maybe I -- just to  
11 follow through on that. In the protocols where there  
12 was a comparison to Trental, what did the protocol say  
13 about the screening process for the study in terms of  
14 patients who may previously have been receiving  
15 **Trental**?

16 DR. FORBES: Okay. Let me start with the  
17 U.S. trial. The U.S. trial just required that  
18 patients were off Trental, and we instructed the  
19 centers that they had to be off Trental for 30 days.  
20 And there **was** an exclusion criteria that if patients  
21 did not tolerate Trental or had to come off **Trental** in  
22 the past that they were not allowed into the trial.

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1 So hypersensitivity to Xanthenes. And for the  
2 European trial, it was very much the same. The use of  
3 Trental, if they had previously used it, if they had  
4 come off of it, they weren't allowed to be in the  
5 trial for adverse events.

6 CHAIRPERSON PACKER: The reason for asking  
7 the question is what percentage of the patients in  
8 those two trials had never received Trental?

9 DR. FORBES: I don't believe I can answer  
10 that question.

11 CHAIRPERSON PACKER: The reason for asking  
12 that question is that it may be different in the two  
13 trials, and that might be instructive. The reason it  
14 might be instructive is if you are doing a -- if  
15 patients can have a history of being able to take the  
16 drug that is being evaluated in the trial, and their  
17 only criteria for being allowed to enroll in the trial  
18 is being off the previous drug for a certain period of  
19 time, that will create a bias in terms of who is  
20 actually enrolled in that trial. Because in general,  
21 if you ask patients if they are already taking a  
22 commercially available drug whether they want to enter

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1 a trial, patients who are doing well will say no.  
2 Patients who are doing poorly may be more inclined to  
3 say yes. So it could be that the patients that you  
4 are enrolling in the Trental comparator trials are  
5 **Trental** non-responders. So my question is have you  
6 done an analysis in both studies of the patients who  
7 have never received Trental? In the studies that  
8 actually went against Trental.

9 DR. FORBES: I can take a look at that and  
10 get back to you as far as doing an analysis. I know  
11 that the percentage of patients coming into our trials  
12 is very low for patients that have taken **Trental**  
13 previously. And the other thing I want to mention is  
14 that the enrollment period for 96202 was about five  
15 months. Which means that if you had to be off the  
16 drug for a period of time before you could even come  
17 into the trial, your chances of being around when the  
18 trial was **still** enrolling probably weren't great.

19 CHAIRPERSON PACKER: All right. But would  
20 it be at least possible to, before the end of the day,  
21 find out how many people in the Trental comparator  
22 trials had previously been taking **Trental**?

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1 DR. FORBES: Yes. We will take a look at  
2 that and get back to you.

3 CHAIRPERSON PACKER: I understand you  
4 can't necessarily do an analysis of efficacy in the  
5 people who are Trental naive, but at least we **could**  
6 get an idea of how many people had previously been  
7 taking the drug. Rob?

8 DR. CALIFF: I just -- as I said before,  
9 I would be interested in hearing from Dr. Ware about  
10 two things. One is we are being asked here to accept  
11 a tangible benefit, which appears to be highly  
12 statistically significant, but I wonder -- the three  
13 years off **your** life sounds tremendous, but are there  
14 other synonyms for tangible human benefit from the  
15 quality **of** life data that you see here that **you** would  
16 use? And the second question is what do you currently  
17 recommend **about** people who are lost to follow-up in  
18 quality of life studies? How should their data be  
19 most appropriately counted?

20 DR. WARE : Thank you . First, on the  
21 quality of life benefit, the physical and mental  
22 summaries in the SF-36 offer a psychometric solution

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1 to the problem of multiple comparisons. And these two  
2 summaries capture about 80 percent of the reliable  
3 variance. Not just in the SF-36. We know now that  
4 that is true of the most widely used comprehensive  
5 measures in the U.S. and throughout the world, such as  
6 the sickness impact profile and others. We don't need  
7 to rely on just the results from this study to pick  
8 that as the principle endpoint. There have now been  
9 more than 2 dozen studies in peripheral artery  
10 disease, most of which are ICD studies, in which the  
11 burden of the disease is in those three scales --  
12 physical functioning, the role disability scale, and  
13 bodily pain -- which are the three most weighted in  
14 the physical component. And some of those studies are  
15 treatment studies including surgeries, and those are  
16 the three scales that respond the most. So before I  
17 ever saw any of the results from these trials, I was  
18 sold that the principle component was the one to look  
19 at. That is where the burden is and that is where the  
20 literature says the benefit of treatment should be.  
21 And I am glad the point was corrected that three of  
22 the six trials, the principle component summary is

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1 statistically significant using conventional analyses  
2 in those three trials.

3           The other thing I would like to comment on  
4 related to your question is we have been talking about  
5 this benefit, this quality of life benefit rather  
6 loosely as if it is a benefit in walking a block, and  
7 that is not a fair characterization of the results.  
8 Three of the measures, the treadmill test, the **WIQ**,  
9 and the SF-36 all measure walking, and they include  
10 short distances like one to five blocks, and all of  
11 the measures agree at those distances. The advantage  
12 of the quality of life measure is that it takes --  
13 number one, it takes the result out of the laboratory.  
14 We are not just talking about a treadmill test, but we  
15 have a **double** blind comparison of walking in everyday  
16 life. What we see in the SF-36 is that the percentage  
17 of people that are able to walk a block or that report  
18 this in the follow-up in the study is increased by 40  
19 percent, from 50 percent to 70 percent. So in that  
20 sense, the functional health measure agrees with the  
21 **WIQ** and the treadmill test. But the functional health  
22 measure in the SF-36 extends this to walking several

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1 blocks . Now fewer people do that, 15 percent, but  
2 that is increased to 45 percent with treatment. And  
3 when you look at very long distances such as walking  
4 a mile, only 3 to 5 percent do that, but that number  
5 is 3 times as large, 16 percent in the treated group  
6 relative to the placebo group. But the value of the  
7 functional health and well-being measure, and that is  
8 really what we are measuring here. We are not  
9 measuring the amorphous quality of life concept. We  
10 are focusing very specifically on the dimensions of  
11 quality of life that are most relevant to medical  
12 care. How does disease affect functioning and what  
13 people are able to do? How do they feel and how do  
14 they evaluate that? And that is basically what the  
15 SF-36 measures. So when we look at the results in the  
16 full physical component, these patients are  
17 accomplishing more in their usual role. They are able  
18 to do more things. They are taking less frequent  
19 rests. They are able to do things more quickly.

20 Now if we look at the predictive studies,  
21 everything I said up until now we are not  
22 extrapolating at all. I am just telling you what is

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1 in the questionnaire items that these people responded  
2 to differently in the arms of this trial. But if we go  
3 to the predicted results, these treatment differences  
4 are predictive of if these people are working at a  
5 paying **job**, they are more likely to retain that job.  
6 There are a lot of things in life that require being  
7 able to ambulate. So these have a clinical and social  
8 relevance that is beyond walking a block. We are  
9 talking here about a benefit that is much more than  
10 just **being** able to walk an additional block I would  
11 argue. That is what the quality of life data tell us.

12 DR. KONSTAM: Can I ask Dr. Ware a  
13 question? You know, we had some discussion, as I am  
14 sure you heard earlier, about quality of life  
15 measurements versus treadmill measurements, and I  
16 would just like your view in general about the  
17 discussion and specifically do you view the SF-36 as  
18 looking **at** something different, namely quality of  
19 life, compared to the treadmill test, which is  
20 measuring treadmill time, or rather do you view the  
21 treadmill test as also looking at quality of life in  
22 a different way?

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1 DR. WARE: Thank you. The treadmill test  
2 is a very -- its strength is its objectivity and it is  
3 highly standardized and it is measuring a basic human  
4 health value. If you look at the literature on  
5 quality of life over 3,000 years, ambulation is a  
6 basic human value. There aren't people that are  
7 happier not being able to walk. We all want to do  
8 that. So it happens to be a specific measure that is  
9 affected by this condition and other conditions that  
10 affect large joints and ambulation. But it is in  
11 every -- you would not consider a quality of life  
12 measure comprehensive if it didn't include something  
13 that either directly or indirectly measured  
14 ambulation. So it is a key component of **health-**  
15 related quality of life. And I think that is the  
16 standard.

17 DR. KONSTAM: So if I hear you correctly,  
18 the treadmill time is an indicator of quality of life?

19 DR. WARE : Of that component of the  
20 physical dimension of quality of life.

21 DR. KONSTAM: Of that component of quality  
22 of life.

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1 DR. WARE: What is important here, though,  
2 is that **number** one, because we always worry about side  
3 effects 'with these conditions, to see no detriments in  
4 the mental component is very important because these  
5 patients had some GI symptoms and they had some  
6 headaches. And what this says net of all that is that  
7 these lives are better physically and they are no  
8 worse mentally. Again, this is a very comprehensive  
9 measure. We know that adding 40 other measures to the  
10 equation only increases the variance explained in  
11 health related quality of life 5 percent over what is  
12 in the SF-36. so I had no role in picking the  
13 measures for this study, but when I saw the array, the  
14 treadmill measure, the WIQ, and the SF-36, this is a  
15 very good example of measuring the specific effect to  
16 make sure that you are getting the quality of life the  
17 way you want. You are not just blunting the pain. You  
18 are actually changing the physiology of the disease.  
19 so to prove that and then to see the social and  
20 clinical value of that, this is a nice measurement  
21 model for really understanding the dynamics of this  
22 condition and how treatment changes those dynamics.

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1 DR. LIPICKY: I would just like to echo  
2 the comments that were made. I mean in **anti-anginal**  
3 trials, we have always considered increase in exercise  
4 tolerance a direct symptom benefit, and that that is  
5 in fact the clinically relevant thing that happens, a  
6 symptom **is** relieved, so to speak, if you can walk  
7 longer. The quality of life issue is trying to, I  
8 guess, evaluate whether if people can walk longer, and  
9 you conclude that from the treadmill, whether somehow  
10 or another it makes them into better people, so to  
11 speak. And it is pretty clear it doesn't make them  
12 into football players when in fact the first time they  
13 can't walk 50 feet. So I am not sure what -- I am not  
14 sure what you want to know about the quality of life.

15 DR. KONSTAM: Well, I hear Dr. Ware's  
16 comments as saying it a little bit differently. I  
17 hear him saying that, in fact, the treadmill time is  
18 in fact measuring the physical component of quality of  
19 life.

20 DR. LIPICKY: Well, that is okay, but that  
21 is still symptoms.

22 DR. KONSTAM: Okay. But I think that --

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1 I mean, I get mixed up between referring to the  
2 quality of life instrument, namely the SF-36 --

3 DR. LIPICKY: Well, maybe this is -- I  
4 don't mean **to** interrupt, but the business of feeling  
5 better is a very nondescript term. And it could be  
6 taken as everything in life is better. Relief of  
7 symptoms is, in fact, feeling **better**, and **quality** of  
8 life instruments basically don't get at relief of  
9 symptoms, per se. They get more at do the relief of  
10 symptoms improve one's interaction with the outside  
11 world.

12 DR. KONSTAM: Well, I don't --

13 DR. LIPICKY: You don't think so? What  
14 does it try to get at, then?

15 DR. WARE: Well, there is probably nothing  
16 you can say about quality of life measures that would  
17 be true **of** all of them. But basically quality of life  
18 measures have to be comprehensive in their  
19 representation of the -- and again, I think it would  
20 help us to focus on health-related quality of life.  
21 We are not talking about the neighborhood or the  
22 schools. But we are talking about three things. What

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1 people are able to do in everyday life and how that is  
2 affected by disease and treatment. We are talking  
3 about how they feel. And we are talking about how  
4 they evaluate that. And all three of those things are  
5 in this outcome measure.

6 DR. LIPICKY: Right.

7 DR. WARE: And I can tell you for every  
8 five point change in that measure, people are much  
9 more likely to say they are happy, **pleased, and**  
10 satisfied with the quality of their life than they are  
11 when it was five points lower.

12 DR. LIPICKY: I understand. But it could  
13 be that because now I can walk from my living room to  
14 the dining room, I can see that the dining room is  
15 dirty and that makes me feel bad. And when I wasn't  
16 able to **do** that, I was feeling pretty good. So it  
17 does have that component, no?

18 CHAIRPERSON PACKER: But I don't think  
19 that the SF-36 addresses that issue at all.

20 DR. LIPICKY: Well, that is the third  
21 component of comprehensive quality of life.

22 CHAIRPERSON PACKER: No. My understanding

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1 -- help us out here. My understanding is that when  
2 you are assessing the physical domain of SF-36, you  
3 actually are asking direct questions about the  
4 limitations that **people** have, not necessarily how they  
5 feel about those limitations as far as it relates to  
6 the **physical** domain. Is that correct?

7 DR. WARE : Well, yes and no. These  
8 descriptive measures include reports like walking  
9 distances, but we also ask people to tell us the  
10 difficulties. So that is getting pretty evaluative.  
11 But on **the** well-being side in the physical domain, we  
12 are talking about pain and we are talking about energy  
13 level and we are talking about confidence in health.  
14 And all of those things are weighted in this  
15 component. I mean what this component does is takes  
16 all of the reliable physical variance from all of the  
17 measures and puts it all into one number. So now we  
18 have two outcomes instead of 8 or 10 or 12. And that  
19 **is** the solution to the multiple comparisons problem.  
20 In this case, what was summarized was all going in the  
21 same direction. So if anything, it increased the  
22 precision of the analysis, but it certainly simplified

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1 it.

2 CHAIRPERSON PACKER: I think, Ray, that  
3 there is a general concept that quality of life  
4 instruments are measures of happiness, but they are  
5 not.

6 DR. WARE: They include happiness. Mental  
7 health is an important part of quality of life.

8 DR. LIPICKY: They include that in the  
9 total score if it is comprehensive. The component of  
10 that.

11 DR. WARE : Right. The message there is  
12 that these individuals are at the 12th percentile, the  
13 average of all the trials at baseline, the 12th  
14 percentile of the U.S. population. They are at the  
15 25th percentile of the seniors population. They are  
16 normal in mental health. ICD is not a psychiatric  
17 disorder, And there are about 2 dozen studies I think  
18 in the literature now that confirm that. This is a  
19 disorder of functional performance and capacity.

20 DR. KONSTAM: You know, I think we have a  
21 little semantic problem and maybe it is different ways  
22 of looking at it or maybe it is just semantics. I

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1 think that you might -- and we can ask Dr. **Ware** if  
2 this is right -- use the term quality of life more  
3 comprehensively maybe than you are using it, Ray. And  
4 I think you are focusing in on what are referred to as  
5 quality ~~of~~ life questionnaires or quality of **life**  
6 instruments. We could use the concept of quality of  
7 life more comprehensively to include specific  
8 symptomatic indicators which are direct measures, as  
9 I hear it, of the physical component of quality of  
10 life like of health-related quality of life. In this  
11 case, health related quality of life as it is  
12 influenced by the physical limitation of claudication.  
13 And that can be directly measured by the treadmill.  
14 So therein lies a direct quality of life indicator,  
15 namely the treadmill time.

16 DR. WARE: But as Dr. Hiatt stressed, we  
17 don't know what the treadmill is going to be from the  
18 **ABI**, and likewise, we don't know what life is going to  
19 be from the treadmill. And that is why we want all  
20 three levels of measurement. And they serve our  
21 understanding very well.

22 CHAIRPERSON PACKER: Ray I think has a

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1 direct response.

2 DR. LIPICKY: But then I think it is not  
3 appropriate to ask the question of what does 25 meters  
4 increase mean. Because what one can use the 25 meters  
5 of increase or 75 meters of increase is as a metric of  
6 whether this drug is active or not active with respect  
7 to increasing exercise tolerance and/or whether there  
8 is a dose response, but that it would be unreasonable  
9 to think that that particular metric, whether it was  
10 the median **or** the mean or whatever derivative that one  
11 took of **any** of the results, would be applicable to  
12 what any individual patient that one was going to  
13 prescribe the medicine for would get. And therefore,  
14 the issue sort of isn't to translate 25 meters into  
15 clinical relevance. What one can do is conclude this  
16 is not placebo. That it does increase exercise  
17 tolerance. That overall interaction with life is not  
18 adversely affected or may be positively affected, or  
19 however it is that one wants to look at the  
20 conglomerate of the quality of life instrument data.  
21 And that is probably the limit that one can go, and  
22 one should not translate ' just like with an

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1 antihypertensive, one should not say, well, the mean  
2 antihypertensive effect is 5 mm, so therefore when I  
3 give this drug to patient X in this dose, I can expect  
4 5 mm of mercury change. That is just not right. It  
5 is not going to happen.

6 CHAIRPERSON PACKER : But that wouldn't be  
7 a true statement even if there were no quality of life  
8 instrument.

9 DR. LIPICKY: I understand.

10 DR. CALIFF: But there is a problem with  
11 what you are putting forward unless you have an  
12 alternative way of translating the trial into  
13 something tangible.

14 DR. LIPICKY: I haven't.

15 DR. CALIFF: You don't have an  
16 alternative.

17 DR. LIPICKY: Right. I think all you can  
18 do is say it is not placebo and that you can decide  
19 that it is related -- that the effect that you believe  
20 is a reasonable effect to measure is related to dose  
2 in some fashion and that that is not translatable when  
2 you start to apply it to an individual patient. All

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1 you know is you are not giving them a sugar pill.

2 DR. WARE: Can I try to -- I think that  
3 was more true 5 or 10 years ago than it is now. If I  
4 can use the analogy of a thermometer. There was a  
5 time when we didn't know that 20 degrees centigrade  
6 was the same as 70 degrees Fahrenheit, and we didn't  
7 know that that was shirt-sleeve weather. But by  
8 gaining experience with those two metrics, we began to  
9 attribute meaning to them. And I would argue that  
10 that is kind of where we are with health status  
11 measures now. We can say very confidently that a  
12 quarter of a standard deviation improvement in the  
13 physical dimension of health-related quality of life  
14 is a very important improvement that the public would  
15 agree is important. And my last point --

16 DR. LIPICKY: Fine. But you are asked to  
17 put that metric into translating terms of three months  
18 of life. And you are going to be asked that in just  
19 a little bit. So the more confidence you have in  
20 being able to put that efficacy metric into some real  
21 term -- you just can't do it that way. It won't work.

22 DR. WARE: Well, first of all, let me try

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1 to respond to that in two ways. One is for another  
2 agency of the federal government, we are ranking the  
3 150 treatment studies that have used the SF-36. I  
4 know the physical ranking really quite well. Most of  
5 the treatments are surgeries -- new knees, new hips,  
6 new hearts, new heart valves, new kidneys. Those are  
7 the largest effects. One of the first things I did  
8 when I saw these results was put theirs in. It is in  
9 the top third of all treatments that we have in our  
10 data base of 150 clinical studies in terms of  
11 improvement in the physical component of quality of  
12 life. So it is right up there with a lot of  
13 treatments that we are currently reimbursing. And I  
14 think that is important because I know that this is  
15 going to come down to a risk/benefit discussion.

16 The other good news is a utility, a  
17 preference-based index for the SF-36, will be  
18 published in October in the Journal of Clinical  
19 Epidemiology, and you could actually score the results  
20 from this trial in a quali sense and not argue about  
21 is this life better enough to take a risk. We would  
22 be able to qualify.

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1 DR. LIPICKY: But those are qualitative  
2 statements. I don't think anyone would disagree that  
3 there is an effect and that the effect is up there  
4 very powerfully with respect to other effects that  
5 people have seen. The question is how would you  
6 quantitate that.

7 CHAIRPERSON PACKER: Let's pause for a  
8 moment. Let me just turn and ask, Rob, do you have  
9 any additional questions other than quality of life?

10 DR. CALIFF: It is related to quality of  
11 life. It is just a concept I want to note because we  
12 may want to -- it is not worth going into detail here,  
13 but the concept that one could evaluate differences in  
14 side effects or adverse events by seeing whether there  
15 is a deterioration in global mental health or  
16 subjective assessment of quality of life I think is  
17 worth serious consideration. We don't need to discuss  
18 it in detail, but I want to make sure that that is  
19 noted.

20 CHAIRPERSON PACKER: All right. Ray, do  
21 you have any other questions or comments?

22 DR. LIPICKY: Well, I wanted to change the

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1       sub j e c t   a n   h o u r   a g o .     I t   i s   a   r e l a t i v e l y   s i m p l e  
2       q u e s t i o n ,   I   t h i n k ,   a n d   m a y b e   i t   w i l l   c o m e   u p   l a t e r .  
3       B u t   a s   I   l o o k e d   a t   y o u r   s l i d e   0 2 ,   w h i c h   w a s   t h e  
4       d r o p o u t s     b e f o r e     t h e     f i r s t     p o s t - r a n d o m i z a t i o n  
5       m e a s u r e m e n t ,   t h e   s o r t   o f   a v e r a g e   n u m b e r   o f   p e o p l e   t h a t  
6       m i s s e d   t h e i r   f i r s t   p o s t - r a n d o m i z a t i o n   m e a s u r e m e n t   w a s  
7       6 . 6 ,   a n d   i t   r a n g e d   f r o m   1 7   p e r c e n t   t o   4   p e r c e n t   o r  
8       s o m e t h i n g   o n   t h a t   o r d e r .     A n d   t h e   r e a s o n s   t h a t   a r e  
9       g i v e n   f o r   d r o p o u t s   a n d   f o r   s i d e   e f f e c t s   a n d   s o   o n   a r e  
10      t h i n g s   l i k e   h e a d a c h e   a n d   d i a r r h e a .     I t   d o e s n ' t   q u i t e  
11      f i t   t o   m e   t h a t   t h a t   n u m b e r   o f   p a t i e n t s   w o u l d   d r o p   o u t  
12      b e t w e e n   t h e   t i m e   t h a t   t h e y   a r e   r a n d o m i z e d   t o   t h e   t i m e  
13      o f   t h e   f i r s t   p o s t - r a n d o m i z a t i o n   t e s t   m e a s u r e m e n t   i f  
14      t h e y   a r e   a l l   s t a b l e   P A D   a n d   t h e   w o r s t   t h i n g   t h a t  
15      h a p p e n s   t o   t h e m   i s   t h e y   g e t   h e a d a c h e   a n d   d i a r r h e a .  
16      H o w   d i d   --   h o w   c o m e ?     O r   d o   y o u   t h i n k   I   a m   n u t s ?

17                     D R .   F O R B E S :   N o ,   n o .

18                     C H A I R P E R S O N   P A C K E R :   I t   w a s n ' t   s u p p o s e d   t o  
19      b e   t w o   q u e s t i o n s .

20                     D R .   F O R B E S :     C a n   I   h a v e   b a c k - u p   s l i d e   N -  
21      1 5 ?     L e t ' s   s e e   i f   t h i s   a n s w e r s   y o u r   q u e s t i o n s   o r   a t  
22      l e a s t   a u g m e n t s   i t .     C a n   y o u   m o v e   m e   t o   N - 1 7 ,   p l e a s e ?

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1 We have the treatment groups up here plus a 150  
2 placebo and **pentoxifyline**. And as you can see, in  
3 fact, the majority of the reasons why the patients  
4 drop out is **adverse** events. I want to point out that  
5 the failed screening, the patients that were enrolled  
6 that were on concomitant medications that were  
7 excluded by the protocol. So in fact, they got  
8 randomized and the failed screening is a little bit of  
9 a misnomer. They were randomized and perhaps were on  
10 Warfarin. And because they were on Warfarin and we  
11 didn't have information on Warfarin early in the  
12 development, we excluded them or pulled them out. But  
13 this gives you a breakdown of why patients decided not  
14 to continue. And I don't know if I can answer the  
15 question **any** more directly than this, but in fact I  
16 think that was the biggest reason why patients decided  
17 to come out was for the adverse experience.

18 DR. LIPICKY: Am I misreading the numbers  
19 on your slide 02? What it says is that there were 172  
20 patients that didn't make their first **post-**  
21 randomization measurement. And that must include lots  
22 of people with adverse experiences then because that

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1 is a big number, 173.

2 DR. FORBES : Yes. The totals are down  
3 here and I believe they add up to 172.

4 DR. LIPICKY: I see. So this is --

5 DR. FORBES: That is everybody.

6 DR. LIPICKY: Oh, I see. So the headache  
7 and diarrhea then were pretty bad things? I mean the  
8 problem I am having is that I can't put headache and  
9 diarrhea into adverse experience dropouts.

10 DR. FORBES : I see. so you need a  
11 breakdown of the adverse experiences.

12 DR. LIPICKY: Somehow. Because it doesn't  
13 seem to quite hang together that things that I would  
14 consider usually to be relatively trivial things  
15 caused people to quit as soon as they get into a  
16 study .

17 CHAIRPERSON PACKER: But , Ray, headache  
18 and diarrhea can be pretty bad.

19 DR. LIPICKY: Well, but that is the  
20 question. Is that the case? That they are really bad  
21 and people just can't --

22 CHAIRPERSON PACKER: I am just saying that

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1 we have seen --

2 DR. LIPICKY: So maybe this will come up.

3 CHAIRPERSON PACKER: Maybe we should talk  
4 about this in the safety part of this.

5 DR. LIPICKY: Yes, okay. So this will  
6 come up.

7 CHAIRPERSON PACKER: And in fact, why  
8 don't we hold -- I am sure you will talk about this in  
9 safety.

10 DR. LIPICKY: Okay.

11 DR. FORBES: Yes, we can talk about it in  
12 safety. I think that is perhaps our problem in  
13 bringing up a slide here.

14 CHAIRPERSON PACKER: We will talk about it  
15 in safety. Okay. Ray, anything else? Okay, does  
16 anybody **on** the committee have -- Bob, we are going to  
17 end with **you**. But does anybody have anything on the  
18 committee? And please, it should not be about quality  
19 of life.

20 DR. THADANI: But I think Ray pointed out  
21 with the headaches and diarrhea, the quality of life  
22 should **be** worse. So if you drop out those patients,

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1 they are feeling lousy. So if you are not going to do  
2 carry forward analysis, the quality could be worse.  
3 So what **you** are showing as positive may be negative.  
4 I think it **is** a relevant issue. Other issues, I don't  
5 know when you are administering quality of life  
6 issues. **Because** you only give them a **questionnaire on**  
7 the day **of** their visit on exercise. I have done it in  
8 angina. And they cannot remember what they ate two  
9 days before. And I don't know how reliable this is to  
10 remember how much they walked in the last four weeks  
11 and if what they tell you is what they did maybe the  
12 day before and they say, oh, they have been doing  
13 great. you put them on the treadmill and they only  
14 walk **three** minutes and they are actually worse off  
15 than when they started. So I buy the point that there  
16 is a placebo point and the data is qualitative, but in  
17 absolute terms, have you ever put a speedometer on  
18 their ankles and coordinated with your quality of  
19 life, especially talking about the physical. Is there  
20 a correlation between speedometer walking in everyday  
21 life or **maybe** the last day versus your quality of life  
22 questionnaire?

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DR. FORBES : We actually looked at the correlation between the treadmill test --

DR. THADANI: No, no. Forget about the treadmill because that is inside. But say for outside. You are talking about a patient who is able or say **claims** that rather than walking one block, I am walking two blocks. Have you put a speedometer to show me that he really walks more distance or is it just his perception?

DR. FORBES: No, we haven't done that.

CHAIRPERSON PACKER: Let me -- there is one -- we are going to deal with this after the break. But Rob did ask Dr. Ware a question about handling dropouts which was not answered. And that relates, **Udho**, to your specific issue about how -- if you don't -- if you only measure or take the actual values of the SF-36 or any other quality of life and don't include -- and if you don't include the adverse effect of having 'chosed symptoms on the SF-36 because it is not measured at the time of dropout, then the scales could be biased. Don't answer that right now because we don't have time. But we will ask you that question

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1 after the break, and we will end with Bob's last  
2 question.

3 DR. TEMPLE: I was just going to suggest  
4 again **the** idea that quality of life issues become  
5 over-mystified. I think it is partly the problem of  
6 the field and partly a persistent semantic problem.  
7 The efforts to measure the physical consequences of a  
8 condition are not **fundamentally** different but are  
9 better than the way clinicians have always done that.  
10 You know, can you walk three block or two blocks, can  
11 you do this or can you do that? But those are  
12 unstructured and not very good. It is not that they  
13 are wrong. You can develop symptom scores and  
14 basically get the idea. Doctors aren't always wrong.  
15 These are some components of the quality of life  
16 scales, and the ones that are most successful in my  
17 experience here are the ones that try to in a  
18 rational way describe just what the consequences of  
19 having a disease are. There are some very good scales  
20 for asthma that correspond very well with how your FEV  
21 is going. **And** those things really ought to correspond  
22 in a rough way, anyway, to how you are doing on a

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1 treadmill. Because they are attempts to measure the  
2 outcome consequences or the daily life consequences of  
3 being **able** to walk better. So that doesn't mean they  
4 are going to correspond perfectly. We know from  
5 angina trials that angina rates and nitroglycerin use  
6 don't correspond one to one with exercise, but we do  
7 think they are measuring roughly the same thing and I  
8 think they probably are. It is when you try to  
9 translate those into life experiences and how is your  
10 family that as Ray said, now you can walk and you can  
11 see the room is dirty. It is not as easy to predict  
12 what the consequences of those things are. And what  
13 happened here is that those things didn't actually  
14 change that much. They just didn't deteriorate. But  
15 the physical consequences of being a claudicant did  
16 improve, just as you would predict, and it is not  
17 qualitative only. It is potentially quantitative,  
18 just as the treadmill is. And it is not surprising  
19 that they go together. You would be sort of amazed if  
20 they didn't. If they didn't, you would ask whether it  
21 is doing something else bad to you, like making you  
22 depressed or something.

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1 CHAIRPERSON PACKER: Okay. We will take  
2 a break. After the break, we will begin with the  
3 safety presentation. But before doing that, we will  
4 ask Dr. Ware to come up to the microphone to address  
5 the issue **of** dropouts, because that will be directly  
6 **pertinent** to the safety presentation. We will  
7 reconvene at 1:45.

8 (Whereupon, the meeting was adjourned for  
9 lunch at 12:50 p.m. to reconvene this same day at 1:45  
10 p.m.)

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1 A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

2 1:45 p.m.

3 CHAIRPERSON PACKER: If we can ask Dr.  
4 Ware if he could -- here he is. One of the questions  
5 that came up before the break, and Rob Califf was the  
6 one that asked and he is not here. But nevertheless,  
7 how does one go about and what is your experience in  
8 analyzing quality of life in general and perhaps  
9 specifically with the SF-36 in patients who drop out?  
10 What do you do about that? Because that happens in  
11 every clinical trial.

12 DR. WARE: Right. I think I would only  
13 underscore what has already been said because the  
14 situation is very similar in a health status measure  
15 as it is for the other measures that have been talked  
16 about. You want to avoid it as much as possible.  
17 Given that -- this doesn't help these trials, but  
18 given that these are standardized telephone  
19 interviews, you can follow patients even if they are  
20 lost to treatment assignment and know they are  
21 functioning even if they -- so you can do a more  
22 complete intention to treat analysis. But they have

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1 done a regression analysis where they have looked at  
2 outcome predicted from initial score. These are  
3 substantially intercorrelated over time. We don't  
4 have available the actual correlation that they  
5 observed in their study, but in my experience over a  
6 six-month interval, even at that long, these are very  
7 substantial correlations. So their model has already  
8 helped a lot to deal with any initial differences that  
9 are related to dropout. But we are also concerned  
10 about the differences that happen after an initial  
11 assessment.

12 CHAIRPERSON PACKER: Well, there are two  
13 separate issues. One is an issue of what happens to  
14 patients after they drop out because you want to  
15 maintain the concept of an intention to treat  
16 analysis. I guess I am more concerned about the  
17 specific issue that was raised before the break, which  
18 is one of the -- I think it is our general perception  
19 that quality of life instruments incorporate into them  
20 not only the benefits that can accrue from therapy,  
21 but the adverse side effects that can be caused by  
22 drugs. And somehow there is a question or questions

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1 that would be adversely affected if a drug produced  
2 side effects. However, the side effects that a drug  
3 produces, especially one that may be significant  
4 enough to lead to withdrawal, would never be reflected  
5 in an SF-36 if the dropout occurred between scheduled  
6 **assessments.**

7 DR. WARE: Right.

8 CHAIRPERSON PACKER: So that as Ray was  
9 saying earlier, if someone had headaches and diarrhea,  
10 they may or may not have had headaches or diarrhea the  
11 previous visit, but clearly continued therapy so that  
12 at some point in time between scheduled visits, they  
13 said this is bad enough that I don't want to continue  
14 and consequently -- but an SF-36 **isn't** measured at  
15 that point in time. So that the adverse reaction  
16 profile of the drug is not incorporated into the  
17 quality of life instrument.

18 DR. WARE: You are right. These generic  
19 measures are not specific at all, but they are  
20 sensitive to a fault. They collect everything. And  
21 specifically, the side effects that were observed in  
22 all the groups including the placebo group in these

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1 trials have been linked in the empirical literature.  
2 GI symptoms and headaches are among those that affect  
3 the scores the most. Not so much the physical score,  
4 but the other scores.

5 CHAIRPERSON PACKER: They do affect the  
6 scores the most, but they wouldn't affect the scores  
7 in this study.

8 DR. WARE: If you don't have the score.

9 CHAIRPERSON PACKER: If you don't have the  
10 score.

11 DR. WARE: Exactly. Well, then all I can  
12 say there is, number one, as has already been said by  
13 the panel, I would very interested in how many of  
14 those people there are. My recollection from the  
15 report is that the rates are fairly small, 5 to 10  
16 percent. The next thing I would be concerned about is  
17 whether they are balanced. Is it 2 percent in one and  
18 15 in another? They looked fairly balanced. And then  
19 I would want to look at the initial values of those.  
20 All the usual things.

21 CHAIRPERSON PACKER: All the usual things,  
22 right.

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1 DR. WARE: There is nothing really magical  
2 about quality of life that gets you out of any of  
3 these. They are the same problems that you have with  
4 the ABI or anything else.

5 CHAIRPERSON PACKER: Yes, Bob?

6 DR. TEMPLE: I hear what you want, but I  
7 would **argue** that it is a mistake for you to want it.  
8 What is not useful is a score that mixes good things  
9 and bad things, if you ask me. Other people disagree,  
10 I know. I think what you want to know is what are the  
11 good things it does, how does it help your heart  
12 failure symptoms, and what are the bad things it does?  
13 How much diarrhea does it give you? So you can weigh  
14 those things and look at them separately. Because if  
15 a person -- you want to know when a person doesn't get  
16 diarrhea enough to drop out of the study he is going  
17 to benefit from. You also want to know how frequently  
18 the diarrhea is a problem. I know there are lumpers  
19 and splitters, but I think on this we should be  
20 splitters. I don't want a single score that combines  
21 five different things together. That is a way to lose  
22 information. So I would argue that you want something

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1 focused on the symptomatic benefits and the  
2 consequences to your life of being able to walk more,  
3 and then **you** want a separate assessment of how much  
4 trouble you have to buy in order to get that thing.

5 CHAIRPERSON PACKER: But, Bob, I guess I  
6 am confused because one of the things that I guess we  
7 heard a little bit earlier in terms of one of the  
8 benefits of quality of life instruments and one of the  
9 benefits that Dr. Ware emphasized is that they are  
10 comprehensive. That is that they not only incorporate  
11 things that can be good. Otherwise, you are only  
12 asking -- **it** would be almost impossible for a drug to  
13 adversely affect quality of life, even if it produced  
14 terrible adverse reactions. You could actually get a  
15 situation where a drug produced side effects in 90  
16 percent of people, but the quality of life instrument  
17 showed that the people were better.

18 DR. TEMPLE: You have just got to focus on  
19 what the questions are. You have lots of ways of  
20 finding out about adverse effects. If people drop out  
21 of a trial because of an adverse effect, you have  
22 learned something about it. You don't need a quality

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1 of life scale to tell you that. This is part of a  
2 longstanding debate about disease specific and more  
3 general quality of life scales. Just as an example,  
4 there is a widely used -- there are several widely  
5 used quality of life scales in asthma. They ask you  
6 are you able to do the things you want to do. How  
7 often do you have to not go out of doors because of  
8 this? And they mostly don't ask you about whether the  
9 drug does something bad. You could have -- I guess I  
10 would argue that you should devise a separate scale  
11 for **that** because it is important to keep the thing  
12 separate. But that is a longstanding debate.

13 CHAIRPERSON PACKER: Let me try. I would  
14 have no problem with what you are saying if you said  
15 you are going measure claudication specific quality of  
16 life. **And** I guess you could do that.

17 DR. TEMPLE : Because physical things  
18 mostly do.

19 CHAIRPERSON PACKER: No. This physical  
20 domain is supposed to incorporate issues like headache  
21 and gastrointestinal distress or whatever. But in  
22 this trial, it didn't do that because those events

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1 were not incorporated into the physical dimension  
2 because they occurred between visits. In other words,  
3 it --

4 DR. TEMPLE: I guess I would argue that  
5 you should keep those things separate and not lump  
6 them altogether. so that I guess I think that is  
7 good .

8 DR. WARE : I would want to do both. I  
9 mean, the answer to the lumpers and splitters is that we  
10 are different ways on that on different days. And  
11 just like the Z specific and generic measures, I think  
12 we know now the answer is yes to both. We know much  
13 more when we know both. People have adverse side  
14 effects who are followed. And so the generic measure  
15 helps us to understand the treatment benefit net of  
16 some dizziness and some GI. So I really would -- I  
17 think we are both right.

18 CHAIRPERSON PACKER: I guess that my  
19 difficulty is saying that this drug improves the  
20 physical domain of quality of life when in fact many  
21 of the components that would adversely affect the  
22 physical domain were not included in the analysis

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1 because they occurred between visits. Maybe the  
2 problem here is what we are referring to. If we are  
3 referring to a general physical domain that is  
4 benefitted by thin drug, I would have problems with  
5 that conclusion. Because they are not incorporating  
6 adverse effects that can adversely affect the physical  
7 domain. If, on the other hand, what is being measured  
8 here is a disease-specific quality of life, very, very  
9 focused, such as you suggested, Bob, asthma, and there  
10 are disease-specific quality of life's for a number of  
11 disorders. I guess I would feel more comfortable with  
12 that, but I would feel very uncomfortable with the  
13 description that this was a general physical domain  
14 because there is a systematic bias in taking out the  
15 things that can adversely affect the physical domain.

16 DR. WARE: I think maybe I understand the  
17 problem here. We don't have the measure that you are  
18 interested in for the people that dropped out after  
19 the last measurement. That is a sampling problem with  
20 respect to time. The other sampling issue here is the  
21 domain of health-related quality of life. We never  
22 try to measure all of that. Just like we sample

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1 people, we sample domains and items. And from that,  
2 we can estimate a health-related quality of life  
3 score. The problem is we don't have that score for  
4 the **people** that dropped out after the last assessment.  
5 But if the rates are low enough and evenly  
6 distributed, we are not as concerned as --

7 CHAIRPERSON PACKER : One, they are not  
8 equally distributed.

9 DR. WARE: Then we should be concerned.

10 CHAIRPERSON PACKER: Here the dropout rate  
11 because of side effects is significantly higher in  
12 active therapy than on placebo. And I guess one  
13 possible way of estimating what we are talking about  
14 is to repeat the quality of life questionnaire, the  
15 analysis of SF-30, assigning to every patient who  
16 dropped out because of an adverse effect a worst rank.

17 DR. GRABOYS : I was mentioning to Lloyd  
18 Fisher and to Udho before lunch that people who drop  
19 out for an adverse event -- it is true at the time  
20 they drop out that the quality of life is bad. But  
21 they don't take the drug and it disappears. So this  
22 is not some longstanding effect on quality of life.

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1 It is very transient. They get no benefit from the  
2 drug because they are not taking it. But also, I  
3 don't think those adverse events are nearly as  
4 important because they are transient in this data  
5 base. It would be one thing if it was a stroke or  
6 something like that. so in that sense, that is not  
7 nearly as important clinically, because these people  
8 are not going to be taking the drug, whereas the  
9 people who are, if you have an adverse effect, then  
10 that is an effect on their life over a long time  
11 period. And I think you have to weight that in there.  
12 I don't -- I mean to me there is no change in quality  
13 of life and there is no benefit in **claudication**  
14 distance.

15 CHAIRPERSON PACKER: Yes, Milt?

16 DR. KONSTAM: I think I look at it a  
17 little differently from you. I think that the  
18 efficacy endpoints here relate to claudication and to  
19 what **effect** this drug has on how health-related  
20 quality **of life** is influenced by **claudication**. And I  
21 think that is the set of efficacy questions that I  
22 think we should be asking. And so then your point

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1 then becomes cogent to the extent that you might be  
2 concerned that the dropout rate is somehow occurring  
3 as a consequence of worsening claudication. If that  
4 were true, then that would be a bigger problem. But  
5 if we are not so concerned that that is very likely,  
6 then we may be okay here. Let me just finish. But  
7 the other issue is, well, but there are these other  
8 aspects of what makes a patient happy or what may be  
9 important. And Bob is saying, well these are actually  
10 adverse events that might be cataloged separately. I  
11 think that really would be what I would do. I would  
12 ask that question separately. Are we somehow under-  
13 gauging the overall adverse potential of this agent.  
14 But I am not concerned about the possibility that we  
15 are overestimating the efficacy benefit because of the  
16 dropout, because I think the efficacy resides in just  
17 the constrained portion of the overall quality of life  
18 question.

19 CHAIRPERSON PACKER: If I understood what  
20 the discussion was this morning, the benefits of  
21 measuring quality of life is not simply to reiterate  
22 the data which is obtained by an exercise time,

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1 because exercise time measures one aspect of quality  
2 of life and the WIQ measures another way of thinking  
3 about **claudication** tolerability. What I actually  
4 thought I heard about the SF-36 was it not only  
5 measures what people can do, but it measures the  
6 change in their general health that results from that.  
7 So that the assumption is that there is added value.  
8 There is incremental information that is being added  
9 here. It is not just reiterative of exercise  
10 **tolerance**. And if that is true then what you are  
11 saying is, look, intermittent claudication is getting  
12 better, so people are going to feel better because of  
13 that. But if the drug produces side effects that  
14 makes them feel worse, then the net effect on their  
15 general perception of health is not positive.

16 DR. KONSTAM: No, I think it is a little  
17 different from that. I think that the SF -- and Dr.  
18 Ware can comment on this. I think the SF-36 here, to  
19 the **extent** that it is looking at the efficacy  
20 **question**, it is actually looking at the same thing as  
21 the **treadmill** is but just looking at it a different  
22 way. And **then** besides that, it is looking at other

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1 things. And I think the question would then be is  
2 there some adverse thing going on that are affecting  
3 other things that may influence health-related quality  
4 of life. And that, I think, is an adverse effect.  
5 But I think to the extent that we are asking the  
6 efficacy question, the only place we are going to see  
7 an efficacy influence on the SF-36 is the same way  
8 that we **see** it on the treadmill, and that is that  
9 **claudication** gets less.

10 CHAIRPERSON PACKER: Maybe this is the  
11 best example -- and Bob, let me focus this because I  
12 think this is something that you have spoken to or  
13 about in the past. Just suppose you had a drug for  
14 the treatment of angina. Forget about this agent.  
15 And the drug relieved angina, but the drug caused  
16 fatigue -- a lot of fatigue. So that when you  
17 measured exercise time on the treadmill, it didn't get  
18 better because, yes, angina was relieved, but fatigue  
19 was produced, so the net result on the treadmill test  
20 was neutral. The sponsor, though, goes back and says,  
21 well, we didn't really mean total exercise time. We  
22 meant exercise time to angina. And if we look at

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1 exercise time to angina, that is prolonged. But total  
2 exercise time isn't because this drug produces  
3 fatigue. The analogy here is exactly the same.

4 DR. KONSTAM: No, I don't think it is.  
5 And the reason I don't think -- and I think you are  
6 really hitting on it. I don't think it is because I  
7 don't **think** that either headaches or diarrhea  
8 influences treadmill exercise time. So I think that  
9 the --

10 CHAIRPERSON PACKER: But it influences the  
11 instrument that we are talking about.

12 DR. KONSTAM: No, it doesn't.

13 DR. THADANI: How can you say that it  
14 doesn't affect it. If the guy is having diarrhea and  
15 a headache, he won't be able to walk on the treadmill.  
16 It will affect it. Do you mean to say if you are  
17 dehydrated you can walk the same distance?

18 DR. LIPICKY: But Milton, I need to  
19 comment **on** what you just said. That is not a standard  
20 angina exercise tolerance thing that you described.  
21 A standard exercise tolerance thing is everyone who  
22 enters the trial stops because they get angina. After

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1 the trial is over or after they are randomized,  
2 everyone stops for some symptom, which might be  
3 fatigue. **But** the total time is the time that counts,  
4 not the time to angina.

5 CHAIRPERSON PACKER: That is right. Which  
6 is why --

7 DR. LIPICKY: That is the same way that  
8 these tests were done, right?

9 CHAIRPERSON PACKER: No.

10 DR. LIPICKY: Yes.

11 CHAIRPERSON PACKER: No.

12 DR. LIPICKY: Yes.

13 CHAIRPERSON PACKER: No.

14 DR. LIPICKY: Yes.

15 DR. THADANI: Let's vote.

16 DR. LIPICKY: Everybody who entered and  
17 got randomized had intermittent **claudication** as their  
18 endpoint. for the reason to stop and then had symptom  
19 limited exercise after they were randomized, and it  
20 could have been fatigue and not intermittent  
21 **claudication**.

22 CHAIRPERSON PACKER: Tom?

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1 DR. GRABOYS: I think I can put closure on  
2 this and then we should move along. There are about  
3 4 million men out there recently put on Viagra whose  
4 quality of life has improved significantly. There is  
5 no question about that.

6 CHAIRPERSON PACKER : I thought you were  
7 going to put closure on this.

8 DR. GRABOYS: I am going to put closure on  
9 this. That was very authoritative. And in fact if  
10 this drug not only gave you an erection and improved  
11 intermittent claudication, then you would really have  
12 a winner. There is no question about that. But I am  
13 really trying to emphasize the fact that quality of  
14 life depends really upon the perception of what the  
15 problem is. so if the problem is some diarrhea  
16 because you get a little bit of intermittent  
17 claudication, well then it may be a toss up in terms  
18 of quality of life and maintaining the drug. On the  
19 other hand if the downside is a little bit of diarrhea  
20 but the upside, for example with Viagra, is so great,  
21 then you are just going to forget about that.

22 CHAIRPERSON PACKER: It is clear -- it is

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1 obvious I am not making my point clearly. You have a  
2 test. You may call it a treadmill test. You may call  
3 it a **quality** of life questionnaire. You designate the  
4 test as the variable that you are designating as a  
5 measure **of** efficacy. Performance on that test is how  
6 you judge whether the drug works. However, what  
7 effects that performance on the test is not only the  
8 ability of that drug to improve the symptom that  
9 influences the test, but is also the net result of any  
10 other factors that drug may have on the performance of  
11 that test. So if one does an exercise test and a drug  
12 relieves angina but produces fatigue, you get the net  
13 result of that. If you do a quality of life  
14 instrument and you get an improvement in quality of  
15 life because of the relief of claudication but an  
16 adverse effect because of headache and diarrhea, the  
17 instrument reflects the net result of that. The  
18 problem here is that the instrument was not measured  
19 at the times that headache and diarrhea were  
20 experienced, so you do not get the measurement of the  
21 adverse effect that should be combined with the  
22 beneficial effect to get a total assessment of quality

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1 of life. So that if you say the total treadmill time  
2 is your standard for angina trials or **claudication**  
3 trials, then you are melding together factors that can  
4 be good or bad as determinants of the variable. The  
5 same principle should apply to the SF-36, but the  
6 problem is that the SF-36 here wasn't assessed at the  
7 time patients dropped out because of side effects.

8 DR. TEMPLE: I still think it is mixing  
9 two things. If you really believed that diarrhea or  
10 something like that would interfere with function  
11 related to heart failure like ability to walk to the  
12 store and things like that, then that concern might be  
13 legitimate. But I think that is not the form those  
14 kinds of adverse reactions take. You can still walk  
15 to the store, it is just that you are having more  
16 stools than you want. And I guess I would again put  
17 them on somewhat different scales and also point out  
18 that there are ways to assess that. You can look at  
19 the adverse dropout rate. If you want an assessment  
20 of how much trouble that aspect of it is, that is the  
21 place to look. Those are people who have so much of  
22 something that they are unwilling to stay in the

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1 study, perhaps even in the face of improved exercise  
2 ability because they are unhappy with it. But the  
3 role -- I guess different people have different views  
4 of these. One of the things that a quality of life  
5 **assessment** kind of thing does is it gives some idea of  
6 what the measured benefit, which is not easy to  
7 translate into a clinical benefit, that is, increased  
8 ability to be on a treadmill, does to the person's  
9 actual life. I will give you an example. The drugs  
10 available for Alzheimer's disease to date have shown  
11 small effects on cognitive function with a very **well-**  
12 **defined and** well-developed scale, and it turns out  
13 that astute clinicians can also see some difference in  
14 them. So far, though, they haven't had any effect on  
15 so-called activities of daily living scales. And a  
16 lot of people would say that until you get something  
17 that actually moves that kind of scale, it is not so  
18 clear you have accomplished a great deal. One of the  
19 things **ADL** scales or quality of life scales of this  
20 kind can tell you is what the impact of this hard to  
21 define **change** in exercise that you measure has. It  
22 gives you one more look at the same thing. It is not

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1 that it gives you a different answer. They are both  
2 measuring something that is related to the same thing.  
3 But it does give you a look at what the impact on the  
4 person's existence with respect to the thing you are  
5 treating is. Personally, I wouldn't confuse that with  
6 the side effects. I would measure them, but I  
7 wouldn't try to put them on the same scale. I think  
8 you lose information that way, I think.

9 CHAIRPERSON PACKER: Bob, you have a  
10 situation of a drug here that in the patients who  
11 dropped out that they had an improvement in walk  
12 distance. Then the SF-36 measured at the time they  
13 had an improved walk distance would probably reflect  
14 an improvement in the scale. Let's just assume --  
15 reasonable.

16 DR. TEMPLE: Right. And that would be  
17 true.

18 CHAIRPERSON PACKER: Ten days later,  
19 between scheduled visits, they experience headache and  
20 diarrhea, and enough for them to say that any  
21 improvement that they may have experienced in trial  
22 because of the drug isn't worth it. They can't take

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1 it any more. They are dropping out. But they are  
2 recorded in the data base as having gotten better when  
3 they actually experienced side effects from the drug  
4 that adversely affected their quality of life.

5 DR. TEMPLE : Right. But that is not  
6 different from the fact that you do treadmills up to  
7 the point where someone drops out. If they drop out  
8 for an adverse event and their treadmill values were  
9 high beforehand, they still get credit for increased  
10 exercise, but they also get credit for an adverse  
11 dropout. They are two relevant things, but they are  
12 different things. There is no reason to put them on  
13 the -- you don't have to subtract the adverse dropouts  
14 from the people who improved on treadmill. You just  
15 need to know that there is a cost for the benefit. I  
16 mean it is what you have to do with every drug all the  
17 time. They all do some bad things and they all do  
18 some good things. This is no different.

19 DR. THADANI : so, Bob, you had a severe  
20 headache --

21 DR. TEMPLE : I wouldn't put them on the  
22 same sea;e, that is all. I wouldn't subtract one from

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1 the other.

2 DR. THADANI: If you had a migraine  
3 headache, you are not going to walk. Your walking  
4 distance is going to go down to zero. So YOU could  
5 argue that if the headache is severe and you are  
6 having diarrhea, it is going to affect your quality of  
7 life walk scale. The patient is going to be tired and  
8 rather than going a block, he might go half a block.  
9 So I **think** it applies to care too. I am not denying  
10 that. **But** I think if you are going to have the  
11 **totality** of the data, you should include those  
12 patients and probably include it if there is really a  
13 dropout because of the headache or diarrhea, which  
14 could definitely affect your walking test. I don't  
15 know if anybody has had severe diarrhea and then you  
16 try to walk, you don't. So I think it has a definite  
17 influence, and I think it should be imputed.

18 DR. TEMPLE: But let's take a hypothesis.  
19 Suppose you had a drug where you could actually tell  
20 it **improved** 50 percent of the people and that half of  
21 those people -- but also 50 percent of the people who  
22 took the drug couldn't stand it and had to drop out.

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1 Now what I would say you would want to know is -- but  
2 there are some people who improve and but **don't** drop  
3 out and there are some people who don't improve but do  
4 drop out and so on. It is a mixture. They are not  
5 overlapping. Now what I would think you would want to  
6 know about that is this drug improves people a lot but  
7 it also causes side effects that make a lot of people  
8 unable **to** tolerate it. And then you can rationally  
9 use the **drug**. It is not a problem. You don't have to  
10 subtract the 50 from the 50 and end up with zero.

11 DR. THADANI: But you ruin the  
12 randomization rules, though, because you are  
13 randomizing patients up front. This will be okay if  
14 you give a test dose and drop the patients out and we  
15 don't like that.

16 DR. TEMPLE: But see one rule could be I  
17 count -- I am going to take the fraction of people who  
18 improve and then I am going to take the fraction of  
19 people who have to drop out for an adverse effect. So  
20 one is 50 and the other is 50 and I decide at zero.  
21 That is not right. That is not what you want to do.  
22 You want **to** notice that there are two effects, one

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1 good and one bad. Sometimes they happen in the same  
2 person and then you have to figure out what happens.  
3 But if you know what the rate of both of them are, you  
4 know what to say to the patient about the drug and you  
5 know how to think about whether you want to use it.  
6 You have all the information you have and you don't  
7 need to put them on the same scale. That is really  
8 what this is about, whether you have to have one scale  
9 that summarizes everybody.

10 CHAIRPERSON PACKER: Rob and then Ray.

11 DR. CALIFF: At the risk of backing up  
12 Milton and therefore prolonging this even more than we  
13 already have, the reason I can't accept, Bob, your  
14 argument totally and believe that no matter what you  
15 do you have to impute something in-between the two  
16 extremes is that even if you don't have to account  
17 directly for the side effects, the fact is that those  
18 who drop out are not -- dropping out is not a random  
19 event. From the point of randomization, those who  
20 drop out are different from those who stay in. If you  
21 look at study after study, that has been well  
22 demonstrated. And in fact in most studies, those who

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1 are most. likely to drop out due to side effects or  
2 other things happening tend to be sicker patients from  
3 the baseline point, and that means you are left -- the  
4 most obvious case is heart failure, whether it is a  
5 dropout or dead, and you are left with healthier  
6 survivors. And when you do your analysis not  
7 accounting for dropouts in any way, just assuming that  
8 those patients never existed, you overestimate the  
9 effect of the drug on the health parameter that you  
10 are interested in. Now I agree that the extreme case  
11 of attributing the worst possible outcome for quality  
12 of life to those people is a mistake too. The answer,  
13 it seems to me, is obviously somewhere in-between. We  
14 are probably not going to resolve it today because  
15 there are hordes of biostatisticians around the  
16 country concocting models to deal with this and nobody  
17 is yet satisfied with an answer.

18 CHAIRPERSON PACKER: Ray?

19 DR. LIPICKY: I am not going to say  
20 anything, but I would suggest that we won't resolve it  
21 today. I said I don't really want to say anything,  
22 but I suggest we won't resolve this today and we

1 should move on. But I do want to ask one question  
2 that is yes and no. The exercise tolerance tests in  
3 this set of data were symptom-limited exercise  
4 tolerance, and the symptom limited thing for exercise  
5 at the time of randomization was intermittent  
6 **claudication**. After randomization, it was a **symptom**  
7 still. Sometimes it was intermittent **claudication** and  
8 sometimes it was something else. And that is a yes or  
9 no.

10 DR. CALIFF: Yes.

11 DR. LIPICKY: Okay.

12 CHAIRPERSON PACKER: Let's proceed with  
13 safety.

14 DR. INGENITO: Good afternoon. My name is  
15 Gary **Ingenito**, and I would like to review the safety  
16 of **cilostazol** for you. **Cilostazol** has been marketed  
17 overseas for ten years. During this time, more than  
18 850,000 patients have been prescribed the product.  
19 **Cilostazol** continues to be safely used for the  
20 treatment of vascular disease symptoms in those  
21 markets. The phase 3 trials provide data on over  
22 2,700 **patients** treated with **cilostazol**, placebo, or an

1 active comparator. Additionally, an ongoing open  
2 label trial provides safety information on patients  
3 who crossed over from double blind into long-term  
4 **cilostazol** therapy, up to four years. Patients  
5 continue to be followed in the ongoing open label  
6 trial.

7 A breakdown of the patient exposure in the  
8 double **blind** and open label trials is presented here.  
9 For up to six months, 776 patients were exposed.  
10 Between 6 months and one year, 495 patients, and for  
11 greater than one year, 542 patients have been exposed  
12 to **cilostazol**.

13 Treatment emergent adverse events include  
14 preexisting conditions which worsened during therapy,  
15 new events occurring on treatment or occurring 30 days  
16 following treatment. This display includes those  
17 adverse events, regardless of drug causality,  
18 occurring in greater than 3 percent of the total  
19 **cilostazol** population, and having a greater incidence  
20 in the 1,00 mg bid dose group versus placebo.

21 The most frequently reported adverse  
22 events were headache, diarrhea, and abnormal stools at

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1 32, 17, and 14 percent respectively in the total  
2 population. Other AE's in this population are shown  
3 in decreasing incidence here and on the next slide.  
4 A complete list of the adverse events is found in your  
5 briefing packet. All of these adverse events were  
6 generally reported as mild to moderate in severity.

7 Data on discontinuation of study  
8 medication due to adverse events is presented here.  
9 The mild to moderate nature of the adverse events is  
10 reflected in the need to increase the reporting  
11 sensitivity to greater than or equal to 1 percent.  
12 Had we left the threshold at 3 percent, only headache  
13 would have remained in the chart. Discontinuations  
14 for other adverse events ranged from 1 to 1.1 percent.

15 Serious adverse events were defined  
16 according to FDA criteria. The incidence of adverse  
17 events versus serious adverse events is shown here.  
18 The incidence of SAE'S decreased within each treatment  
19 group. For an overall comparison of 13 percent in  
20 **cilostazol** total, 12 percent in placebo, and 14  
21 percent in the pentoxifyline group. For any  
22 individual event defined as serious, the incidence was

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1 low and did not exceed 2 percent in the total  
2 **cilostazol** group. Based upon the underlying disease,  
3 intermittent **claudication**, patients are expected to  
4 have an increased risk of cardiovascular adverse  
5 events. We will explore these further.

6 In addition to the adverse event reports,  
7 a question was raised and we also had looked into the  
8 metabolism of **cilostazol** and its potential  
9 interactions with concomitant medications. We agree  
10 this is important information to appropriately label  
11 the product. I would therefore like to take a minute  
12 and ask **Dr.** Steven Bramer to present this critical  
13 data and respond to the question that was raised  
14 earlier today.

15 DR. BRAMER: Good afternoon. My name is  
16 Steven Bramer, and I am the director of  
17 pharmacokinetics and pharmacodynamics and metabolism  
18 for Otsuka. I would like to present a brief overview  
19 of drug metabolism and drug/drug interactions. We  
20 have been communicating with the FDA regarding these  
21 issues, and this afternoon I would like to address the  
22 questions they have posed.

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1                   We have carried out numerous studies in  
2           order to understand cilostazol's absorption,  
3           distribution, metabolism, and excretion in humans.  
4           **Cilostazol's** disposition in plasma was **well-**  
5           **characterized** by single dose and multiple dose  
6           **pharmacokinetic** studies in normal volunteers and in  
7           patients with peripheral arterial disease. Carbon-14  
8           labeled **cilostazol** masked balance studies identified  
9           metabolizes and routes of excretion. Only **cilostazol**  
10          and three of its metabolizes were found circulating in  
11          the plasma and warrant further exploration. These are  
12          **OPC-13015, OPC-13213, and OPC-13217.**

13                   In-vitro experiments involving recombinant  
14          DNA , abbreviated cDNA, and human liver microsomes  
15          identified the cytochrome P450 isozymes responsible  
16          for the metabolism of cilostazol and its metabolizes.  
17          **Cilostazol's** metabolism has been well-characterized.  
18          Based on the chemical structure in non-clinical  
19          results, there are possibly 11 expected metabolizes of  
20          cilostazol. However, the human carbon-14 labeled  
21          **cilostazol** Study revealed only two metabolizes found  
22          circulating in plasma -- OPC-13015 and OPC-13213. A

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1 third metabolize, OPC-13217, was only found in trace  
2 concentrations. These metabolizes were at 28 percent  
3 and 9 percent of cilostazol's systemic exposure.  
4 **Cytochrome** P450, abbreviated CYP, isozymes are a  
5 clinical concern regarding drug/drug interactions.  
6 **Cilostazol's** metabolism is primarily by **CYP3A4** and to  
7 a lesser extent by **CYP2C19**, and even to a **lesser**  
8 extent by **CYP182**.

9 We have studied the inhibition of  
10 **cilostazol's** metabolism clinically by probe drugs  
11 known to inhibit specific cytochrome P450 isozymes.  
12 **Erythromycin**, an inhibitor of **CYP3A4**, increased  
13 **cilostazol** systemic exposure measured by AUC and Cmax  
14 by 73 percent and 47 percent respectively. Also  
15 **omeprazole**, inhibitor of **CYP2C19**, increased **cilostazol**  
16 AUC and Cmax by 26 percent and 18 percent  
17 respectively. CDNA data suggested that **CYP2D6** may be  
18 involved in the metabolism of **cilostazol**. However,  
19 **quinidine**, a very important inhibitor of **CYP2D6**, had  
20 no impact on the metabolism of **cilostazol**. These  
21 findings are consistent with in-vitro metabolism  
22 studies.

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In addition to the work I just summarized regarding drugs that may inhibit **cilostazol's** metabolism, we also look at **cilostazol** as an inhibitor of metabolism. One of the questions raised by the FDA is whether or not **cilostazol** is an inhibitor of CYP3A4 . The cDNA data suggest that 50 percent inhibition of CYP3A4 will occur at plasma concentrations two to six-fold greater than the mean maximum plasma concentrations observed clinically. However, the human liver complete **microsomal** preparations show that **cilostazol** is not an inhibitor of CYP3A4 at concentrations studied up to 28-fold greater than the maximum clinical plasma concentrations in a more complex and physiological based system.

Hepatic microsomal results more closely represent the intact human liver. In addition, the results from a clinical interaction study support the **microsomal** results that **cilostazol** is not an inhibitor of CYP3A4.

I would like to discuss the appropriateness of our war friend to detect CYP3A4

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1 inhibition. 20 percent metabolism of R-warfarin by  
2 CYP 3.84 is based on a point estimate from one paper  
3 published by Bill Treger.

4 Interaction with diltiazem and **fluconazole**  
5 results in greater than 20 percent and 52 percent  
6 decrease in R-warfarin clearance. KI, the  
7 concentration necessary to cause 50 percent inhibition  
8 of **CYP3A4** shown here in parenthesis for **diltiazem** and  
9 for **fluconazole**. Keep in mind the smaller the KI, the  
10 more potent the inhibitor. Please note that **diltiazem**  
11 is an inhibitor of CYP3A4 and increases **cilostazol**  
12 concentrations as agrees with the **microsomal** data.  
13 Our analytical assay had a sensitivity of 3 nanograms  
14 per ml versus the previous referenced studies which  
15 had an assay sensitivity of 100 nanograms per ml. Our  
16 study had greater than 80 percent power to detect a 9  
17 percent difference in R-warfarin clearance and an  
18 alpha equal to .05. In addition, the **microsomal** data  
19 shows that **cilostazol** is not an inhibitor of **CYP3A4** or  
20 any of the other isozymes.

21 R-warfarin is a weak substrate of **CYP3A4**,  
22 and several published results that have shown

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1 previously have shown that inhibition of CYP3A4 leads  
2 to increased R-warfarin concentrations. To test the  
3 losses on its metabolize effects on **CYP3A4**, the impact  
4 of **R-warfarin** concentrations were assessed. If  
5 **cilostazol** and its metabolizes inhibited **CYP3A4**, **R-**  
6 **warfarin** concentrations would have increased.  
7 However, **cilostazol** and its metabolizes had no effect  
8 on R-warfarin concentrations and thus do not inhibit  
9 CYP3A4 .

10 The metabolism of **cilostazol** has been well  
11 **characterized**. The plasma concentrations of  
12 **cilostazol** are increased by drugs that are inhibitors  
13 of CYP3A4 and CYP2C19. **Cilostazol** does not inhibit  
14 **cytochrome P450** isozymes as shown by the CYP3A4  
15 example. We recommend a dose adjustment when **co-**  
16 **administering cilostazol** with inhibitors of CYP3A4 and  
17 **CYP2C19**.

18 We have discussed phase 1 drug/drug  
19 interaction studies listed on the slide. Additional  
20 analyses were carried out on the phase 3 population  
21 data where we looked at the safety profile of  
22 **cilostazol** coadministered with other medications.

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1       **Shown** here are the most frequent type of conmeds  
2       **administered** during our phase 3 trials. As you can  
3       see, there is a large number of individuals that were  
4       exposed to calcium channel blockers, beta blockers,  
5       nitrovasodilators, beta-selective agonists,  
6       **vasodilators**, the ACE inhibitors, Digoxin, and **H1**  
7       **receptor** antagonists. Drugs that fall into these  
8       categories are either P450 substrates or could be P45  
9       inhibitors.

10               Shown here is the list of CYP3A4  
11       inhibitors coadministered during our phase 3 trials.  
12       Our analysis showed a 50 percent increase in  
13       **cilostazol** concentrations upon coadministering  
14       diltiazem. However, there are no remarkable  
15       differences in the adverse event profiles as shown on  
16       the next slide.

17               We have looked at the type, incidence, and  
18       severity of adverse events and found coadministration  
19       with **diltiazem** to be well tolerated. There were no  
20       greater incidence of serious adverse events  
21       **contributable** to coadministration with **diltiazem**.

22               Shown here are the five most frequent

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1 adverse events associated with **cilostazol**. There were  
2 no greater incidence of headaches, diarrhea, and  
3 abnormal stools. Compared to on or off conmed and  
4 compared to placebo, there appears to be a slight  
5 trend for an increased incidence of palpitations and  
6 dizziness.

7 A similar approach to the data is shown  
8 here following coadministration of **cilostazol** with  
9 P450 inhibitors as a group. There was no greater  
10 incidence of serious adverse events in patients taking  
11 P450 inhibitors. There appeared to be a slightly  
12 greater incidence of palpitations upon coadministering  
13 these drugs. Therefore, caution is recommended when  
14 coadministering CYP3A4 inhibitors with **cilostazol**.  
15 That concludes my presentation.

16 CHAIRPERSON PACKER: I know we are going  
17 to go over more safety data, but I just wanted to find  
18 out if the committee had any specific questions on the  
19 **pharmacokinetics**. JoAnn?

20 DR. LINDENFELD: I just didn't understand.  
21 The **R-warfarin** data, what model was that in? How was  
22 that done?

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1 DR. BRAMER: I am sorry, I couldn't hear  
2 your question.

3 DR. LINDENFELD: The R-warfarin, what  
4 model system was that? I missed that. You showed  
5 that R-warfarin levels did not increase --

6 DR. BRAMER: R-warfarin is metabolized by  
7 CYP3A4 .

8 DR. LINDENFELD: Right. But tell me how  
9 that was done, just the mechanics of that quickly.  
10 Normal volunteers?

11 DR. BRAMER: Oh, it was basically, we  
12 had a priming dose of warfarin and then we had a  
13 single dose pharmacokinetic profile of warfarin. We  
14 gave cilostazol, multiple dosing for a period of time,  
15 and then we looked at the R-warfarin pharmacokinetic  
16 profile again. So we compared R-warfarin before and  
17 after multiple dosing of cilostazol.

18 CHAIRPERSON PACKER: Bob?

19 DR. TEMPLE : One of the metabolizes is  
20 active and is maybe five times as potent or something  
21 like that?

22 DR. BRAMER: Correct. OPC .

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1 DR. TEMPLE: So if you think that and it  
2 is 9 percent of the total, then it is responsible for  
3 something like half the activity. What happens to  
4 that in the presence of **Erythromycin**, or actually it  
5 would **be** more interesting to know what happens in the  
6 presence of **ketoconozol**, which I guess you don't have.

7 DR. BRAMER : We -- obviously -- we have  
8 looked at the metabolizes, **OPC13015** and **OPC13213** and  
9 **cilostazol** in all the drug/drug interaction studies --  
10 diltiazem, **Erythromycin**, **omeprazol**, and **quinidine**.  
11 And therefore, as expected, upon coadministration of  
12 **omeprazol** as an example, which inhibits the 2C19  
13 pathway, **we** had increased concentrations of **cilostazol**  
14 and decreased concentrations of **OPC13213**. That  
15 metabolize by that particular pathway. Similar  
16 results were observed as you inhibit 3A4. **OPC13015** is  
17 formed by the 3A4 pathway. And therefore, **cilostazol**  
18 concentration is increased and there was not a change  
19 in **OPC13015** concentrations.

20 DR. TEMPLE : Right. But you were also  
21 recommending decreasing the dose in the presence of  
22 certain things that increased the parent. But those



1 might decrease the metabolize. So it is not so clear  
2 that that is good advice.

3 DR. BRAMER: Actually, our recommendation  
4 was based upon a 73 percent increase in AUC. So what  
5 I recommended was a dose adjustment or starting dose  
6 of 50 mg, just based on comparison of AUC values.

7 DR. TEMPLE: But that is just AUC for the  
8 parent. It doesn't take into account the AUC for the  
9 metabolize, which may be responsible for half the  
10 activity. Maybe you are just being cautious, but that  
11 doesn't necessarily seem like it is so obvious.

12 DR. BRAMER: No, actually we were just  
13 being cautious.

14 DR. THADANI: A couple of questions. You  
15 give the drug concentration or metabolize  
16 concentration of your drug. What happens to the other  
17 drug concentrations such as diltiazem or other drugs?

18 DR. BRAMER : To answer your question,  
19 based on the microsomal data that Dr. Flockhart  
20 performed, which he is in the audience, we knew the  
21 pathways of metabolism of cilostazol. And therefore,  
22 we used probe drugs -- Erythromycin, which is a

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1 mechanism based on suicide inhibitor of 3A4, a very  
2 potent inhibitor, and we looked at the concentrations  
3 at steady state of Erythromycin. Therefore, we expect  
4 **Erythromycin** to have an impact on **cilostazol** and not  
5 vice **versa** based on the science. The same logic was  
6 followed for the other drug/drug interactions.

7 DR. THADANI: Have you any data on  
8 statins? Because in peripheral vascular disease, a  
9 lot of patients have dislipidemia. And is there any  
10 interaction with statins, which is also through 3A4?

11 DR. BRAMER : There is the potential for  
12 drug/drug interactions with other substrates of 3A4.  
13 But as **far** as looking at inhibitors of 3A4 or the  
14 other **isozymes**, we do not feel that there is any  
15 safety concerns.

16 DR. THADANI: Is there assurance without  
17 having data or do you think you need data or are you  
18 pretty sure there will be no interaction?

19 DR. BRAMER : Actually, I feel very  
20 confident that we know the interactions because we  
21 chose very potent inhibitors. As I mentioned before,  
22 quinidine is a very potent inhibitor of 2D6 .

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1 Erythromycin is a suicide inhibitor of 3A4. And  
2 quinidine is also a potent inhibitor of **2C19**. So  
3 based on understanding the metabolism, I feel fairly  
4 **confident** in making recommendations with inhibitors.

5 DR. THADANI: And other issues on safety,  
6 I don't know if somebody else is going to discuss  
7 about the QTC issue. Is somebody else going to deal  
8 with that?

9 DR. BRAMER: Dr. Ingenito will address the  
10 QTC issue if necessary.

11 DR. THADANI: Okay. There is some --  
12 obviously the heart rate goes up. You correct it  
13 different- ways, as you have told. Looking at the  
14 helter data, one of the difficulties you run into --

15 CHAIRPERSON PACKER: We have not heard the  
16 rest of the safety presentation, right?

17 DR. THADANI: All right.

18 CHAIRPERSON PACKER: So hold. I leana?

19 DR. PINA: My question was similar. It  
20 was about the statins. I know you know the concomitant  
21 therapy on the group of patients. Were there a lot of  
22 patients on statins? Because that is not mentioned.

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1 You have got calcium blockers, you have got beta  
2 blockers.

3 DR. BRAMER: Yes, give me one moment and  
4 I will answer your question.

5 DR. PINA: It is a population that I would  
6 expect that many of them would be on statins.

7 DR. BRAMER: Of the entire population, 29  
8 percent were on lipid-lowering agents which are  
9 predominantly the statins.

10 DR. THADANI: Which ones? Can you define  
11 which statins or no?

12 DR. BRAMER: I can give you a list of the  
13 statins if you like.

14 DR. TEMPLE : Only two of them are  
15 susceptible.

16 DR. THADANI: Yes, the lovostatin.

17 CHAIRPERSON PACKER: Bob?

18 DR. BRAMER : That was lovostatin,  
19 **sinstatin**, prevastatin, flustatin, and toravastatin.

20 DR. TEMPLE: But you don't actually have  
21 blood level measurements of those. You just know that  
22 they were given together and that nothing -- nobody

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1 had rabdomyelysis, say.

2 DR. BRAMER: Correct.

3 DR. TEMPLE: You have not done any actual  
4 in-vivo studies to look at interaction with drugs that  
5 are metabolized by say 3A4? You have deduced that  
6 from in-vitro studies in which you say you didn't see  
7 any inhibition of that pathway at relevant  
8 concentrations, is that correct?

9 DR. BRAMER: No. Let me correct that  
10 assumption. Because we have -- again, we understand  
11 inhibition of other drugs and their effects on  
12 cilostazol by looking at the Erythromycin study and  
13 the omeprazol study --

14 DR. TEMPLE: No, no. That is not what I  
15 am asking. Did you test for the inhibition of drugs  
16 that are metabolized by the 3A4 pathway like cisopride  
17 or synthetatin or something like that? And I think  
18 the answer was no, you did that in-vitro.

19 DR. BRAMER : Well, no. We have the R-  
20 warfariri study to show. R-warfarin is a weak  
21 substrate of 3A4. And therefore, in addition to the  
22 microsomal work which supports that cilostazol is not

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1 an inhibitor of 3A4 or other isozymes.

2 DR. TEMPLE: Okay. I guess I don't have  
3 data in mind to know what you would expect from a  
4 serious inhibitor of 3A4 on R-warfarin. Do you know?

5 DR. BRAMER: Take diltiazem as an example.

6 DR. TEMPLE: No, no. Take a really good  
7 inhibitor. Take ketoconazol.

8 DR. BRAMER : Ketoconazol is -- actually  
9 **diltiazem is** a very potent inhibitor of 3A4, more  
10 potent than ketoconazol. Ketoconazol is a broad-based  
11 inhibitor.

12 DR. TEMPLE: No, no. That is not **correct**.

13 DR. BRAMER: Diltiazem is a very specific  
14 inhibitor for 3A4 and its metabolizes are a specific  
15 inhibitor of 3A4.

16 DR. TEMPLE: I am sorry, the antifungal  
17 cause virtually 100 percent inhibition of that  
18 pathway. You can't get more potent than that. I mean  
19 I am speaking about data on trefenadine and things  
20 like that. But Erythromycin is not nearly as good an  
21 inhibitor as they are. Now I can't speak to **R-**  
22 warfarin because I haven't seen those data. But the

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1 usual 3A4 pathways, the ones that get you in trouble,  
2 I don't think diltiazem is nearly as strong on those,  
3 although it is a partial inhibitor.

4 DR. BRAMER : You mentioned **ketoconazol**.

5 I did make reference --

6 DR. TEMPLE : There are other people who  
7 know these things.

8 DR. BRAMER : You mentioned **ketoconazol**.

9 I did make reference to fluconazol, where we did see  
10 a 52 percent change in R-warfarin concentrations or  
11 clearance.

12 DR. TEMPLE: Okay. Fluconazol is not as  
13 good an inhibitor of 3A4 as itriconazol and  
14 ketoconazol, but it is something of an inhibitor.

15 DR. BRAMER : I would like to ask Dr.  
16 **Flockhart** to address this issue.

17 DR. FLOCKHART: Just to try and state it  
18 clearly, Bob. The clinical study that is being done  
19 has not been done with the statins that you described.  
20 The clinical study that has been done is giving  
21 **racemic warfarin** and then measuring the R-warfarin as  
22 a result. Now the precedents there are that -- there

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1 are four -- ketoconazol, Erythromycin, itriconazol,  
2 and diltiazem, all of which have effects on R-  
3 warfarin. From an in-vitro studies perspective, about  
4 20 to 30 percent of R-warfarin metabolism is by that  
5 route. It is by 3A. It is also metabolized by  
6 cytochrome P451A2 and some by 2C9. So it is not an  
7 ideal probe for 3A. But having said that, the answer  
8 to your question is if you use a high octane 3A  
9 inhibitor, you reduce the clearance of R-warfarin  
10 using ketoconazol or Erythromycin by about 50 percent.  
11 If you use diltiazem, it is about 20 to 30 percent,  
12 reflecting the fact that it is a weaker entity.

13 DR. TEMPLE: so that is not a really  
14 great probe for the capacity --

15 DR. FLOCKHART: It is not a perfect probe,  
16 but major league inhibitors -- big guns, the ones you  
17 get scared about, the ones that you guys all have on  
18 your warnings -- change it 40 to 50 percent. Weaker  
19 ones do. And in this study, cilostazol didn't change  
20 the R-warfarin at all.

21 DR. TEMPLE : Yes, that sounds somewhat  
22 reassuring. But if you wanted to have the most

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1 sensitive test of whether it could inhibit it, you  
2 would pick synthetatin, which goes up a nice 20-fold  
3 with --

4 DR. FLOCKHART: That would be the most  
5 sensitive.

6 DR. TEMPLE: You don't have to fool around  
7 with 30 percent.

8 DR. FLOCKHART: Right.

9 DR. TEMPLE: 2000 percent.

10 DR. FLOCKHART: Right.

11 DR. TEMPLE: Okay. So there is that and  
12 then there is also in-vitro data that make you feel  
13 that you need much more of the parent to get any  
14 inhibition, and that is why you think it is not going  
15 to inhibit that pathway much.

16 DR. FLOCKHART: I think the simple answer  
17 to the question is we don't absolutely know, but it  
18 seems very unlikely based on the in-vitro data which  
19 requires pretty high concentrations of cilostazol to  
20 inhibit 3A. In a setting I would point out -- and  
21 this is a very important point -- in exactly the same  
22 conditions where one does see inhibition by cilostazol

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of 2C19 and 2C9 probes at relatively high concentrations. so the argument that there is some kind of funky in-vitro thing going on here doesn't apply. Because there is enough free cilostazol around to inhibit a 2C9 probe and a 2C19 probe, but it doesn't touch a 3A probe.

DR. TEMPLE: Okay. That sounds relatively unlikely. Let me ask while you are there about the inhibition by 3A4 inhibitors. Erythromycin -- there may be some settings in which it is just as potent as the big guns, but in most it isn't. It gives you a 4 to 5-fold increase of synthestatin instead of a 20-fold increase. Even grapefruit juice does better than that. So if you have a 70 percent increase in area under the curve of the parent with Erythromycin, doesn't that suggest that one ought to at least know what the antifungal would do or a more potent inhibitor? That is not a hard thing to do.

DR. FLOCKHART: Yes, the reason we -- obviously it is not hard to do. But the reason we didn't do it in this setting is that as you are aware, ketoconazol in a clinical setting -- one of the

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1 reasons for its great potency is although in vitro, it  
2 is very specific and you use a very, very low  
3 concentration, in-vivo when it is given at 100 mg or  
4 200 mg by mouth twice a day, it is a **pleomorphic**  
5 inhibitor. It becomes a significant useful inhibitor  
6 of **2C19** and of 2C9, some of the **flavin** monostatin  
7 agents as well. Here we were going to figure out  
8 specifically if we nailed 3A what change we would get.  
9 And the size of the changes in the studies you report,  
10 Erythromycin universally is lower, but it is not  
11 always that big a difference. Often it is half as  
12 effective, for example, in the trefenadine studies as  
13 ketoconazol. So I think we were going for a more  
14 specific scientific answer to the question rather than  
15 the **huge** size effect. But we did have data that  
16 suggests that you are not looking at huge numbers  
17 here. **Because** you are not looking at a 14 to 24  
18 change in the AUC like you are with trefenadine.

19 DR. TEMPLE: And it also could be that the  
20 metabolize goes down instead of up.

21 DR. FLOCKHART: Exactly. A very good  
22 point. A very good point.

1 DR. TEMPLE : As a kind of protection, I  
2 suppose. ;

3 DR. FLOCKHART: Whatever the mechanism of  
4 the drug is. But it is possible its efficacy could be  
5 somewhat decreased by a decrease in the metabolize.

6 II DR. THADANI: You showed the palpitation  
7 incident goes higher on diltiazem.

8 DR. BRAMER: Correct.

9 DR. THADANI: What happened to the heart  
10 rate? Do you have any data? Because we heard that  
11 the drug can increase heart rate by 5 or 6 beats. I  
12 saw the sample size is very large, so I presume that  
13 is from **open** label studies, the data you showed. Have  
14 you any idea of the heart rate you should expect if  
15 you are on diltiazem? Will it go up to 20 beats or 15  
16 beats or what?

17 DR. BRAMER: No. Actually we did not see  
18 that subpopulation have a heart rate increase greater  
19 than what we have seen with the rest of the population  
20 that were not on diltiazem.

21 DR. THADANI: You expect the heart rate  
22 will go up if they are complaining of palpitations,

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1       though . In the 11 persons who had palpitations, the  
2       heart rate could be 20 or 30. I am just curious. You  
3       have no data on that?

4               DR. BRAMER : As to why the heart rate  
5 II       increases?

6               DR. THADANI: No, no. Actual heart rate  
7       data. All you said is symptoms of patients. Did the  
8       physicians look at the heart rate on patients who  
9       complained of palpitations?

10              DR. BRAMER: We -- actually there is -- we  
11       have looked at this data base, and we didn't see  
12       anything with these conmeds that would lead us to have  
13       a greater increase in heart rate.

14              CHAIRPERSON PACKER: Okay. Can we go on  
15       with the rest of the -- hold on one second. Can we go  
16       on with the rest of the presentation? In saying that,  
17       let me say that because of certain limitations in  
18       terms of the availability of this room, it really is  
19       critical that we begin the questions no later than  
20       3:15. And that means that we have to get through the  
21       committee questions on the safety issues. So if I  
22       could ask you to proceed with the safety issues, but

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1 for the sake of time you can skip some of the  
2 narratives which I see are coming up and we can  
3 hopefully get through much of this. Because I am sure  
4 the committee has some questions on the slides which  
5 are coming up.

6 DR. INGENITO: Very good. If I may take  
7 one second to clarify a point earlier about **cilostazol**  
8 pharmacology. Quickly, Dr. Califf had asked about the  
9 relevance of our in-vitro PDE<sub>3</sub> comparative studies.  
10 And clearly we have not fully defined the effects of  
11 **cilostazol** and its metabolizes on PDE<sub>3</sub> activity **or** the  
12 clinical implications of such activity. The reason we  
13 showed you the study was to suggest, as your following  
14 discussion also implied, that different PDE<sub>3</sub>  
15 inhibitors can differ in their effects on specific  
16 tissues even if they are similar to others. And  
17 therefore, while PDE<sub>3</sub> inhibition raises legitimate  
18 concerns, we can't necessarily draw specific  
19 inferences about the clinical effect merely from the  
20 presence of the inhibition. That was the only purpose  
21 in demonstrating that.

22 CHAIRPERSON PACKER: Nor can you provide

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1 reassurance from the data that you showed.

2 DR. INGENITO: Yes. The safety of  
3 **cilostazol** will be further examined in the target  
4 population through ECG, helter, cardiovascular  
5 morbidity, a review of cardiovascular mortality and  
6 all cause mortality as well as a brief review of the  
7 laboratory data.

8 Evaluation of the ECG parameters showed  
9 the PR interval and QRS interval as decreasing, and  
10 the QT interval also showing a decrease with the heart  
11 rate **having** an average 7 beat per minute increase.  
12 And as you can see, a dose-dependent increase across  
13 the three dose groups.

14 I have not included here the QTC  
15 information. However, I would be happy to do so if  
16 you would like. It was summarized in the briefing  
17 packet. would you like me to go into that, Mr.  
18 Chairman?

19 CHAIRPERSON PACKER: Yes.

20 DR. INGENITO: May I have back-up slide **H-**  
21 **29?** The patient population used in these clinical  
22 trials **was** evaluated at baseline prior to study drug

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1 treatment. They were evaluated for the model which  
2 allowed the most accurate QT correction. I would like  
3 to emphasize that this was prior to study drug  
4 treatment. This figure shows that at baseline, again  
5 prior to any treatment, Bazett's model had a slope of  
6 6.5 milliseconds for each 10 beat increase in heart  
7 rate. We have been aware that cilostazol produces an  
8 increase in heart rate, and this model may therefore  
9 overestimate the QTC.

10 If we look at other accepted models -- we  
11 reviewed Fredericias correction and found that it may  
12 underestimate the QTC as the slope of the line  
13 decreases with the increasing heart rate.

14 Linear regression as a correction for QT  
15 versus heart rate appeared to give the most accurate  
16 correction when evaluated prior to drug treatment.

17 To summarize the QTC data, we see that by  
18 the three methods in the cilostazol total group, a  
19 modest increase of 5.2 milliseconds if you use  
20 Bazett's, a decrease of 1.8 milliseconds by  
21 **Fredericias**, and a change of .1 milliseconds using the  
22 linear regression.

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1                   Please return to core slide 11. In  
2 addition, we conducted 24-hour helter monitoring in  
3 two protocols, 92202 and 95201. We evaluated the  
4 increase in ventricular premature beats per hour  
5 according to published criteria. The percent of  
6 patients meeting this criteria was 4.4 percent in the  
7 **cilostazol** group versus 1.2 percent in the placebo  
8 group, producing a non-significant P value of .3. We  
9 also examined non-sustained ventricular tachycardia.  
10 Patients were evaluated for meeting the criteria of  
11 both new or increased non-sustained V-tat. Out of the  
12 **cilostazol** patients who had a baseline and **post-**  
13 **baseline** helter, 12.8 percent met the criteria. out  
14 of the placebo patients, 7.1 percent met the criteria.  
15 This gave a P value of .2. However, it was noted that  
16 in 18 of the 23 patients who had either new or  
17 increased non-sustained ventricular tachycardia on  
18 **cilostazol** and who had more than one helter, in 14 of  
19 the 18 patients, the presence of new or increased **non-**  
20 **sustained** V-tat was not replicated in both helter  
21 **monitors** on drug. In 5 out of 6 patients in the  
22 placebo **group**, the same finding of lack of replication

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1 of the increase was noted. The data suggests that  
2 spontaneous variability may in part explain these  
3 findings. However, a direct effect of **cilostazol**  
4 cannot **be** excluded.

5 We searched the data base for two cases of  
6 sustained ventricular tachycardia. These are  
7 described in the narratives presented here. One case  
8 of sustained VT was on **cilostazol** 150 mg, and the  
9 second case was identified in our data base on  
10 placebo, both patients having a similar case history.

11 We further evaluated adverse event reports  
12 of arrhythmia and possibly related events through the  
13 phase 3 trials. If we looked at reports of  
14 ventricular tachycardia, you see .4 percent **cilostazol**  
15 and .3 percent placebo. V-fib .1 percent in both  
16 groups. Syncope is .7 in **cilostazol** and .5 in  
17 placebo. Convulsions, none in **cilostazol** and .2 in  
18 placebo. And for atrial fibrillation reports, .9 in  
19 **cilostazol** and .7 in placebo, and 1.7 in  
20 pentoxifyline.

21 Cardiovascular morbidity, that is, non-  
22 fatal myocardial infarctions and strokes revealed no

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1 difference in the incidence between the **cilostazol** and  
2 the placebo groups, being at 1.2 percent for MIs and  
3 .5 percent for strokes.

4 Cardiovascular and all-cause mortality are  
5 presented here. To date this represents the largest  
6 data **base** of controlled clinical trials for  
7 intermittent claudication. The cardiovascular  
8 mortality incidence is .6 percent in the total  
9 **cilostazol** group, .5 percent for placebo, and was .6  
10 percent in **pentoxifyline**.

11 . If I may clarify a few of the points on  
12 these slides that were reasons. These were listed by  
13 the investigator as the cause of death. In the  
14 ventricular fibrillation, this patient was status post  
15 coronary bypass surgery and was off drug for 8 days.  
16 Kidney failure you see here as a cardiovascular event  
17 was listed. The patient underwent bypass surgery and  
18 subsequent complications were renal failure and then  
19 ventricular fibrillation. And in the angina cases  
20 listed as mortality, one case was status post bypass  
21 surgery, and the other case was a patient who had  
22 reported to his physician angina and was evaluated and

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1 found to have obstructions, refused PTCA, went home  
2 and discontinued medication and died two days later.

3 If we include other events, we find that  
4 the mortality is .8 percent in the total cilostazol  
5 group, .7 percent for placebo, and .6 percent in the  
6 pentoxifyline group.

7 To summarize our review of laboratory  
8 data, lipid parameters were the only significantly  
9 different laboratory measurements between cilostazol  
10 and placebo-treated patients. As an example, an  
11 increase of 10 percent in HDL and a decrease in  
12 triglycerides of 30 percent was observed in study  
13 93201. I list this particular study because lipid  
14 changes were prespecified as an endpoint. However,  
15 this was reflective of our other clinical trials.

16 In conclusion, cilostazol has extensive  
17 clinical exposure. The adverse events we saw were  
18 manageable, tolerable, and had comparable profiles in  
19 patients on cilostazol plus or minus various  
20 concomitant' medications. No significant lab  
21 abnormalities associated with cilostazol were  
22 observed, and the all cause mortality and

1 cardiovascular morbidity in the target population  
2 appeared comparable to placebo. Questions, sir?

3 CHAIRPERSON PACKER: We will begin with  
4 JoAnn.

5 DR. LINDENFELD: Let me start -- I want to  
6 come back to mortality, but just start with bleeding.  
7 It is mentioned a number of times in the reviews that  
8 both ticlopedine and warfarin are not allowed to be  
9 used in Japan with this drug because of an excess of  
10 gastric hemorrhages. Can you give us some idea of  
11 what the data is there?

12 DR. INGENITO: When we talked to our  
13 colleagues, our understanding is that it was more of  
14 a precautionary measure rather than having strict  
15 adverse event data showing an increased or dose effect  
16 with those two drugs.

17 " DR. LINDENFELD: Okay. And you have about  
18 -- as I understand it, about 1,000 patients who have  
19 also taken aspirin along with cilostazol?

20 DR. INGENITO: Yes.

21 DR. LUCEY: And there is no excess  
22 bleeding or problem there?

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1 DR. INGENITO: No, there is not. And I  
2 can actually provide you with the percentages.

3 DR. LINDENFELD: How about just the  
4 percentages. It is probably not enough numbers to be  
5 significant.

6 DR. INGENITO: Well, what we did was --  
7 because you are correct. There were not enough  
8 numbers if you just looked at hemorrhage as an event.  
9 So we actually -- if I may have back-up E-16 just to  
10 show you how we tried to evaluate this. We combined a  
11 number of COSTART terms. We took a lot of the terms  
12 which **would** code to various hemorrhages. This is the  
13 list of what we combined in our data base in order to  
14 get a significant number of patients who might have  
15 some form of hemorrhage. So we tried to take a  
16 conservative approach to this. And if I can go to  
17 slide E-18. Based upon that compilation of  
18 hemorrhage, when we looked at the total **cilostazol**, we  
19 had the rate on aspirin being 8 percent versus 6.9  
20 percent off aspirin and placebo is 12 percent versus  
21 4.9. So *we* did not see an increase in hemorrhage for  
22 those patients on aspirin versus off within the data

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1 base.

2 DR. LINDENFELD: Okay. And you have seen  
3 -- I know you showed your own mortality data, but I  
4 think you have probably seen Dr. Rodin's FDA analysis  
5 of mortality based on patient exposure, and although  
6 not significant, it shows a disturbing trend for  
7 increasing mortality with increased dose. Can you  
8 just comment on that a little bit or tell me if you  
9 agree or disagree with that?

10 DR. INGENITO: Sure. If we go back to the  
11 core slide on mortality and look at that slide for  
12 you. I think the difference that causes the  
13 appearance of a dose response -- you are referring to  
14 the .7, .9, and 1.1. In the overall incidence of  
15 events, this percentage is made up of one patient. So  
16 when we look at it in terms of crude incidence, you  
17 are seeing only one patient reflected there.

18 DR. LINDENFELD: Maybe we can get Dr.  
19 Rodin to comment on this. Because his point estimates  
20 really -- although the confidence intervals are wide,  
21 go up with increasing doses.

22 DR. RODIN: Dr. Rodin, FDA Cardio-Renal.

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1 I would have to check my report here for a second, but  
2 I know we have been in constant communication, so any  
3 discrepancies have had to have come up and been spoken  
4 of. One thing to check on is whether we are dealing  
5 with the same total sample sizes because the data did  
6 continue to accrue over time. I will need -- I will  
7 look. But I know we have had enough conversations  
8 that any discrepancies should be well on your mind.  
9 But I will look but perhaps you can address it.

10 DR. LINDENFELD: Well, I think page 138 of  
11 your report.

12 DR. RODIN: Okay.

13 DR. LINDENFELD: Because I think this will  
14 be an important point. Although this is not  
15 statistically significant and again the confidence  
16 intervals a're wide. There is exposure, adjusted rate,  
17 placebo 1.9, 50 mg bid, 1.58, 100 mg 2.63, 150 mg 6.3.  
18 Again, not significant -- not even close, but maybe we  
19 could just have some comment about that.

20 DR. KAZEMPOUR: May I add the comment.  
21 The rates that you just mentioned are PEY adjusted,  
22 but the **ones** that you see over there are proportions.

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1 So there is a difference between those that you just  
2 mentioned because they are PEY adjusted.

3 DR. LINDENFELD: But they were adjusted  
4 because there was less exposure to cilostazol than in  
5 the placebo, is that right?

6 DR. KAZEMPOUR: In a controlled trial,  
7 they are parallel. But if you multiply them by about  
8 somewhere around 3. something -- because we run them  
9 for about a four month trial on average. They are 6  
10 months, **but** if you multiply them, you will get about  
11 the same increase. Because you are multiplying the  
12 difference that you observe over there between .7 and  
13 .8. When you multiply by about 4, you will get the  
14 same differences that you just mentioned.

15 DR. LINDENFELD: I guess what I am looking  
16 for is some reason not to be disturbed a little bit by  
17 this in a drug that has similar characteristics of  
18 others that increase mortality.

19 DR. INGENITO: In actuality, as Dr.  
20 Kazempour stated, the PEYs are similar as mean  
21 exposure per patient. It comes out to be  
22 approximately four months for both groups when you

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1 take it across the whole cilostazol population.

2 CHAIRPERSON PACKER: Dr. Rodin?

3 DR. RODIN: The best I can do right now  
4 unless you can identify a specific discrepancy for me  
5 to focus further on, I can describe my analysis. The  
6 sponsors produced this analysis for me. I know the  
7 dates. The confidence intervals are only shown in my  
8 analysis and not here. Is that a concern? Are these  
9 conference intervals correct? What is the discrepancy  
10 that is of concern here?

11 DR. CALIFF: You show a relative risk of  
12 1.3, which is not huge.

13 CHAIRPERSON PACKER: Maybe I need to ask  
14 everyone to tell me what they are asking. Because I  
15 am -- I think that the -- I don't think that anyone is  
16 saying that there is a difference between what the  
17 sponsor is showing and what the FDA review has shown.  
18 So I don't think we are looking for an explanation or  
19 an outline of any discrepancies. I think that what  
20 everyone is saying is pretty much the same thing,  
21 which is that at the lowest dose the observed  
22 incidence is 0.7 and then it goes to 0.9 and then it

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1 is 1.1, and that is not statistically significant. Is  
2 there any additional comment on that is the only  
3 question. I don't think we need to pursue whether  
4 there are discrepancies. Whether there are or not,  
5 you can settle later on.

6 DR. LIPICKY: But there are none. Those  
7 are exactly the same numbers. Someone may have  
8 written down that that looks like a dose response, and  
9 if they did, they shouldn't have.

10 CHAIRPERSON PACKER: Maybe I should ask  
11 the question just to follow-up from JoAnn in a  
12 different way. The point estimate that can be  
13 calculated from the data with very wide confidence  
14 intervals is a relative risk of 1.3?

15 DR. INGENITO: The relative risk is -- on  
16 the overall mortality?

17 CHAIRPERSON PACKER: Overall.

18 DR. INGENITO: Overall mortality relative  
19 risk, the difference is 1.3.

20 CHAIRPERSON PACKER: Okay. Now I guess we  
21 have to remind ourselves that as opposed to most  
22 controlled trials which come up with point estimates

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1 of **mortality** where all patients are followed for death  
2 until the end of the planned duration of therapy. The  
3 mortality **data** we have here is not for the intended  
4 duration of -- original intended duration of therapy.  
5 This is on therapy plus 30 days.

6 DR. INGENITO: We also followed the  
7 patients and accounted for all but 2 patients for the  
8 intended therapy duration.

9 CHAIRPERSON PACKER: Okay. And that has  
10 a point estimate of 1.3?

11 DR. INGENITO: Yes, sir.

12 CHAIRPERSON PACKER: Okay. Do you find  
13 that -- I understand this has huge confidence  
14 intervals that go probably as far as this room, but I  
15 guess I need to ask you do you find that reassuring,  
16 worrisome, or uninformative?

17 DR. INGENITO: I think when we look at the  
18 overall number of events, which is small, and we look  
19 at the confidence intervals there and we compare it to  
20 patients who have crossed over from placebo into open  
21 label and we follow our open label trial, which we  
22 followed patients there at 2, 4, 6, 8, 18, 20 -- every

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1 12 weeks after. So they are followed quite often in  
2 the open label and we are finding that the relative  
3 rate is staying fairly constant. I find that to have  
4 some reassurance.

5 CHAIRPERSON PACKER: Let me maybe ask the  
6 question a different way.

7 DR. INGENITO: Okay.

8 CHAIRPERSON PACKER : The most  
9 interpretable data on mortality is data that has a  
10 control group. If you look at the data that you have  
11 where you have a parallel control and you **look** at  
12 death, you come out with a point estimate of 1.3 with  
13 very, very wide confidence intervals. Do you find  
14 that to be worrisome, reassuring, or uninformative?  
15 Can you conclude anything from that?

16 DR. INGENITO: My conclusion is that I  
17 think we are certainly dealing with a  
18 phosphodiesterase inhibitor which has a negative  
19 history in patients with severe heart failure. And we  
20 as a sponsor agree that cilostazol should be  
21 contraindicated in patients with heart failure. In  
22 absolute terms, I think the point estimates suggest

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1 that the mortality in our target population may be  
2 greater than placebo by a small amount with a wide  
3 confidence interval. Based upon the benefit that you  
4 have seen in the previous presentations and  
5 understanding of the disease, it would be reasonable  
6 and not imprudent to, given the limited alternatives  
7 available --

8 CHAIRPERSON PACKER: I am sorry, I am not  
9 asking for a risk/benefit assessment.

10 DR. INGENITO: Okay.

11 CHAIRPERSON PACKER: I just want to know  
12 whether you think a point estimate of 1.3 with  
13 extremely wide confidence intervals is reassuring,  
14 worrisome, or uninformative. In other words, have you  
15 learned anything from a total of 20 events with  
16 confidence intervals that include the possibility of  
17 a 20-fold increase in mortality? What are the  
18 confidence intervals on the 1.3? I mean with 20  
19 events, they are going to be huge confidence  
20 intervals. I mean what I -- I think most of the time  
21 when we look at a small number of events, we conclude  
22 that we cannot conclude very much. And if you think

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1 that the point estimate teaches you something, because  
2 you must believe that the point estimate teaches you  
3 something because you seem to be reassured that it is  
4 close to 1. Let me just stay that a point estimate of  
5 1.3, if you believed it -- I don't know if I can  
6 possibly understand how one would believe it -- but if  
7 you believed that 1.3 were real, that would represent  
8 a 30 percent increase in mortality. And let me just  
9 remind you that in the Proms Study, **milrinone**, a  
10 phosphodiesterase inhibitor, was associated with a 28  
11 percent increase in mortality.

12 DR. INGENITO: And yet we are separating  
13 or we are really looking at in the mortality rates  
14 there a difference of .1 percent or actually .15. So  
15 1.5 events in 1,000 patients.

16 CHAIRPERSON PACKER: I think what you are  
17 saying **is** that you don't think it tells us very much.

18 DR. LIPICKY: Right. I think he is saying  
19 it is not informative.

20 CHAIRPERSON PACKER : It is not  
21 informative. That is fine.

22 DR. FISHER: Can I make a comment. This

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is one of the few times I didn't leap up on my own accord. I was pushed up by my colleagues. But there have been some --

CHAIRPERSON PACKER: That is a bad prognostic sign, Lloyd.

DR. FISHER: There have been some things learned. The first thing I have learned is the event rate is relatively low and I would -- having had the benefit of hearing Jeff Borer's talk, I would suggest that you wait until he talks because he will address this somewhat. Because you cannot talk about risk benefit without thinking about it. Now if this were not a PDE<sub>3</sub> inhibitor, we actually wouldn't even be having this discussion. But there is rational reason in some populations that anybody familiar with cardiology is going to be worried. So I find it uninformative, but having been involved in some of the same trials as Milt, I have some of the same emotional reactions. so it is a low rate, but you certainly cannot rule out within this low rate. So the absolute difference may not be tremendously large, but the relative risk might be moderately substantial as

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1 suggested, and it is uninformative for that. There  
2 just aren't enough events.

3 CHAIRPERSON PACKER: Yes, I think the most  
4 important point is when you have very little data, you  
5 can reach very few conclusions.

6 DR. CALIFF: Right. But there is a  
7 critical issue which is does the underlying event rate  
8 represent what is going to happen if this drug is  
9 turned loose on people with claudication. Because if  
10 it does, then although it is uninformative as to the  
11 true relative risk, it is pretty informative that  
12 there is not a whole lot to worry about. If this was  
13 really the true underlying event rate. But if the  
14 underlying event rate in the population of interest in  
15 the real world is much higher and you have the same  
16 sort of modest concern about relative risk, it is a  
17 different issue.

18 DR. FISHER: Yes, I would agree with that.  
19 But I would suggest that you get on to Jeff's talk  
20 because for one thing, we are really tight for time.  
21 And then he will address these issues from his point  
22 of view and then you can debate it. It comes up in

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1 the questions again, of course, too.

2 CHAIRPERSON PACKER: Lem, did you have a  
3 question'?

4 DR. MOYE: Just briefly. How many adverse  
5 events **post-6** months follow-up come from a double  
6 blind placebo-controlled environment?

7 DR. INGENITO: I didn't hear your  
8 question.

9 DR. MOYE: How many adverse events post-6  
10 months follow-up come from a double blind **placebo-**  
11 controlled environment?

12 DR. INGENITO: Post-6 months?

13 DR. MOYE: Post-6 months.

14 DR. INGENITO: From the double blind  
15 placebo-controlled?

16 DR. MOYE: Yes.

17 DR. INGENITO: The longest trials were six  
18 months and then we actively tried to collect any  
19 adverse events within 30 days after.

20 DR. MOYE: 30 days afterwards. Okay.

21 DR. INGENITO: 30 days after, yes.

22 DR. MOYE: But the issue on the table that

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1       **we will** eventually have to address is not six months  
2 plus 30 day label. It is long term label, **isn't** that  
3 correct?

4                   DR. INGENITO: Yes.

5                   DR. MOYE: Okay. So I really am concerned  
6 about this issue of uninformative. I mean I agree  
7 that saying anything about a rate of 1.1 or 1.3 is  
8 uninformative. But I think we do have to have some  
9 information about potential long-term **sequelae** if we  
10 are providing a long-term label. I mean we are  
11 talking about chronic therapy here, and we don't have  
12 any information that I have been able to discern  
13 dealing with long-term consequences, of the 8 trials  
14 that were done, which has to be a record in  
15 somebody's book. Of the 8 trials that were done, not  
16 one **looks** at long-term issues, yet we are looking at  
17 long-term labeling.

18                   DR. LIPICKY: But you never have that  
19 data, Lem, for almost anything.

20                   DR. MOYE: I know, and I am never happy.

21                   DR. LIPICKY: Right. I understand. So  
22 that is fine.

1 DR. THADANI: Also one of the issues is  
2 you wouldn't say the risk ratio is 1.3 to 1. A lot of  
3 these patients with peripheral vascular disease have  
4 cardio disease. And when you throw it in the open  
5 market, **some of** them are going to have **asymptomatic** LV  
6 dysfunction. And that might be more prone to problems  
7 as has been previously reported with this class of  
8 drugs. So I think one can't be reassured when you are  
9 going to throw it in the open population of which way  
10 it is going to go. So does one need a trial of 20,000  
11 patients to address this? That is a different issue.  
12 Perhaps your drug looks so good and if it also affects  
13 platelet function maybe that is the way to go. But I  
14 think those are issues which have to be -- at least  
15 the committee members would like to be reassured of.

16 CHAIRPERSON PACKER: Bob?

17 DR. TEMPLE : One of the adverse  
18 consequences of the good instincts expressed  
19 repeatedly to look at all events is that we now see a  
20 bunch of deaths, some of which are not very plausible,  
21 and we **don't** even try to analyze the cause of death.  
22 Now I **don't** want to overdo that and say that you

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1 should believe everything you think you see, but it  
2 does seem looking at them. One of them says accident.  
3 I mean I would like to know a little more, if a person  
4 was a passenger say, probably the drug didn't do it.  
5 Or some of them are called oncologic deaths. I would  
6 like to know a little more. You can die suddenly of  
7 a cardiovascular thing even though you have a cancer,  
8 but there may be something to learn from some of those  
9 and some of them are post-procedural deaths. so you  
10 could link that, I suppose, to the thing that led to  
11 the procedure, but that may not be the same as the  
12 things we are worried about when you are talking about  
13 a phosphodiesterase inhibitor. So I guess I would  
14 think you might want to say something and our people  
15 eventually might want to say something about the  
16 specific ways these people died because that may be  
17 relevant here.

18 CHAIRPERSON PACKER: Can we go on to  
19 another question that came up and could I ask the  
20 sponsor to have someone who knows more about the ways  
21 that one can correct for the QT interval to talk about  
22 the three methods? Because in taking a brief survey

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1 of the committee, no one on the committee wanted to  
2 volunteer to discuss those three methods. So could  
3 someone do that briefly? I think it would be fair to  
4 say that some of us hadn't -- didn't even know there  
5 were three methods.

6 DR. MORGANROTH: My name is Joel  
7 Morganroth. The traditional method of correcting the  
8 QT interval, which is obviously dependent on heart  
9 rate, is to take that QT measurement and extrapolate  
10 it to what that QT duration would be at a heart rate  
11 of 60. In order to do that, you apply the 1929, which  
12 was when Dr. Bazett came up with this principle, and  
13 it is essentially a square root function. And that is  
14 what is traditionally programmed into almost all EKG  
15 machines and it is what everyone generally does.

16 As you saw from the slope of the graph  
17 that shows you what heart rate corrections would do at  
18 various heart rates, it is clear that when you become  
19 tachycardic that the Bazett formula is not very  
20 precise in extrapolating down to what that QT duration  
21 would be at a heart rate of 60. And so others like  
22 Dr. Fredericia from Europe said the best way to do it

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1 is with his formula, which is a cubed root function,  
2 and when you do that, you essentially get the opposite  
3 effect. You get a slightly different correction that  
4 isn't as precise at high heart rates and may be better  
5 at slower heart rates.

6 The linear regression model essentially --  
7 Sagi reported on this -- essentially takes a linear  
8 regression statistical approach against all heart  
9 rates over time, and you tend to get a better  
10 correction. It is a very complicated formula, so  
11 almost nobody uses it. And you saw the results of  
12 that slope was pretty flat.

13 This is an interesting drug because it  
14 does have an increase in heart rate that is fairly, I  
15 wouldn't say huge, but 7 beats per minute isn't small  
16 either. And it therefore affects the QT interval.  
17 And if you just look at the QT interval, you saw it  
18 actually decreases. So here is a drug that decreases  
19 the QT interval virtually at the heart rates that are  
20 seen in this study, which is averaged at a 7 beat per  
21 minute increase, and yet when you apply the  
22 traditional garden variety Bazett formula, you get

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1 this **small** increase of 5 milliseconds. But when you  
2 use the other corrections, you get either a shorter **QT**  
3 interval by Fredericia or a no effect on the QT.

4 So we generally, having talked about this  
5 -- Dr. Ruskin, Dr. Moss, and myself and all having had  
6 different subsets of experiences with drugs and **QT**  
7 intervals -- sort of concluded that this doesn't  
8 appear to **be** an important issue relative to looking at  
9 depolarization issues and torsad du point and the  
10 usual things that you do with drugs that prolong the  
11 **QT** on the basis of the fact that at least two out of  
12 the three formulas seem not to show a prolonged QTC  
13 and even the one that is traditionally used didn't  
14 show very much of a QTC change.

15 DR. GRABOYS: Joel, are you going to be  
16 the spokesman for the company on this? Or who should  
17 I address.

18 DR. MORGANROTH: Well ask your question  
19 and I may or may not answer it.

20 DR. GRABOYS: Well, there is a couple of  
21 things. One is when I looked over this data, I was  
22 really **upset** that there was no **preclinical**



1 pharmacology at all. I mean, there was nothing on  
2 animal cardiograms. There was nothing on animal  
3 action potentials. So that there was really no  
4 background. If the company had presented some of that  
5 stuff, I think we could accept these mean data with a  
6 little more confidence. But what you are really  
7 looking at with these curves is you are just looking  
8 at the means and I don't see any data about how many  
9 -- I mean, we know this isn't sodalol. I mean, are  
10 there people in the group who had greater than 30  
11 millisecond changes? Are there people who had greater  
12 than 60 millisecond changes? Those are the people who  
13 are likely to get torsad, and I don't care how you  
14 correct it if you want to look for those changes.

15 DR. MORGANROTH: I will say that when one  
16 looked at the categorical changes as I call them --  
17 you know, greater than 20 percent or greater than 500  
18 millisecond absolute when you didn't have that at  
19 baseline -- there was no signal of any QT  
20 depolarization effect. The only signal came on the  
21 mean whet? you used Bazett's up to 5 milliseconds. And  
22 I can't answer why in the preclinical they didn't do

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1 this before they went into clinical. I guess at the  
2 time they started, it wasn't as routine to do that as  
3 it is now. And since they never saw anything in the  
4 clinical area and no one raised the issue, they didn't  
5 go back to do it would be my guess. But they could  
6 obviously be --

7 DR. GRABOYS: What are the actual data  
8 about changes over -- I mean, I thought someplace in  
9 the thing that they had -- almost everybody who had  
10 prolongations to greater than 500 were on drug. It  
11 was like 1.5 percent on drug and zero maybe,  
12 Arthur, you could report.

13 CHAIRPERSON PACKER: Maybe Art knows that  
14 data.

15 DR. MOSS: Dr. Moss. We looked at all of  
16 the QT interval data and particularly looked at all of  
17 the patients who were identified as having a QT  
18 interval as read as being greater than 500  
19 milliseconds at any time, but in particular after drug  
20 initiation. There were 13 such patients. 12 of the  
21 13 had either left bundle branch block or pacemaker,  
22 so that there turned out to be only one patient out of

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1 the 13 that had modest QT prolongation. There is also  
2 no significant morphologic change in the  
3 repolarization. And I think because of the prior  
4 experience that they had with the drug where they had  
5 never identified Torsad or QT prolongation, that I  
6 suspect that that was why there were no animal  
7 studies. I came into this long after that, but I  
8 suspect that was the rationale.

9 DR. THADANI: On one of the slides they  
10 showed, I thought I saw several patients above 500  
11 QTC .

12 DR. MOSS: They showed them around 560.

13 DR. THADANI: Yes. That is what I was  
14 interested in. You showed dots on one of the graphs  
15 of three corrected models and there were several  
16 patients above 500, somewhere around 560. So I know  
17 the drug is causing tachycardia. But is there any  
18 correlation of the three methods with actual Torsad,  
19 or is it only the Bazett's formula that has been  
20 evaluated in the past?

21 DR. MOSS : You mean unrelated to this  
22 study because there were --

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1 DR. THADANI: No, say unrelated to this  
2 study . If you took all of the studies which have been  
3 published with prolonged QTC, most of the patient  
4 people have used corrected QTC. Now we are bringing  
5 in two new formulas. Is there any information on the  
6 clinical outcome of those new formulas versus the  
7 Bazett's?

8 DR. MOSS: No. The Bazett is the one most  
9 traditionally used here in the United States.

10 DR. THADANI: So we should rely on that?

11 DR. MOSS: And the linear regression was  
12 also an outgrowth of the Framingham study. The  
13 Fredericia tends to be used a little bit more  
14 frequently in Europe, but generally I would say 80 to  
15 90 percent are still Bazett in all the published  
16 literature.

17 DR. THADANI: So if you took **sodalol**,  
18 quinidine, peparin --

19 DR. MOSS: It is all based on Bazett.

20 DR. THADANI: So that the others are  
21 superfluous. Are we camouflaging by showing other  
22 data when there is no data on that -- clinical outcome

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1 data?

2 DR. MOSS : Well there is data on the  
3 length of the QT and the relationship.

4 DR. THADANI: I realize that, but no  
5 outcome data.

6 DR. MOSS: No outcome --

7 DR. THADANI: No outcome in Torsad terms?

8 DR. MOSS: Yes, there is unrelated to this  
9 study . If you want me to comment on it, I will be  
10 glad to. But fundamentally there is an exponential  
11 relationship between the length of the QT interval and  
12 the risk of developing Torsad, and this has been  
13 reported out in a meeting that Dr. Lipicky was at in  
14 Philadelphia several years ago. But that is the only  
15 information that we really have between QT  
16 prolongation by Bazett and Torsad.

17 DR. THADANI: Sure.

18 CHAIRPERSON PACKER: Maybe I can ask one  
19 question, Jeremy, before you start. Does anyone --  
20 milrinone increased heart rate about 7 beats per  
21 minute in its trials. So a very similar increase is  
22 seen with this drug. But I never -- I guess I can't

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1 remember that the issue of QT ever came up with  
2 **milrinone**. I assume that it just didn't. Was that  
3 because **no** one actually measured the QTC?

4 DR. L.PICKY: I think that is the case.

5 CHAIRPERSON PACKER: Okay.

6 DR. RUSKIN: Jeremy Ruskin. Just a brief  
7 comment. **It** is important to point out that there is  
8 still some debate about what is more significant  
9 clinically, the absolute QT or the QTC. And in fact  
10 in Europe, regulatory bodies are relying more on the  
11 absolute QT. So I don't pretend to have an answer to  
12 that, but it is important to point out that there is  
13 nothing sacrosanct about the QTC. And it is  
14 interesting that this drug, in terms of what happens  
15 when you give it to patients, is that the QT comes  
16 down -- the absolute QT interval shortens.

17 DR. THADANI: But if you are treating a  
18 patient -- say if I put a patient on a drug, I know  
19 absolute QT is important, but say QTC goes up to above  
20 500, wouldn't you be worried and stop the drug in case  
21 the patient goes on some drug which causes bradycardia  
22 and induces Torsad? It may be at that point, but if

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1 something happens.

2 DR. RUSKIN: Yes, I think I would. Other  
3 things being equal, I think I would be concerned about  
4 that.

5 CHAIRPERSON PACKER: Okay. Anybody else  
6 on the committee have any questions about safety?  
7 Alan?

8 DR. HIRSCH: One very quick question. I  
9 didn't see the blood pressure data presented.  
10 Whenever I see heart rate go up 5 to 7 beats a minute,  
11 I like to know the systolic and diastolic blood  
12 pressure response with a vasodilator. Do you have  
13 that data?

14 DR. INGENITO: There appeared to be a  
15 minimal decrease of approximately 6 mm of mercury, 3  
16 to 5 mm in the systolic blood pressure and no change  
17 in the diastolic blood pressure in our population.

18 CHAIRPERSON PACKER: Does anyone else have  
19 any questions about safety? Why don't we go on to Dr.  
20 Borer's presentation. Jeff, I know you have lots of  
21 receptors for the time issue having been up here  
22 before and pressed for time. So we will ask you to do

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1 the best you can.

2 DR. BORER : I will try to do that. I  
3 won't be able to present the formal comments that I  
4 have in the time that I think you have left, but let  
5 me see if I can give you an overview. First of **all**,  
6 the data show that cilostazol consistently results in  
7 greater activity tolerance than placebo. The  
8 magnitude is pretty impressive and I think that  
9 translates into a meaningful improvement in quality of  
10 life, **not** just a statistical improvement. But yOU  
11 know that the drug approvability isn't based on  
12 efficacy only, but on the relation between efficacy  
13 and safety for the intended use.

14 The reason I am talking about these things  
15 is that I chaired the data and safety monitoring  
16 committee and the event adjudication committee **in**  
17 **blinded** fashion for the two largest trials. So I  
18 didn't perform the studies, but I had an unusual  
19 window on the data and it may be useful for you to  
20 hear what I think about them.

21 I am not a peripheral vascular disease  
22 expert, so I needed to transform these data in some

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1 way so I could understand them. And to do that, I  
2 used some of the ancillary analyses you have already  
3 heard. The two large trials that I was specifically  
4 monitoring are listed here. You have heard about them  
5 in great detail, and I don't want to go through the  
6 details again. The key point is that I come from New  
7 York and a typical city block in New York is 80 meters  
8 long. **With** an 80 meter block in that first big **trial**  
9 -- I am sorry, I will go back to it -- there was a one  
10 and a third block increase in walking distance, but it  
11 wasn't just one and a third blocks, it was one and a  
12 third blocks after placebo was subtracted on a  
13 treadmill that was at a constant uphill grade. Now  
14 using the usual METs relationship formulas that people  
15 in the field, which I am not, use, that treadmill  
16 grade made walking about three times more difficult  
17 than on flat ground. So if you use the usual  
18 transformations, on average that trial resulted in  
19 about a four block improvement in exercise tolerance  
20 if you are walking on the flat -- much less for some  
21 people but much more for some other people. You know,  
22 that is pretty good. And it was associated with the

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1 quality of life improvement, et cetera.

2 The important point here is that that is  
3 enough walking to be able to get people to  
4 **neighborhood stores** in the city or from their cars to  
5 stores in a suburban shopping mall or rural shopping  
6 mall or to walk to their seats in a baseball stadium  
7 or to walk to their seats in a theater, even if they  
8 had to walk up a moderately steep hill to do it.

9 In the other trial, the improvement -- the  
10 other trial used a slightly different treadmill  
11 protocol. There was clearly an improvement. It was  
12 about a half a block on treadmill, more than placebo.  
13 Also a half a block more than pentoxifyline on the  
14 same ramp treadmill protocol. So there is some  
15 variation here, but again the improvement was clear  
16 and it was seen.

17 I don't think this kind of **interstudy**  
18 variability is surprising, particularly when we are  
19 talking symptom-based endpoints, but I was concerned  
20 about it and Rob Califf mentioned this and Udho  
21 Thadani mentioned this and I had thought about it too.  
22 So to evaluate the drug, I figured we had to look at

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1 the variability. And for my own edification, I  
2 combined all the placebo control trials of at least 12  
3 weeks duration, that is the phase 3 trials, to look at  
4 the **average** change in walking distance on the  
5 treadmill. Now remember in addition to any of the  
6 flaws that were mentioned about this kind of  
7 combination, nonetheless it should be a conservative  
8 analysis because the data suggests that on **cilostazol**  
9 walking distance continues to increase for at least  
10 the 24 weeks on the long studies, and several of these  
11 studies were shorter than that. Also, some treadmill  
12 protocols were vigorous and some were more vigorous.  
13 All involved exercise that was two to three times more  
14 difficult than walking on the flat. And as you heard,  
15 one trial, the 94301 here that was the European  
16 comparator of pentoxifyline and cilostazol, reported  
17 results based on tests in some cases that were taken  
18 as long as two weeks after the drug was stopped. And  
19 of course although I wouldn't make a big issue of  
20 this, the measurements were made at trough all other  
21 times. The drug effect plausibly might have been a  
22 little greater than at trough. SO, again, there are

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1 reasons to consider this analysis to be conservative.

2           Despite these variations, when you combine  
3 the 8 trials, cilostazol 100 mg bid increased placebo  
4 corrected walking tolerance slightly more than **three-**  
5 quarters of a city block down here, walking on an  
6 uphill treadmill. If you make the transformation  
7 again based on METs differences, on a flat that would  
8 be about two blocks on average for all these trials,  
9 short and long or whatever, and some people did much  
10 less well in that but some did a lot, lot better.

11           The benefit was seen consistently across  
12 all the trials, even allowing for the usual intertrial  
13 variability that is usually a feature of these kinds  
14 of studies, and the data are supported by the quality  
15 of life measures which can be thought about the way  
16 John Ware discussed, and I certainly can't add to  
17 that. In practical terms, that sounds to me like a  
18 pretty solid benefit.

19           Nonetheless, for approvability, the  
20 exercise tolerance increase must not be offset  
21 unreasonably by safety concerns. And the concerns  
22 here need to be met head-on really. This drug, as we

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1 have heard so many times today, like **pentoxifyline** but  
2 quantitatively different, has some PDE inhibiting  
3 activity. PDE inhibition in **myocytes** raises  
4 legitimate concerns in heart failure, but in this NDA,  
5 patients whose exercise tolerance was limited by heart  
6 failure were excluded from study, so that we could  
7 evaluate drug effect specifically on **claudication**  
8 relief. The result is that really we can't say  
9 anything about safety for patients with heart failure.

10 Also, **cilostazol** causes a dose-related  
11 increase in resting heart rate that you just heard  
12 about, and these two pharmacological effects raise the  
13 possibility of drug-related heart attack and sudden  
14 death, and the patient selection factor here limits  
15 the target population by circumscribing the **group**  
16 about which we can assess safety. On the other hand,  
17 the drug has pharmacologic effects like reduction of  
18 platelet **aggregability**, antithrombotic activity,  
19 **vasodilation**, HDL cholesterol increase, decrease in  
20 the smooth muscle mitogenesis, you heard about all of  
21 them, and in theory they could minimize cardiovascular  
22 events. So it seems to me that what we have to do is

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1 to look at the data. This is the same problem that we  
2 commonly face when the focus of drug evaluation is  
3 symptom relief.

4 What we have to do is to measure the  
5 theoretical concerns against the actual data. Now if  
6 you consider the dossier in the context of NDA's of  
7 other **drugs** for exercise tolerance improvement in  
8 peripheral arterial disease, this program is really  
9 uniquely rich in placebo-controlled trial data. There  
10 are more than 2,700 patients observed from 12 to 24  
11 weeks in placebo-controlled trials. Unfortunately,  
12 though, the patients with peripheral arterial as a  
13 group form a high risk population, as you heard, with  
14 a 20 to 30 percent five year mortality risk and major,  
15 major lifestyle limitations. But our population  
16 presents the same problem as many NDA's focused on  
17 symptom relief, that is, to enable evaluation of  
18 **claudication** relief. The study population was  
19 designed to include people who were limited  
20 specifically by claudication. The result is that  
21 morbid and lethal event rates were sufficiently low on  
22 **cilostazol**, on placebo, and on pentoxifyline that

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1 statistical power just isn't sufficient to identify  
2 small **intertreatment** differences, even if they exist.

3           Nonetheless, these are the data. And  
4 despite the limitation in power to discriminate  
5 between drugs for different events, I think at least  
6 some plausible inferences can be drawn for the  
7 population for which the drug is targeted, which is  
8 the population that was studied. First, in absolute  
9 terms, the rates of mortality and infarction on the  
10 drug are low for the target population and they are  
11 comparable to those reported in the literature in  
12 similar populations. More importantly, these  
13 relatively "low rates of major problems have to be  
14 weighed against the relatively large improvement in  
15 activity tolerance.

16           Second, even though we lack the power to  
17 exclude differences rigorously at these event rates,  
18 there is no significant difference in mortality and in  
19 **myocardial** infarction among **cilostazol**, placebo, and  
20 **pentoxifyline**, and probably more importantly in  
21 absolute terms the differences are relatively small  
22 and seem at least reasonable for the benefit we

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1 observed. Also, there is no difference in the rate of  
2 progression to vascular surgical procedures among the  
3 **treatments** and that wasn't discussed earlier. In  
4 fact, in the two largest trials for which I chaired  
5 the monitoring committee, there was a modest tendency  
6 to reduction in vascular operations for patients on  
7 **cilostazol** compared with placebo.

8 Now you know it is very hard to draw any  
9 conclusions based on performance or non-performance of  
10 a therapy as an outcome event. However, I think it is  
11 worth considering the surgical data for a minute  
12 because decisions to operate were made by  
13 investigators blinded to drug treatment and were made  
14 after development of arrest pain or early tissue  
15 devitalization. Now these are conditions universally  
16 accepted as indicators of drug failure. And as Bill  
17 Hiatt said, in this population vascular surgery isn't  
18 undertaken lightly and is seldom undertaken at all for  
19 **claudication** relief in the United States because  
20 perioperative risk is relatively high. So it is  
21 reassuring at least that claudication reduction with  
22 **cilostazol** wasn't associated with an excess in the

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1 need for surgical procedures.

2           Finally, I think it is useful to look at  
3 the post-marketing data. No question, there is an  
4 important weakness here. Uncontrolled post-marketing  
5 observational data can be influenced by factors that  
6 confound interpretation and of which we are unaware.  
7 But at **least** it is reassuring that in 10 years of  
8 post-marketing experience involving more than 3,300  
9 patients in formal surveillance studies, more than  
10 7,000 other patients in pre-approval and post-approval  
11 trials, all drawn from more than 850,000 patients who  
12 have received the drug, no concerns about drug-related  
13 mortality have been raised. No regulatory body or  
14 evaluator has identified safety concerns that outweigh  
15 the benefits of cilostazol in patients with peripheral  
16 vascular disease.

17           In summary, it seems to me that **cilostazol**  
18 improves exercise capacity meaningfully and  
19 impressively. This benefit is apparent in patients  
20 with a disease that is severely debilitating and for  
21 which medical and even surgical alternatives are very  
22 limited. Mortality data need to be balanced against

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1 efficacy, and these are relatively sparse in the NDA  
2 because of the modest rate of major untoward events in  
3 all the groups. Nonetheless, I believe that despite  
4 this limitation, which is common in NDA's for exercise  
5 tolerance improvement indications, the controlled  
6 trials and post-marketing experience taken together  
7 suggest that cilostazol is acceptably safe for its  
8 intended use. In the final analysis, I believe the  
9 benefits of the drug in the intended population  
10 outweigh the theoretical concerns that aren't borne  
11 out in the NDA studies, and as in most similar NDA's,  
12 that can't be rigorously evaluated without patient  
13 exposure of greater magnitude than usually is a part  
14 of an NDA for symptom relief. For these reasons, I  
15 believe approval of the drug is appropriate now with  
16 labeling that expresses the current knowledge about  
17 benefits and risks, and I hope as you consider the  
18 issues that you will agree with me.

19 CHAIRPERSON PACKER : Any specific  
20 questions to Dr. Borer? Umho?

21 DR. THADANI: Dr. Borer, the data on the  
22 absolute meters, is that a median or mean value?

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1 DR. BORER: Those were mean.

2 DR. THADANI: Because after you gave us --  
3 I think if we have the light, I could see the page.

4 DR. BORER : Those are the mean values,  
5 Udho .

6 DR. THADANI: On page 23, I think when  
7 they **give** the median values, they are **only** about  
8 anywhere from 20 to 25, with the exception of one  
9 study which is 61.

10 DR. BORER: Right. These --

11 DR. THADANI: So that might translate into  
12 lesser **if** you mean those numbers.

13 DR. BORER: These are the mean values, not  
14 the median.

15 DR. THADANI: Rather than the median,  
16 okay.

17 DR. BORER: And the entire issue of which  
18 you use, of course, is open to some interpretation.  
19 You heard what Lloyd thought about the mean versus the  
20 median, and you may have other views of it. But I  
21 used the mean, which I thought was perhaps reasonably  
22 **representative** of the totality.

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1 DR. THADANI: The other issue is the **post-**  
2 marketing data is mostly from Japan and the Pacific  
3 Islands, where the coronary artery incidence is not  
4 high. So how much reassurance one could get from  
5 where the coronary disease is not that prevalent, I am  
6 not sure, **as** opposed to other countries where the  
7 coronary artery disease is more prevalent. The **post-**  
8 marketing data may not be that accurate because they  
9 don't have many deaths.

10 DR. BORER: Yes, there is no question that  
11 one must interpret with great caution post-marketing  
12 data **from** anyplace, and I think your comment is  
13 absolutely right. Nonetheless, here are the data and  
14 they didn't show anything that was worrisome.

15 CHAIRPERSON PACKER: Marvin?

16 DR. KONSTAM: Jeff, I just wonder how far  
17 you could go in quantifying or quantitatively  
18 expressing your degree of comfort. And maybe this is  
19 the way Rob might ask this question. So given the  
20 efficacy, and I agree with you that it is **pretty**  
21 impressive efficacy. That is my view. Would you say  
22 in this population -- would you for example tolerate

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1 a doubling of mortality? Or rather than my asking it  
2 in a leading way, what level of mortality increase  
3 would you tolerate, either in absolute terms or in  
4 percent terms, given the degree of efficacy that you  
5 see?

6 DR. BORER : That is, of course, the key  
7 question here. I have been thinking about that  
8 question ever since I saw the final data set. I don't  
9 think there is any right answer. But I will tell you  
10 what I personally believe. Let me begin by reminding  
11 you that these are very limited patients. They can't  
12 do the everyday things they want to do. They are  
13 dependent on other people. They have economic costs  
14 that most of us don't have. Even just to deal with  
15 survival issues. And currently there is a very  
16 limited armamentarium to deal with this. Now this  
17 drug seems to provide real and important benefits. It  
18 is not just a block of walking or two blocks of  
19 walking. In some people it is a lot more than that.  
20 But there are many, many benefits that you heard about  
21 today that alter in a beneficial way the way these  
22 people live that are possible with cilostazol and not

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1 without it. And this kind of benefit allows people to  
2 be, I would think, self-reliant and to live with some  
3 dignity and to have some fun. Against these benefits,  
4 the risk seems to me reasonable and acceptable.  
5 Mortality and MI risk are low. That risk might prove  
6 to be higher on cilostazol. None of the data, as  
7 everybody has said, are sufficiently precise or stable  
8 alone for a final estimate. But let's take the worst  
9 case. If you take the point estimate for the time  
10 adjusted mortality risk, the 2.6 -- it is 2.57 now --  
11 but the 2.6 versus 1.9, that is about a 1.3 point  
12 estimate. Let's take that. What does that mean? You  
13 start from a 2 percent annual placebo risk. Let's  
14 think about a 65-year-old man, the average age of the  
15 people here, who can expect, Bill Hiatt told us, to  
16 have stable claudication for the next five years. So  
17 let's talk about the next five years. During the next  
18 five years, he would have one chance in 10 of dying  
19 before age 70 without drug and one and a third chances  
20 in 10 of dying with the drug worst case scenario. Now  
21 Rob suggested a doubling. Okay, one chance in 10 of  
22 dying within five years without the drug and two

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1 chances in 10 of dying within five years with the  
2 drug. You know, in people who have to call on other  
3 people to help them get their food and to move about,  
4 I must say as a doctor I have no problem at all  
5 offering this trade-off to a patient as a rational and  
6 reasonable option. They might not choose to take it,  
7 but I think that many or even most would take the  
8 risk. And that is in a worst case sort of scenario,  
9 and there are other ways to deal with the data that  
10 might be more sympathetic, but no more accurate. so  
11 I think that the benefit of this drug outweighs the  
12 risks as well as we can assess them at this time. And  
13 I don't know if that absolutely answers your question,  
14 but that is the way I think about it.

15 DR. KONSTAM: So, let's see -- it sounds  
16 like if you say it is a baseline 4 percent mortality  
17 is what you are talking about -- 4 percent annual  
18 mortality. This population had about a 2 percent.

19 DR. BORER: Right.

20 DR. KONSTAM: But in the -- I guess saying  
21 1 in 10 means 20 percent 5 year and meaning 4 percent  
22 per year is what you are talking about for the

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1 baseline.

2 DR. BORER : Two percent per year would  
3 give you 20 percent in 10 years.

4 DR. KONSTAM: Ten years, sorry. Okay,  
5 sorry. Ten years. so 2 percent then -- it sounded  
6 like you said in your view, and this is just your view  
7 and maybe nobody else agrees with it, you would  
8 tolerate based on the efficacy that you see a doubling  
9 to 4 percent per year?

10 DR. BORER: That is right, to 4 percent  
11 per year. That is right.

12 DR. KONSTAM: Is that the limit? Is that  
13 as far as you would go?

14 DR. BORER: Well, no, it is not as far as  
15 I can go. But, you know, making a stab at a number is  
16 difficult for me. The way I derived this was to look  
17 at the numbers that were as close to real as I had  
18 them. And I said, okay, in this population that  
19 actually perhaps sustained this risk, did the benefit  
20 they achieved outweigh that risk. And the answer to  
21 me was plausibly yes. someone might choose no, but it  
22 is not irrational to choose yes. To pick another

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1 number is just to be shooting at blanks. I picked  
2 these numbers out of the data.

3 CHAIRPERSON PACKER: Rob?

4 DR. CALIFF: This is really tough.  
5 Because as the day has gone on -- actually from  
6 looking at the original package, and the case is  
7 convincing about the clinical benefit, I agree with  
8 you. But the baseline data that I am seeing is not  
9 telling me that most of these people were having to  
10 get help to get to the grocery store. And I guess the  
11 big concern -- I would agree that if the **whole**  
12 population couldn't walk across the room and now they  
13 could live independently -- if it was that kind of a  
14 change, that sounds very exciting. But let's work at  
15 it the other way. You've said that you can't say  
16 anything about patients with heart failure. You have  
17 had a lot of experience over the years with this and  
18 you are in this position now of the really big  
19 overview. What would the label look like that would  
20 keep doctors and patients from inadvertently taking a  
21 risk which has been unquantified? Would you extend it  
22 to anyone with left ventricular dysfunction? Should

1 the label say if the doctor offers this to a patient,  
2 it is a horrible thing to do? I mean, we have drugs  
3 that have labels and most doctors never know what the  
4 labels say. In my poll of house staff in our  
5 institution, there is not a one that knows that oral  
6 hypoglycemic all have a label that says this drug may  
7 kill you. So just putting it in the label, seeing  
8 what has happened recently with some of the drugs that  
9 have been put out, seems like a worrisome thing. Sort  
10 of on the other side of what you are saying. Yes, if  
11 people are really completely disabled, the opportunity  
12 to help may be worth the risk. But just sort of  
13 saying that we didn't want to look at that population  
14 or that is not our target population so we are going  
15 to pick a low risk group where there is no chance that  
16 we will see that the drug could be harmful, that is  
17 what I see happening with most of these trials. And  
18 then we are left like we are today. Where would you  
19 -- what would the label read that would keep patients  
20 from being exposed?

21 DR. BORER : You raise a lot of crucial  
22 issues. Let me just say, though, that it is probably

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1 not really fair to infer that the population was  
2 selected as low risk so you wouldn't see a problem.  
3 The population was selected because that was the  
4 population in which you could study **claudication**.  
5 People who are limited by something, it is not the  
6 same as claudication.

7 DR. CALIFF: But you would agree that if  
8 in the planning of the trials it had been the intent  
9 of those who planned it to understand the risk for  
10 cardiovascular events, that there would have been  
11 **something** else done besides just exercise studies? Is  
12 that true or not?

13 DR. BORER: Yes, of course it is true. If  
14 the intent of the development program was to  
15 understand the absolute magnitude of cardiac risk,  
16 then one would perform a study, if you wanted to **get**  
17 it done during the time of the NDA, involving an  
18 extraordinarily large population, which really hasn't  
19 been done before. It hasn't been one of the standards  
20 of **evidence** that has been employed and it is  
21 economically' -- you know, it is a tremendous burden.  
22 Now that doesn't -- I am not saying that it is wrong

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1 in any way. But if it isn't the standard that has  
2 been applied and it entails a tremendous economic  
3 burden, you wouldn't undertake it unless there was a  
4 requirement to do it. Absent a tremendous population  
5 in a short period of time, you have to perform a study  
6 in a smaller population over a much longer period of  
7 time, which again entails a number of burdens that  
8 would be difficult. That doesn't mean that I wouldn't  
9 like to have those data and you wouldn't like to have  
10 those data. They aren't the data on which these kinds  
11 of decisions usually are based because they usually  
12 don't exist, which doesn't mean we wouldn't like to  
13 have them. However, in this population described in  
14 this way, I think we can be reasonably comfortable.

15 Now then we come to the more important  
16 point you are raising. How do you prevent other  
17 people from taking the drug, people who don't fall in  
18 the labeling restrictions, and I don't have an answer  
19 for that. The usual way that this is done is by  
20 putting a black box on the label and expecting that  
21 the detail people, et cetera, et cetera, will be **very**  
22 responsible in the way they present the drug **to**

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1 doctors. Is that effective? Obviously it is not as  
2 effective as it might be. And do I have a remedy for  
3 that? No, I don't.

4 DR. LIPICKY: Just to be sure that the  
5 record is straight, the lack of a morbidity/mortality  
6 data base with this drug lays right at our feet, not  
7 at the company's feet. We did not say that that was  
8 required. And in fact, during the time -- and I  
9 understand none of this has any meaning. It doesn't  
10 change the circumstance. So I am not offering it.  
11 But I just want to be sure that the record is  
12 straight. So I am not offering it as an excuse or  
13 anything else. It is just so you know. And at the  
14 time that the development program was going on, the  
15 adverse consequences of phosphodiesterase inhibitors  
16 was not known. And in fact, I am not sure why the  
17 people at the table think that the past experience  
18 with other phosphodiesterase inhibitors applies here.  
19 That is just the bias you are bringing.

20 DR. HIRSCH: Can I amplify that after you  
21 are done, Ray?

22 DR. LIPICKY: Yes.

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1 DR. HIRSCH : Finish and let me continue  
2 with that. I want -- if I have any purpose for being  
3 here as sort of a PAD physician, I have to speak up  
4 now or forever hold my peace. This is not like the  
5 other markets -- again, heart failure that we are  
6 dealing with and other patient populations. I mean  
7 first of all, we just simply don't have confident  
8 mortality data. So we can debate and try, Rob, to try  
9 to put numbers on our confidence, but we are not going  
10 to be able to do it. The confidence limits are too  
11 wide to predict, number one.

12 Number two, again, like Dr. Lipicky just  
13 said, we have never asked for -- when I say we, I mean  
14 everybody in the PAD field including FDA -- have not  
15 asked for mortality data to antecede efficacy for  
16 symptom improvement. Now when you translate that to  
17 an unusual market -- this is PAD where patients face  
18 different choices. When we ask about risk/benefit  
19 ratios, what I see going on in the real world is  
20 patients doing not the SF-36 but the standard gamble.  
21 They are facing their physician and they have to ask  
22 the question, would you be willing to take this short-

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1 term, let's say for a vascular surgical operation --  
2 this short-term risk of an adverse outcome for this  
3 better risk of walking improvement? In other words,  
4 patients face these choices and they make their  
5 choices, and frankly in this population the patient is  
6 usually willing to take the choice to walk even facing  
7 a short-term or cumulative risk of an adverse outcome  
8 or death. I think these patients know that they are  
9 not going to live forever and they are usually willing  
10 to make the choice. That is just an anecdote.

11 But without mortality data, these patients  
12 face other choices where again we don't have data, but  
13 they make the choice for efficacy. We tell patients  
14 who don't face vascular surgery that we don't have a  
15 medication to work and to exercise. And actually  
16 asking a patient with PAD with a coronary disease  
17 burden to undergo vigorous exercise in a program,  
18 which almost always in our country happens without  
19 monitoring or ST segment monitoring, is also asking  
20 the patient to take a risk, and the patient takes the  
21 risk. And frankly the patient is willing to because  
22 they get better.

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1           The point is, I guess, to me when we ask  
2           the patients to take the gamble, the usually take it  
3           in **favor** of symptomatic improvement in this  
4           population. Now that is not heart failure where there  
5           are other modalities. You have diuretics, you have  
6           **Digoxin**, you have ACE inhibitors, and you have A2  
7           antagonists and you have other choices. So in the  
8           lack of a marketplace -- again, I think we are looking  
9           at new drug approval -- we should be very careful when  
10          we do the efficacy/safety analysis to be careful to  
11          weigh efficacy. And if we don't have better mortality  
12          data, we can ask for that later. End of speech, I  
13          think.

14                 DR. LIPICKY: But I want to add just one  
15          more comment to what he said before he says something.  
16          That is that if one could have elected say to do  
17          mortality trials and found that mortality was  
18          increased or decreased, but then one would not know if  
19          the patients felt better in a trial of that nature,  
20          right? So in fact many -- there are tradeoffs in all  
21          of the approaches to developing drugs. Morbidity and  
22          mortality trials, I suppose, one argues that if people



1 aren't in the hospital that they must be feeling  
2 better. I am not convinced that that is true, but I  
3 understand that one could argue that. So in the large  
4 scale real life morbidity and mortality trials, you  
5 have some kind of hardcore real clinical benefit, so  
6 to speak, that you can anchor to, but you **don't know**  
7 that people want to have that. You don't know that  
8 they are feeling any better or that their symptoms are  
9 any **better** or anything else.

10 DR. CALIFF: Well, but you are almost as  
11 bad as Milton in this unfair option in some of the  
12 ways that he has posed questions. I have already said  
13 that I think that the series of studies on symptoms --  
14 this is a great series of studies, well performed and  
15 well presented. The issue for me is not either/or.  
16 The issue for me is that you've got 4 million people  
17 potentially eligible to take this drug and many of  
18 them **have** substantial comorbidities of the type that  
19 look to me like they were not included in this trial.  
20 We have an environment, particularly in the U.S. now,  
21 where most practitioners have 12 minutes to see a  
22 patient, and I think you have recently seen evidence

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1 of what that can do in terms of people keeping things  
2 straight about what indications and contraindications  
3 and complexity of administering therapy can bring.  
4 And also to set the record straight, I am not saying  
5 that the lack of the data is the sponsor's fault. It  
6 is your fault.

7 DR. LIPICKY: Yes, I understand.

8 DR. CALIFF: But it doesn't relieve my  
9 anxiety about turning something loose in potentially  
10 4 million people, which if it had a 30 percent  
11 increase in mortality and knowing the way things are  
12 done in practice in the U.S. today, the potential for  
13 harm that could be done that might be addressed by  
14 doing in addition to the symptomatic study a fairly  
15 simple study to just measure who lived and who died  
16 and the type of patients who are really going to be  
17 treated in practice. But I have said my piece.

18 CHAIRPERSON PACKER: As in many examples  
19 today, we are not going to resolve this. And, Bob,  
20 with your permission, I am really anxious to get on to  
21 the questions. I promised JoAnn that I would give her  
22 the last. word since she is the primary reviewer. We

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1 have to get out of this room by 5:30. We have no  
2 alternative. Our lease expires. So, JoAnn?

3 DR. LINDENFELD: A quick question.  
4 Knowing that this is one of the few alternatives for  
5 these patients, we have said that they could walk a  
6 block and a third longer. But in the patients that  
7 were most limited, they had the least improvement. In  
8 a patient who could walk less than a block to start  
9 out with, what improvement might we have expected with  
10 this drug? It is not a block and a third. It is  
11 substantially less than that.

12 DR. BORER : Right. That is a very good  
13 question. I really can't answer that. What I can  
14 tell you is that the block and a third increase on the  
15 treadmill came from a block and a half baseline. So  
16 it is a substantial improvement on what was there.  
17 How many were less than a block I can't tell you.

18 CHAIRPERSON PACKER: All right. Thanks a  
19 lot. That concludes the sponsors presentation. While  
20 Jeff is returning to his seat, I guess both he and I  
21 are aware of data that blocks in New York are shorter  
22 than blocks almost anywhere else. There are 20 city

1 blocks to a mile in New York and an average of 10 city  
2 blocks to a mile almost anywhere else in the United  
3 States. The reasons for that are beyond the scope of  
4 today's meeting.

5 DR. GRABOYS: Doesn't it make a difference  
6 if you are going across town or uptown or downtown?

7 CHAIRPERSON PACKER: Yes, it makes a big  
8 difference.

9 DR. GRABOYS: So it depends which way.

10 CHAIRPERSON PACKER: It does. And that is  
11 true of most things in life. Okay. We will get right  
12 to the questions. The first questions deal with the  
13 analysis of exercise data including both absolute  
14 claudication distance and the initial claudication  
15 distance. We will turn to our primary reviewer and  
16 ask the first question. Actually, JoAnn, with your  
17 permission I will direct this to Lem. Lem, a  
18 logarithmic transformation was conducted on the  
19 analysis on the raw data. I know you have addressed  
20 this, but we need to just state it briefly because  
21 Joan needs it for the records. Was its use  
22 appropriate in this case?

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1 DR. MOYE: I believe it was appropriate.  
2 I think that they went the additional required step of  
3 doing the analysis on the untransformed data and the  
4 results did not change.

5 CHAIRPERSON PACKER: Okay. Does anyone  
6 disagree? Question number 2, were the patients  
7 studied in the reported trials reasonably  
8 representative of American patients with intermittent  
9 claudication? Let's say this is the first example  
10 that I know of of a patriotic slant to a question.  
11 Usually we are not so country-specific in the way the  
12 questions are asked. JoAnn, what are your thoughts?

13 DR. LINDENFELD: I think these were  
14 reasonably representative. They were certainly, I  
15 think, a lower risk of a high risk subset in that they  
16 had no heart failure. We know that. But they also  
17 didn't have angina limiting their exercise capacity at  
18 all and in fact could be off Isordil. But I think  
19 they are reasonably representative.

20 CHAIRPERSON PACKER: Okay. Bob?

21 DR. TEMPLE : Well, I want to ask a  
22 question because this has come up a number of times,

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1 especially in the form of Rob's concern that a  
2 different group of people would be included. Could  
3 people be specific about how they think this was a  
4 relatively low risk group? And I ask that because you  
5 obviously can't include people who don't get  
6 claudication. So the people with bad heart failure,  
7 they can't be in the trial and they wouldn't have  
8 heart claudication. So that is not it. So what else  
9 about this group is different? And I think that is  
10 relevant to how one might label the drug later, so we  
11 should pin that down.

12 DR. LINDENFELD: Well one thing I think  
13 might be low risk is that they could be taken off of  
14 **Isordil**. So that meant they didn't have a lot of  
15 angina I would think.

16 DR. THADANI: But a lot of patients had a  
17 previous MI, I think about 20 percent. They were  
18 smokers and there were other risk factors. If **you**  
19 take the general patient population of peripheral  
20 vascular disease, when I see the consults on those  
21 patients or do angina studies, some of them have both  
22 problems, but they can't go to angina because their

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1 intermittent. claudication stops them first. And if  
2 you were to do a cardioangiogram or even a stress on  
3 these patients, a lot of them will have underlying  
4 CAD. The peripheral vascular disease correlates  
5 better than carotid. So although you are saying lower  
6 risk -- because the data base is only 3 to 6 months  
7 here. If you look at Creakey's study, he is talking  
8 about 20 percent mortality. I realize they are all-  
9 comers. so I don't think we can say low risk in  
10 mortality or morbidity terms from the data given.

11 DR. TEMPLE : Well, they had to be six  
12 months away from an MI, right?

13 DR. THADANI: Well, I realize that.

14 DR. TEMPLE : And they had to be some  
15 distance away from surgery. I mean, it would be  
16 helpful to pin down those aspects because labeling  
17 could conceivably reflect that in some way.

18 DR. HIRSCH: But Bob to make a point that  
19 they are not or they are representative, if you look  
20 at other major national studies, the mid-trial from  
21 the NIH, the McDermott's data from Northwestern  
22 recently, Capri even, really 70 percent or so of the

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1 PAD patients out there who **claudicate** aren't coming to  
2 the doctor with coronary disease or heart failure.  
3 They are. like this.

4 DR. TEMPLE : Okay. Well, I am asking  
5 particularly because of what Rob has been saying.  
6 That when you make the drug available, all of a sudden  
7 the **people** who get the drug are going to be very  
8 different. And it is important to pin down in what  
9 ways. Because if you are really worried about it, you  
10 can -- you know, you can have a patient insert and put  
11 the **patient** in the loop too. So one could do that.  
12 So I think it is important to say what particular  
13 increased risk population one might worry about here.  
14 And I guess I am -- I don't understand how the heart  
15 failure population would be worried because they are  
16 not going to be able to claudicate. So it must be  
17 **something else.**

18 DR. THADANI: But , Bob, the heart failure  
19 population now -- the changing of heart failure is  
20 very different. You can have Class II failure with LV  
21 dysfunction or limited by walking 500 meters by  
22 fatigue. But if there is concomitant peripheral



vascular disease, they are going to claudicate before they get fatigued. So I don't think that --

DR. TEMPLE : But the exclusion here was that you had to be able to exercise enough to get **claudication**.

DR. THADANI: Sure. I realize that. But there will be patients who have an ejection fraction of 30 percent and have no classical symptoms of heart failure unless they --

DR. TEMPLE : Right. But they were in these studies presumably.

DR. THADANI: So they were in these studies. The question is how much confidence one has because of this 1.3 ratio. That is what you are asking. Can you label it that everybody should have ejection fraction measured because of the risk with this class of drugs or what?

DR. TEMPLE: No. I was just wondering how they were going to be different.

DR. KONSTAM: They are different from the **exclusion** of limiting angina and limiting heart failure and limiting dysrhythmias.

1 DR. TEMPLE : Yes, but you can't be  
2 different because if you have limiting of those  
3 things, then you can't -- then you are not a  
4 **claudicant**, right?

5 CHAIRPERSON PACKER: Marv?

6 DR. KONSTAM: Well, I just was going to  
7 say that it seems that there is something different in  
8 terms of the differences in the mortality rates that  
9 we see here compared to what we are told is the  
10 ambient mortality rates in the population of patients.  
11 So it sounds like there is something different. And  
12 I don't know exactly what the answer is, Bob. I hear  
13 what you are saying from a logical perspective, but my  
14 suspicion is that in fact patients with heart failure,  
15 even though they were really limited by **claudication**,  
16 were in fact excluded. I mean that would be my  
17 **suspicion**. As to the type of ways that it was moved  
18 toward a lesser risk population. If you look at the  
19 percentage of patients who were in the studies who had  
20 heart failure, one might find that it was a lower  
21 population than the population out there with  
22 **claudication** who has heart failure.

1 DR. LIPICKY: What is the higher number  
2 that has been cited here?

3 DR. KONSTAM: I am sorry?

4 DR. LIPICKY: What is the higher mortality  
5 rate that has been cited here?

6 DR. KONSTAM: 4 percent.

7 DR. LIPICKY: In people who have six  
8 months worth of claudication stable and no  
9 accelerating, is that a correct number, 4 percent?

10 DR. KONSTAM: We can ask Dr. Hirsch that  
11 question.

12 DR. LIPICKY: I mean, are we dealing with  
13 the right thing? That is, is it not that patients who  
14 have stable claudication and only claudication as  
15 their symptomatology, and who have had it for at least  
16 six months. Is the rate that has been observed in  
17 these trials really different from the rate that one  
18 would see in a population characterized by that? Do  
19 we know that? Because people are assuming that we do  
20 and that the rate that was observed is very low.

21 DR. HIRSCH: I think they are different  
22 populations. The two best things I can think of are

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1 the clopidogrel data set, where 60 Percent of the  
2 patients had had surgery and 40 percent were  
3 claudicants. so you can't necessarily take the 4  
4 percent rate from them and apply that to the 2 percent  
5 rate here. And then you have to look at **Creakey's**  
6 mortality data, which includes asymptomatic to very  
7 severely symptomatic. So I think that this population  
8 is a little bit more narrowly defined.

9 DR. CALIFF: So is it that it is a  
10 population -- so what is the definition of the  
11 population? Is it patients with stable claudication?

12 DR. HIATT: It is stable claudication who  
13 come into these kinds of trials. This is a  
14 representative mortality figure. But it may not  
15 represent the totality of PAD, which is probably --

16 DR. CALIFF: Okay. What is the difference  
17 that is contained in that phrase, "who come into these  
18 trials"? I mean, I guess that is what we are asking  
19 you to define.

20 DR. HIATT: Well, if we look at the  
21 natural history and you are looking just at stable  
22 claudication symptoms. Not unstable claudication.

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1 Not severe PAD. Those patients have higher mortality  
2 rates. This population obviously has a lower  
3 mortality rate, about half of what you would expect.

4 DR. GRABOYS: So you are talking about a  
5 labeling that is going to define a very small segment  
6 of the population. These people are clinically  
7 stable. They don't have LV dysfunction. They may not  
8 be insulin-dependent diabetics. They may not be  
9 continued smokers. I mean this is --

10 DR. LIPICKY: No, they have diabetics  
11 here.

12 DR. HIATT: They have diabetes. They have  
13 lots of comorbid disease. But in fact, you wouldn't  
14 want to treat someone with a medication unless they  
15 had stable limiting claudication symptoms that were  
16 more severe than their heart failure symptoms or their  
17 angina.

18 CHAIRPERSON PACKER: It sounds as if -- I  
19 think what I hear is pretty much everyone saying the  
20 same thing, which is that were this committee to look  
21 at this drug favorably, we would look at this drug  
22 favorably in the patients who were studied, and the

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1 patients who were studied were patients with stable  
2 claudication without angina or heart failure.  
3 Consequently, if further deliberations of this  
4 committee were to say that they felt comfortable with  
5 this, my guess is wording that describes something  
6 like this would be the wording that would appear in  
7 the indications section, that is, that one would --  
8 this drug would be indicated in patients who had  
9 stable claudication without angina or heart failure.

10 DR. HIATT: That is not quite it.

11 DR. LIPICKY: It is for people whose  
12 exercise is limited by claudication.

13 CHAIRPERSON PACKER: Okay. That is fine.

14 DR. HIATT: It is that simple, with an ABI  
15 of less than .85.

16 CHAIRPERSON PACKER: Ileana?

17 DR. PINA: My only question with that  
18 population is in the studies, they had to be taken off  
19 -- and I think JoAnn said this too -- off their  
20 chronic nitrates. They could take sublingual and  
21 intermittent nitrates. And in the average population,  
22 the physicians that are going to give this, even if

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1 they are stable claudicants, are not going to stop the  
2 **anti-anginal** agents. So the population may be a bit  
3 different. I am not that concerned about the heart  
4 failure patients because I don't think they are going  
5 to be in here. The real sick ones are not going to be  
6 in here. There may be some with asymptomatic left  
7 ventricular dysfunction or the Class I's or Class  
8 II's, and I am not that concerned about them. But the  
9 patients who would have angina, have their **anti-**  
10 **anginal** agents been stopped, and we don't know  
11 **anything** about that.

12 CHAIRPERSON PACKER: And there will be  
13 other opportunities to discuss this. But I think we  
14 -- I just want to ask the committee one question  
15 because there is one difference that no one in this  
16 committee has discussed yet with respect to question  
17 number 2, which is the anti-platelet use. Because we  
18 heard and we understand there is a changing paradigm  
19 here, but most of the patients in these trials were  
20 not taking anti-platelet drugs, and the impression we  
21 all have is that maybe the use of anti-platelet drugs  
22 in this patient population will increase and increase

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1 dramatically because of their ability or at least the  
2 ability of one agent to affect the long-term outcome.  
3 so that is not -- there is some experience with  
4 aspirin, but most of the patients in this data base  
5 weren't taking anti-platelet drugs. So that is a  
6 difference in the population that is studied here from  
7 the population which is likely to be the target  
8 population, even if that target population is  
9 described as exercise limited by claudication.

10 DR. THADANI: I think, Milton, that is a  
11 pertinent point. In the earlier discussion the  
12 clopidogrel issue was brought in. And since the drug  
13 has been approved only recently and improves outcome,  
14 one would presume even the PAD expert sitting next to  
15 me is going to prescribe that drug. And if you did,  
16 that patent is already on -- because that is the  
17 benefit. If a patient is on that and then if you give  
18 this drug, are you going to be able to show  
19 improvement in exercise?

20 CHAIRPERSON PACKER: That is not the  
21 question being asked. The only question being asked  
22 the committee in question number 2 is what are the



1 differences.

2 DR. THADANI: That might make a difference  
3 in the safety outcome.

4 CHAIRPERSON PACKER: A totally different  
5 question and we will discuss it later.

6 DR. THADANI: Okay. Then the question  
7 would co-me up too with triase down the road if you are  
8 eluding to that too. Because a lot of oral agents, at  
9 least in coronary artery disease going on at the  
10 moment, and if more cardiologists are going to use  
11 those, then if a patient is put on this, those are  
12 relevant. So the population could be different  
13 because of the background different therapy.

14 CHAIRPERSON PACKER: Okay. Bob?

15 DR. TEMPLE: Milton, filing for later  
16 discussion, one difference is it seems very likely  
17 that people with this disease will be on clopidogrel.  
18 We don't know whether they are going to be on aspirin.  
19 This committee has concluded that aspirin is not  
20 useful in that setting, but they may very well be on  
21 clopidogrel So that is one difference.

22 CHAIRPERSON PACKER : That is the

1 difference I was highlighting.

2 DR. TEMPLE: Okay. I can't help saying I  
3 wouldn't have thought the difference was whether the  
4 drug worked in that population, it is whether **people**  
5 bleed, right? That is what we are worried about, if  
6 anything.

7 CHAIRPERSON PACKER: Yes. We are going to  
8 discuss this again, I promise. Question number 3, the  
9 clinical trials lasted for 12 to 24 weeks. Were these  
10 trials long enough for a study of this indication?  
11 Before I ask JoAnn to address this, let me ask Ray.  
12 There are lots of ways one can interpret this  
13 question. Is the **intent** of the division that this be  
14 a --

15 DR. LIPICKY: I think you can skip it.  
16 Because you have really discussed that business  
17 already.

18 CHAIRPERSON PACKER: That never stops us  
19 from discussing it more.

20 DR. LIPICKY: And it really was intended  
21 to raise the question of if you feel good for six  
22 months and then die in the seventh, is that good

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1 enough. But you have gone through all of that  
2 business.

3 CHAIRPERSON PACKER: We have gone through  
4 all of that.

5 DR. LIPICKY: And is six months a long  
6 enough mortality trial? And we want to give you the  
7 chance to give your milrinone experience all over  
8 again. So skip it.

9 CHAIRPERSON PACKER: Thank you. Question  
10 number 4 is a discussion of dropouts and the analysis  
11 of dropouts. The primary question that is being asked  
12 here is primarily on the exercise tolerance. I think  
13 that is a correct statement. Number 4 is focused on  
14 exercise tolerance and the question that arises --  
15 hold on one second. I just want to make sure that my  
16 notes are right. It does focus on exercise tolerance,  
17 but in fact there is no subsequent place where -- no,  
18 actually we can pick it up in 7 on the secondary  
19 endpoints. So we will focus number 4 on exercise.  
20 And the first two-part question in number 4, are you  
21 satisfied that the dropout patients had been  
22 adequately accounted for? And then please go on and

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1 answer, are the last observation carried forward  
2 analyses acceptable.

3 DR. LIPICKY: And one word answers can do.

4 DR. LINDENFELD: Yes and yes.

5 CHAIRPERSON PACKER: Does anyone disagree?  
6 Udho?

7 DR. THADANI: Just a concern regarding  
8 that some patients who really deteriorate and are  
9 carried forward with the same disease process. I  
10 think we eluded to that before. But accepting --  
11 since everybody does it, we are going to accept it.  
12 But maybe in the future, it would be nice to look at  
13 patients who for some reason started getting resting  
14 leg pain and maybe different ways of doing it. So I  
15 agree with it as it is, but with a proviso.

16 CHAIRPERSON PACKER: I guess I would  
17 reiterate. I would underscore Udho's concern. I  
18 think that in this case, the last observation carried  
19 forward analyses are acceptable. But I have real  
20 concerns about relying on last observation carried  
21 forward analyses if there is a meaningful number of  
22 patients who drop out because of worsening of the

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1 disease which is related to the primary endpoint being  
2 **measured.** And in those cases, I would feel  
3 uncomfortable with a last observation carried forward,  
4 but that is not pertinent to today's NDA. Bob?

5 DR. TEMPLE : Also, analyses were done.  
6 One a not too aggressive one that just attributed bad  
7 outcomes to everybody who dropped out and one that  
8 attributed bad outcomes only to the treated patients  
9 who dropped out, which is certainly the **maxi-**  
10 **punishment.** And the results in this case were still  
11 robust.

12 CHAIRPERSON PACKER: Of course all of  
13 these questions are a lot easier to answer because the  
14 P values were so small.

15 DR. TEMPLE: It really helps.

16 CHAIRPERSON PACKER: These questions would  
17 **be** a lot more interesting if the P values were  
18 borderline. I guess interesting isn't a really good  
19 word. Number 5, which if any of the trials showed  
20 that cilostazol is superior to placebo for the claimed  
21 **indication?** We have already discussed what that might  
22 be, what the sponsor is proposing. Which of any of

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1       them failed to show superiority? So, JoAnn, I guess  
2       what is being asked is of the 8 placebo controlled  
3       trials, how many fall into a superiority category and  
4       how many do not? And if there are any that fall into  
5       -- if there are some that fall into the not category,  
6       is that a problem for you?

7                   DR. LINDENFELD: There are really 5 out of  
8       the 8 studies that are definitely positive, and one  
9       that is positive but that was stopped early but I  
10      think it- would still be considered positive, 92201.  
11      And then two that showed a trend toward being positive  
12      but were not positive. But I think all in all, this  
13      is not a problem. It is a very strong set of data.

14                   CHAIRPERSON PACKER: And so that although  
15      there are two or three that are not in the category,  
16      the answer is that that is not a problem for you?

17                   DR. LINDENFELD: That is not a problem.

18                   CHAIRPERSON PACKER: Okay. Does anyone  
19      **disagree?**

20                   DR. THADANI: I agree with all the  
21      **statements** with the exception of the comparative  
22      study . There are only two trials and one is positive

1 and one is not.

2 CHAIRPERSON PACKER: That is the next  
3 question, Udho.

4 DR. THADANI: oh, okay. Because she is  
5 including just the placebo control. In that case, I  
6 think there are only two trials, yes.

7 CHAIRPERSON PACKER: Okay.

8 DR. MOYE : Milt?

9 CHAIRPERSON PACKER: Yes.

10 DR. MOYE: I guess because I disagree with  
11 three, that the trials were not long enough to study  
12 this indication, then I am going to have a problem  
13 identifying any trials in 5 that do meet the  
14 indication. And my concern here is primarily  
15 duration.

16 CHAIRPERSON PACKER: Lem, let me ask you  
17 about what you just said, because I actually I  
18 think there may actually have been value in having  
19 even briefly voted on number 3. Let me ask the  
20 question in the following way. The question on number  
21 5 really focuses on efficacy, not on the total concept  
22 of approvability. So from a pure efficacy point of

1 view, would you think that a trial that lasted for 12  
2 to 24 weeks, and all of them did, would be sufficient?  
3 I understand safety concerns are different.

4 DR. MOYE: Right.

5 CHAIRPERSON PACKER : And potentially  
6 separable.

7 DR. MOYE: Right.

8 CHAIRPERSON PACKER: So since number 5 is  
9 an efficacy focused issue, would your -- are you **still**  
10 concerned about agreeing with JoAnn if that were only  
11 an efficacy focused question?

12 DR. MOYE: Well, I certainly try to agree  
13 with JoAnn every chance I get, but I don't think I can  
14 agree this time. Because even with the efficacy  
15 issue, we are assuming that there is going to be **long-**  
16 **term** efficacy, efficacy beyond 24 weeks, and we don't  
17 have data here that demonstrates that.

18 CHAIRPERSON PACKER : Let me ask a  
19 **question**, Lem, just if I could. Are you suggesting  
20 that in a disease like this -- I understand it is a  
21 longstanding disease that goes on for years, et cetera  
22 -- that you would like to see efficacy data beyond 24

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1 weeks?

2 DR. MOYE : If the drug is to be used  
3 beyond 24 weeks, yes.

4 CHAIRPERSON PACKER: Okay. Maybe I can  
5 ask the question in a different way. Every disease  
6 this committee sees is a long disease that lasts for  
7 years, and we never ask for efficacy beyond 24 weeks  
8 in any disease that we see. Why should this disease  
9 be different.

10 DR. MOYE: I guess because I disagree with  
11 the precedent, I disagree -- excuse me, I disagree  
12 with the tradition. I mean I don't know why we don't  
13 ask for long-term data for that.

14 CHAIRPERSON PACKER: Well, the average  
15 duration of therapy for an anti-hypertensive drug  
16 trial is about 4 weeks. For angina it is about two to  
17 four -- well, it is a little longer. Okay.

18 DR. TEMPLE: That doesn't have to be. You  
19 can't do a placebo-controlled trial of hypertension of  
20 any duration anymore for ethical reasons. But that  
21 actually doesn't stop you from evaluating long-term  
22 efficacy. You can do a randomized withdrawal trial

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1 after any period you want. Typically, however, even  
2 in do:ng that, we only do it after six months. And to  
3 my best knowledge, we have never found a drug whose  
4 **pharmacologic** effect disappears say after six months.  
5 That doesn't mean we couldn't, but you don't really  
6 expect that.

7 DR. LIPICKY: But we don't demand that.

8 DR. TEMPLE: We actually half demand it  
9 and probably could be more precise. We ask for  
10 evidence of long-term effect in hypertension, but we  
11 accept active control trials, which we know are not  
12 very informative.

13 DR. LIPICKY: Right. But they are not of  
14 lifetime duration.

15 DR. TEMPLE: Oh, no. What Milt says is  
16 right. You never go for the entire duration of  
17 therapy.

18 DR. LIPICKY: Right.

19 DR. TEMPLE: How could you ever?

20 DR. LIPICKY: And the studies we ask for  
21 are are SORT of is there tolerance or does the effect  
22 go away or is there still the drug effect, not is it

1 still really effective in that sense.

2 DR. TEMPLE : For what it is worth, there  
3 are a few situations, just to recount a couple, in  
4 which we have thought longer term information is  
5 important. For example, in weight loss drugs where  
6 there is a history of effects waning, we have asked  
7 for six or sometimes even 12-month data. But again,  
8 I have to say not longer than that.

9 DR. MOYE : Well, is it inadmissible to  
10 suggest that after a program of exercise strengthening  
11 and reduction of risk factors that there might be  
12 reduction of efficacy from the drug? I mean that is  
13 just a possibility for a mechanism by which you might  
14 have reduced efficacy.

15 DR. TEMPLE: You mean you permanently make  
16 **claudication** go away? Wow .

17 DR. MOYE: No, reduced efficacy of the  
18 drug.

19 DR. HIRSCH: Look , there are all kinds of  
20 possible permutations of how people might change their  
21 walking. They might then develop arthritis and they  
22 might have a better arthritis drug. I mean, it is

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1 impossible to think of all the combinations. Let's be  
2 practical .

3 DR. MOYE : Right. But therefore I do  
4 think that we as scientists are at our worst when we  
5 reason in the absence of data, and we have no data  
6 beyond six months suggesting that this drug will be  
7 efficacious .

8 DR. TEMPLE: But, Lem, how far does this  
9 go? If you had data that went to a year, then **you**  
10 could say exactly the same thing. And at two years,  
11 you could still say the same thing.

12 DR. MOYE: You are absolutely right.

13 DR. TEMPLE: And at five years. So where  
14 is the right place to draw it. I would say that  
15 without having necessarily thought it through, which  
16 would have been better maybe, there is sort of an  
17 assumption that when you are dealing with primarily  
18 pharmacologic effects, not sort of event things, that  
19 you don't expect the pharmacologic effect just to  
20 disappear because there is not a lot of history where  
21 that has happened. If there were many examples of it  
22 or a few even, we probably would change our view.

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1 DR. THADANI: Perhaps a more generic  
2 question could be that we know that the drug improved  
3 exercise performance. There is no question to that.  
4 Now if you give it to the general population with PAD  
5 and give them the drug and don't exercise on the  
6 treadmill every four weeks, would they show  
7 improvement? Are you going to write that in order for  
8 the claudication distance to improve, the patient  
9 should take the drug and exercise on the treadmill?  
10 I am raising just the issue of -- I realize -- because  
11 we know that if you just exercise under supervision,  
12 and your first slide showed that exercise is as good  
13 as anything provided it is done under supervision and  
14 not just telling the patient to do it, and I think  
15 claudication distance in some studies might have  
16 doubled. So say if the drug is on the market, you  
17 should tell the person that at least every four weeks,  
18 as in the protocol, you should go on the treadmill?

19 DR. HIATT: I think I can answer that  
20 pretty definitively. We have done a lot of exercise  
21 training trials and the threshold for benefit is six  
22 weeks, three times a week for an hour, for a full

1 hour. So one treadmill test every four weeks is so  
2 far below a training threshold that it is not  
3 meaningful.

4 **DR. THADANI:** But suppose you did not do  
5 **any** treadmills in-between? Angina patients are the  
6 same, so don't take me wrong. Ray remembers **the**  
7 **nitropatch** study, the one on health improvement. Say  
8 **if you** took a patient at point zero and give them **the**  
9 drug anti don't put them on the treadmill, would you  
10 **show** similar benefit?

11 **DR. HIATT:** I will try. We are  
12 speculating.

13 **DR. THADANI:** Say at 24 weeks. You don't  
14 **do** any exercise in-between on the treadmill. You give  
15 **your** drug and the placebos --

16 **DR. HIATT:** Spontaneous sort of activity  
17 here?

18 **DR. THADANI:** Yes. Just let them do what  
19 **they are** doing. Would you show a benefit like this?  
20 I am just asking a question.

21 **DR. HIATT:** What it takes to make a  
22 **training** response in this disease population **isa**

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1 continual pushing into **above-claudication** level  
2 exercise in a very formal, rigorous fashion. And  
3 casual **activity** or pushing people to do this  
4 repeatedly does not produce any clinical benefit. You  
5 really have to put **them on a device** that is moving and  
6 get them to do that for period of time up to an hour  
7 three times a week. So I think that the sort of  
8 casual benefit that you get **from** increased activity or  
9 from repeated treadmill testing is way below a  
10 **training program.**

11 **DR. THADANI:** Now you are seeing placebo  
12 effect to some extent. Placebo with training.

13 **DR. HIATT :** Placebo is not a **training**  
14 **response.** I think it is a familiarization with gait  
15 character.

16 **DR. THADANI:** Udho, your concern would be  
17 understandable if these were open label studies.  
18 These are placebo controlled trials.

19 , **DR. THADANI:** No, I realize that. I am  
20 just saying because the general population may not go  
21 on the treadmill. Suppose you were to do a study in  
22 which the patient is just given the drug and 24 weeks

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1 later put him on a treadmill, would you see the same  
2 effect. That is the issue I was raising.

3 CHAIRPERSON PACKER: I see. Bob?

4 DR. TEMPLE: I am not certainly asserting  
5 that I think it is necessary because six months seems  
6 pretty impressive to me. But if one wanted to pursue  
7 this and there were a cohort of patients still on  
8 therapy who appeared to have responded, one could do  
9 a randomized withdrawal study and gain evidence of  
10 persistent effect out to whatever duration they are  
11 currently on. We could certainly talk with the  
12 company about that. I don't know if there is such a  
13 cohort anymore. Well, there must be because we are  
14 still seeing new data, so there is.

15 CHAIRPERSON PACKER: I guess what we need  
16 to do for the record is to just get a sense on  
17 question 5 of the committee. JoAnn has said that she  
18 feels comfortable that there are more trials that show  
19 superiority than there are trials that don't, with the  
20 ratio being either 5 or 6 to 2 to 3, depending on how  
21 one counts. And Lem says he feels uncomfortable for  
22 it, primarily because of the issue of only 6 months of

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1 efficacy. So I think what we need to do is just get  
2 a sense of the committee. How many of you would vote  
3 the way that JoAnn has voted on question 5? Just  
4 raise your hands. I guess I don't have everyone's  
5 attention, so what we need to do is actually go right  
6 down. I didn't want to do this. JoAnn has put  
7 forward her sense that the trials do show convincing  
8 evidence of superiority of cilostazol over placebo for  
9 the claimed indication. Just say if you agree or  
10 disagree. Rob?

11 DR. TEMPLE: Agree.

12 DR. CALIFF: Agree.

13 DR. KONSTAM: Agree.

14 DR. DIMARCO: Agree.

15 DR. GRINES: Agree.

16 DR. GRABOYS: Agree.

17 DR. THADANI: Agree.

18 DR. HIRSCH: Agree.

19 DR. MOYE: Disagree.

20 DR. PINA: Agree.

21 CHAIRPERSON PACKER: I am sorry, was that  
22 unanimous?

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1 DR. MOYE: No, disagree.

2 CHAIRPERSON PACKER: I agree. Is that  
3 unanimous?

4 DR. MOYE: No.

5 CHAIRPERSON PACKER: Lem disagrees. Okay,  
6 fine. So that vote is 9 to 1. Question number 6,  
7 which if any of the trials showed that cilostazol was  
8 superior to Trental -- 1 always have trouble with that  
9 -- for the claimed indication? It is exactly  
10 analogous to question number 5 except that it now asks  
11 for superiority versus an already approved drug for  
12 the same indication. Can you review the data for us  
13 and reach a conclusion?

14 DR. LINDENFELD: There is one study that  
15 shows a definite benefit of cilostazol over Trental  
16 and one that doesn't show any benefit at all. So  
17 although I think it is probably better, I think I  
18 would be unwilling to say it definitely is better.

19 CHAIRPERSON PACKER: So your vote is that  
20 it is a problem and you think the data are  
21 inconclusive?

22 DR. LINDENFELD: Correct.

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1                   CHAIRPERSON PACKER: Okay. How many would  
2 disagree with the conclusion that the data are  
3 inconclusive? Okay. The committee voted 10 to zero  
4 that the data are inconclusive. Number 7, what was  
5 demonstrated with respect to the effect of cilostazol  
6 on quality of life? JoAnn?

7                   DR. LINDENFELD: I think it shows a  
8 benefit on quality of life. We have heard a lot about  
9 that and I have been educated today to say that I  
10 think this shows that at least physical performance as  
11 a measure of quality of life is improved.

12                   CHAIRPERSON PACKER : Okay. Udho?

13                   DR. THADANI: I think if you -- the FDA  
14 analysis said that none of the parameters were  
15 affected in a positive way. And in quality of life,  
16 I think one has to take -- and we argued on that  
17 before -- if people drop out with sudden side effects  
18 and the event rate is higher, then those should be  
19 taken into account. So I am uncomfortable to accept  
20 that it showed a definite benefit.

21                   CHAIRPERSON PACKER: Okay. Let's vote on  
22 it since there is a disagreement. The question is do

1 you believe that there is demonstration of a favorable  
2 effect of cilostazol on quality of life. Obviously  
3 this is being asked because if you agree, it would be  
4 incorporated into the labeling and if you disagreed,  
5 it wouldn't be. And we will -- I guess -- why don't  
6 we start at the other end, Ileana. Alan, if you have  
7 any comments, that would be terrific. Alan can't  
8 vote, right? The one thing you can't do today is  
9 vote.

10 DR. HIRSCH: But I can comment strongly,  
11 right?

12 CHAIRPERSON PACKER: What was that?

13 DR. HIRSCH: But I can comment strongly?

14 CHAIRPERSON PACKER: If you are going to  
15 comment strongly, you could probably do that now.

16 DR. HIRSCH: There is no data set in PAD  
17 that is more consistently positive showing a quality  
18 of life benefit.

19 CHAIRPERSON PACKER: Okay. Ileana?

20 DR. PINA: I would have to agree that the  
21 trend is there for quality of life in the functional  
22 domain of activity. However, that doesn't embrace the

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1 entire umbrella of quality of life as we have been  
2 discussing. But perhaps for this population that may  
3 be quite an adequate assessment.

4 CHAIRPERSON PACKER: So your vote on this  
5 is that you do not -- I guess you would vote no.

6 DR. PINA: I am not 100 percent convinced,  
7 no.

8 CHAIRPERSON PACKER: Okay. I mean I  
9 understand that one would like to grade their votes,  
10 but it really does have to be a yes or a no. So the  
11 vote -- I guess Ileana, you are voting no?

12 DR. PINA: No.

13 CHAIRPERSON PACKER: No? Okay?

14 DR. PINA: Correct. No.

15 CHAIRPERSON PACKER : Lem?

16 DR. MOYE : I would vote no because of  
17 these nagging concerns we have for how you handle  
18 correctly the patients who had incomplete follow-up in  
19 the quality of life assessment. So I would vote no.

20 CHAIRPERSON PACKER: Udho?

21 DR. THADANI: No.

22 CHAIRPERSON PACKER: Tom?

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1 DR. GRABOYS: Yes.

2 CHAIRPERSON PACKER: Cindy?

3 DR. GRINES: I think yes with regard to  
4 certain components of the quality of life.

5 CHAIRPERSON PACKER: John?

6 DR. DIMARCO: I will agree with that. I  
7 think it is positive for the physical function scores.

8 CHAIRPERSON PACKER: Okay. I would vote  
9 no. JoAnn? You voted yes, right?

10 DR. LINDENFELD: Right.

11 CHAIRPERSON PACKER: Marv?

12 DR. KONSTAM: I am going to vote yes. And  
13 I just have to say I am going I think under a slightly  
14 different construct than maybe some of the other  
15 panelists are. I view the results of the treadmill  
16 exercise time as indicative of improvement of one  
17 aspect of health related quality of life. And those  
18 were the principle endpoints of most of the trials.  
19 And so the answer is, yes, an aspect of health-related  
20 quality of life is improved by that measurement. And  
21 I would further that by saying that those findings  
22 are, to my view, and I think this is what Dr. Ware was

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1 saying, strongly supported by the data in the SF-36,  
2 in the physical component of the SF-36. So all the  
3 data put together, I think, strongly indicate an  
4 improvement in the physical component of health-  
5 related quality of life that was expected to be  
6 influenced by this drug.

7 CHAIRPERSON PACKER: Rob?

8 DR. TEMPLE : I vote yes with a proviso  
9 that there should be an analysis where dropouts are  
10 considered in a nonparametric analysis of worst case.  
11 And if there was still a strong trend, it wouldn't  
12 have to be less than .05. I would keep it that way.  
13 But with the data we have seen, I vote yes.

14 CHAIRPERSON PACKER : Let me ask a  
15 question. Does that mean that if such an analysis  
16 were performed and it *basically* -- it is hard to  
17 quantify it because conventionally one would quantify  
18 it as being statistically significant. But if the  
19 effect were to be substantially reduced, would you  
20 vote no?

21 DR. TEMPLE : Substantially reduced is a  
22 relative thing. I would say if the P value was

1 somewhere less than .10, I would still be happy. If  
2 it was greater than that, I would say I am uncertain  
3 enough and I would like to see more data. Because I  
4 think that is an exaggerated worst case kind of  
5 scenario. But the key issue here I guess is really  
6 would the label be able to say we used Dr. Ware's  
7 analysis and the patients feel great when they take  
8 this.

9 DR. LIPICKY: I am sorry, the question  
10 wasn't in there for labeling actually. At least that  
11 wasn't my purpose.

12 DR. TEMPLE: Okay.

13 DR. LIPICKY: It was to get a feeling for  
14 whether the" committee would accept quality of life,  
15 Dr. Ware's quality of life, as an endpoint without  
16 exercise tolerance.

17 CHAIRPERSON PACKER: No, that is not --  
18 that is a later question.

19 DR. LIPICKY: Because if you would --

20 CHAIRPERSON PACKER: That is not the  
21 question.

22 DR. LIPICKY: Well, Milton -- you are

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1           answering question 7, right?

2                   CHAIRPERSON PACKER:    Right.

3                   DR. LIPICKY:   And you are being asked what  
4           did it show for quality of life.

5                   CHAIRPERSON PACKER:    Right.

6                   DR. LIPICKY:   And if you were overwhelmed  
7           by the quality of life data, then somewhere along the  
8           line you would get asked the question, and maybe it is  
9           in there already, whether you would have done without  
10          the exercise tolerance data.

11                  DR. TEMPLE :    But that is a completely  
12          different question.   It is an interesting question,  
13          but it is a totally different question.

14                  DR. LIPICKY:   I understand.   But that is  
15          what the question -- I am saying that is what the  
16          purpose of the question was.   So as you are going off  
17          on where you are going, I don't care where you are  
18          going because that wasn't the purpose of the question.

19                  CHAIRPERSON PACKER:   The purpose of the  
20          question as I understand it, Ray, had two components.  
21          One is do you believe that the measures that were --  
22          the instruments used are reflections of quality of

1 life, and second whether the drug showed an effect on  
2 those measures.

3 DR. LIPICKY: Correct.

4 CHAIRPERSON PACKER : They are both  
5 incorporated into this question.

6 DR. LIPICKY: That is correct.

7 CHAIRPERSON PACKER: And I think what --  
8 I get a very strong sense from the committee across  
9 the board that they believe that this instrument is  
10 reasonable, but I get a very split vote on the  
11 committee as to whether the drug showed an effect on  
12 this instrument.

13 DR. LIPICKY: Right. That is exactly the  
14 feeling I got and that gives me the answer I need.

15 CHAIRPERSON PACKER: Right. And in fact  
16 everyone who was hesitant was actually almost -- cited  
17 the identical reason for hesitancy.

18 DR. LIPICKY: Yes.

19 DR. TEMPLE: Milton?

20 CHAIRPERSON PACKER: Yes.

21 DR. TEMPLE: I need to ask Rob. In the  
22 analysis you are talking about that takes into account

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1 the people who leave, were you referring to the pooled  
2 analysis or the individual analyses of studies that  
3 you thought ought to have a persistent trend?

4 DR. CALIFF: The pooled analysis.

5 DR. TEMPLE: Okay.

6 CHAIRPERSON PACKER: I guess I would add  
7 to that, Bob, that if you are going to do the pooled  
8 analysis, I would like to actually -- and I would  
9 actually like to see that worst rank analysis as well  
10 for assigning worst rank to the people who dropped out  
11 because of adverse reactions. I would be a little bit  
12 more worried if in the pooled analysis the effect was  
13 no longer statistically significant at a nominal .05  
14 level.

15 DR. TEMPLE: For the pooled analysis.

16 CHAIRPERSON PACKER: From the pooled  
17 analysis.

18 DR. TEMPLE: Yes. There is no particular  
19 way that can happen given the results to date, but it  
20 is worth looking at. Can I just ask one question?  
21 This is because you believe that -- the people who are  
22 not persuaded believe that the quality of life

1 assessment isn't particularly about whether there is  
2 a benefit in claudication terms, but because you  
3 believe that the overall quality of life assessment  
4 ought to tell something about the totality of your  
5 quality of life. Okay. I want to express  
6 reservations about that point of view.

7 CHAIRPERSON PACKER: It is on the record.  
8 Number 8, how does the effect of cilostazol vary with  
9 regimen? Are the regimens less than 50 mg bid  
10 ineffective? Is the 50 mg bid regimen effective? Are  
11 regimens greater than 100 mg bid known to be toxic or  
12 to be no more effective than 100 mg bid? Actually,  
13 JoAnn, I would encourage you to answer this in the  
14 most straightforward way possible in terms of  
15 describing what you think we know about dose response.

16 DR. LINDENFELD: We don't know much about  
17 regimens less than 50 mg. I believe from this data  
18 that certainly 100 mg bid is effective, and I think  
19 that makes me also add to the data on 50 mg bid, which  
20 I believe is also effective. I don't know that we  
21 know that 150 mg bid is more effective or more toxic,  
22 but we do know that there are more adverse reactions.

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CHAIRPERSON PACKER: Does anyone disagree with that summary?

DR. THADANI: The 150, there is only one study, right? So in 150 there is only one study. So really we don't have any confidence. Because that did not beat say 100. I think we really don't know the true dose response because we never studied below 50. And on 50, there are two studies looking at the data given. So as she said, we don't know if 25 would have worked. I am not sure if 150, if given more studies, might not be better than 100. And looking at the toxicity, there was some evidence of slightly higher side effects, but not that much to be sure. So I think we don't know the whole therapeutic rate even of dose response.

CHAIRPERSON PACKER: I guess I need to ask Ray a question. It is actually fairly commonplace for us to see data bases where the sponsor has identified a dose which is pretty consistently effective and then shows that at lower doses, the effective is either there or not there depending on the type of trial. In other words, sometimes the trials there is only one

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1 trial that shows an effect of the low dose and  
2 sometimes the other trials show a trend which is not  
3 statistically significant. In the past, the agency  
4 has always accepted that kind of data with the low  
5 dose as evidence that that could reasonably be a  
6 starting dose of the drug because it seems as if it  
7 beats placebo at least in one trial. It wouldn't be  
8 enough to base the whole indication for it, but it has  
9 been enough to at least expand the dosing range.

10 DR. LIPICKY: Well, that is a very  
11 complicated question you are asking, and we will not  
12 take credit for the dose ranging trials that were  
13 planned here. It would be nicer to have had more than  
14 two doses in one trial, which is what we usually would  
15 recommend. But indeed if you want me to influence  
16 your thinking, each dose studied here beat placebo.  
17 So every dose was effective. You basically don't have  
18 a very good idea for how the magnitude varies as a  
19 function of dose and you really would need to have  
20 more doses in the same trial, which would give a  
21 better idea. If for some reason or another there was  
22 a single low dose study that looked like it beat

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1 placebo, and it was for a drug that was titratable,  
2 and in this case this should be a titratable drug  
3 because there is an endpoint. Can you walk far  
4 enough? No. Well, I will up the dose. Now can you  
5 walk far enough? No. Well, I will up the dose. In  
6 other things, you don't have titratable endpoints.  
7 And it does look as though whatever it is the adverse  
8 effects are are dose related. So it would be nicer to  
9 give people the walking distance they wanted with the  
10 least probability of side effects. So from a thinking  
11 process point of view, every dose that isn't placebo  
12 would be a reasonable dose to market. And it could be  
13 a titrated drug. So that is kind of the thinking  
14 process that would go behind it, but it would really  
15 be much nicer to see more than two doses versus  
16 placebo in a single trial because you get a better  
17 feeling and it would also be nicer to see the interval  
18 between doses larger. Because then you are more  
19 likely to be able to tell whether one dose is  
20 different from another.

21 CHAIRPERSON PACKER: Okay. JoAnn? Bob?

22 DR. CALIFF: Just a brief comment. I

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1 certainly agree with all of that. There are a couple  
2 of things. Just about every time more than one dose  
3 was studied, the larger dose was better, often  
4 significantly so, which I must say you don't see every  
5 day. So there is a fairly strong sense that you have  
6 a dose response, even though as Ray says it would have  
7 been better if there were three or four doses in each  
8 one. But the crucial thing from my point of view  
9 would be that we are somewhat worried about potential  
10 side effects and that there are fairly conspicuous and  
11 dose-related side effects. So you have a better case  
12 here than you have for some other situations, like say  
13 ACE inhibitors, where you are not really seeing  
14 anything dose related, so you say what the heck, give  
15 a good dose. Here there is a pretty good case for  
16 using a lower dose to start.

17 CHAIRPERSON PACKER: Okay. Let me just  
18 make sure JoAnn has summarized her sense about the  
19 doses and she believes the doses of 50 to 150 are  
20 effective, but that doses greater than 150 are  
21 associated with more side effects. I am sorry, doses  
22 greater than 100 have more side effects. Does anyone



1 disagree with that? Okay. That is what question 8  
2 asks. Question number 9, have cilostazol and its  
3 metabolizes been adequately evaluated with regard to  
4 enzyme interactions or do you need more data before  
5 cilostazol could be approved? And the summary of what  
6 is known is presented in the three paragraphs before  
7 the question.

8 DR. LINDENFELD: I think that I would --  
9 before approving this drug, I would like to see levels  
10 of either synthestatin or lovastatin with the drug,  
11 because I think those are going to be increasingly  
12 commonly used and I am not convinced that there is not  
13 a problem there. I think there is other data we would  
14 like to see, particularly how much enzyme inhibition  
15 it has, but I think I am satisfied for the moment with  
16 that exception in this patient group.

17 CHAIRPERSON PACKER : Lovastatin and  
18 synthestatin.

19 DR. LINDENFELD: Synthestatin.

20 DR. TEMPLE: Milton, can I ask the company  
21 if they happen to have any blood sitting around from  
22 people who were on those drugs during the course of

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1 trials? It is not that hard to detect an increase in  
2 the blood levels because it is very large.

3 DR. BRAMER: Yes, I believe we do. And  
4 prior to this meeting, we were looking into that exact  
5 situation of both those statins and any other  
6 medications that may be a weak substrate.

7 DR. LIPICKY: It will only take two days?

8 DR. BRAMER: They will only give me one.

9 DR. THADANI: I think given the  
10 interactions which we have come across recently in  
11 relation to statins, perhaps we ought to look at the  
12 antifungal agents just to be sure. Because wouldn't  
13 you like to see that it doesn't effect --

14 DR. TEMPLE : Well, again, one is  
15 inhibiting a different drug and now it is being  
16 inhibiting by another drug.

17 DR. THADANI: Sure. I realize that. But  
18 for safety reasons.

19 DR. TEMPLE: Well, Dr. Flockhart explained  
20 why they thought they had pinned that down reasonably  
21 well. You can agree or disagree.

22 DR. THADANI: Obviously you had concerns

1 earlier on because there was diltiazem at 50 percent  
2 as opposed to --

3 DR. TEMPLE: Yes. The question gives what  
4 are not mutually exclusive answers. So it is a  
5 somewhat defective question. You could conclude that  
6 it is not adequately worked up.

7 DR. THADANI: Sure.

8 DR. TEMPLE: I certainly would. But that  
9 doesn't necessarily imply that you think it has to be  
10 done before it is approved. So those are two separate  
11 questions.

12 DR. THADANI: No, no. We need some more  
13 data.

14 DR. TEMPLE: All right.

15 DR. KONSTAM: Milton?

16 CHAIRPERSON PACKER: Yes.

17 DR. KONSTAM: I mean it seems -- I am not  
18 sure that we are comfortable that there is sufficient  
19 evidence that there is no clinically relevant  
20 inhibition of 3A4, right? I would say that is --  
21 would everybody not agree with that?

22 DR. LINDENFELD: I think we know enough to

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1 say that with the warnings that have been suggested  
2 here that 3A4 substrates, one may need to watch the  
3 doses. Once we have levels of a couple of these  
4 things.

5 CHAIRPERSON PACKER: Bob, given recent  
6 experience with various drugs and the potential for  
7 drug interactions, is the agency beginning to think  
8 about formalizing what criteria it believes sponsors  
9 should follow or must meet? Because this comes up a  
10 lot. And in the past, we have tended to simply say  
11 that, gee, if you can describe it, that is nice. I  
12 think we have been less compulsive about it. Is there  
13 a movement that is in place to try to define exactly  
14 what needs to be known? Not only in terms of what  
15 enzymes may be inhibited or what drugs may be  
16 metabolized by enzymes or what the clinically relevant  
17 interactions might be?

18 DR. TEMPLE: Well, those are two very  
19 separate questions. We have a guidance already out on  
20 what in-vitro tests we expect. In-vitro tests can, at  
21 least sometimes, serve as a screen that says you don't  
22 have to do anymore. There is no inhibition at good

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1 high doses and that is it. And that is out. We are  
2 well along in the in-vivo guidance, which says if you  
3 can't rule out the need to do things with your in-  
4 vitro tests, here is what you need to do. And  
5 generally it says use the most sensitive system to  
6 pick out the potential. That is, if you are worried  
7 about being inhibited by something, test with  
8 ketoconazol. If you are worried about inhibiting  
9 something, test with synthestatin. We don't want you  
10 to test cisipride, because it is too dangerous.  
11 Something like that. So that is true.

12 Now the other question you have raised I  
13 don't think has been formally addressed. And that is  
14 it how bad is it if a drug blocks a major metabolizing  
15 enzyme? How much trouble is it? Well, in the case of  
16 mibefridil, that was probably its main trouble. It  
17 was a drug that looked very hard to use in the  
18 population that you had to use it in. And you could  
19 argue that the removal of trifenidine from the market  
20 was not really different from that. That was a drug  
21 that got in trouble only if you used it with the wrong  
22 drugs. you could say how to use it properly, but we

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1 knew that it wasn't being used properly. So those are  
2 two cases where you could say how to use the drug  
3 completely okay, or at least we thought so, and yet  
4 the reality was that there would be some bleed-through  
5 and it would not be used okay. So we are thinking  
6 about that. And part of the thinking is what is the  
7 benefit that comes along with this risk.

8 That said, there is very little evidence  
9 that this is an inhibitor of the magnitude of the  
10 kinds of drugs we have been worried about so far, but  
11 that doesn't mean there is no potential.

12 CHAIRPERSON PACKER: Abe?

13 DR. KARKOWSKI: There was one additional  
14 concern we had based on the trifenidine experience,  
15 which is what is the bioavailability of this drug.  
16 This drug will be given potentially on an empty  
17 stomach and people might take it with grapefruit juice  
18 and what are the consequences of this drug. If this  
19 drug had a high bioavailability, one wouldn't care.  
20 We don't know the bioavailability. How does that  
21 impact on your decisions for post-marketing or  
22 whatever studies you would like to see?

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1 DR. TEMPLE : I think there were figures  
2 given for its bioavailability, aren't there?

3 DR. THADANI: No absolute.

4 DR. KARKOWSKI: Those are estimates based  
5 on assumptions that we did not accept and I think the  
6 company doesn't feel strongly about them either.

7 DR. TEMPLE: Okay.

8 DR. THADANI: There is no IV data.

9 DR. LIPICKY: There is nothing relative to  
10 solution? Are you talking about absolute bio or what  
11 are you talking about?

12 DR. KARKOWSKI: IV to PO studies.

13 DR. LIPICKY: You are talking -- absolute  
14 bio is unknown. That is what you are talking about.

15 DR. KARKOWSKI: Correct.

16 DR. LIPICKY: Not that there were not  
17 bioavailability studies.

18 DR. KARKOWSKI: There was a number given  
19 in the briefing booklet which was an estimate.

20 DR. LIPICKY: Yes, fine.

2 DR. RODIN: Dr. Rodin, FDA. I saw some  
2 small sample preclinical data, oral suspension versus

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1 IV, and they looked like the mean. I didn't have a  
2 take on the variance, but the mean was quite a low  
3 bioavailability there. Something like 16 percent.

4 CHAIRPERSON PACKER: Does the sponsor have  
5 any comments on this issue?

6 DR. BRAMER: Yes, I do. Several things.  
7 We did a C-14 study with an alcoholic solution, and  
8 basically you see 74 percent of the radioactivity  
9 excreted in the urine. That means 74 percent of the  
10 drug was in the body with an alcoholic prep. If YOU  
11 look at the performance of suspension versus the  
12 alcoholic solution, they were fairly comparable, 80  
13 percent in suspension. And then if you look at the  
14 tablet performance versus the suspension, again you  
15 have with tablets versus suspension, it is 100  
16 percent. So, therefore, even though we don't have the  
17 absolute bioavailability or did not do a particular  
18 study, I do believe that this drug is not on the low  
19 side of its availability.

20 DR. TEMPLE: You can't say that. There is  
21 substantial metabolism. There could be gut metabolism.  
22 You have to know what the absorption of the active

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1 stuff is. What you know is that it gets in, but it  
2 could have been mostly in the form of a not very  
3 active metabolize. I mean, you don't really know until  
4 you look. Right? And this is a candidate for having  
5 variable bioavailability because it is a 3A4 drug.

6 DR. BRAMER: No, I agree that there are  
7 limitations to the argument I am making, but I do want  
8 people to realize that we have looked at different  
9 formulations, tablet, suspension, and solution, and we  
10 haven't really seen marked increases in absolute  
11 bioavailability when we go from a tablet to a  
12 solution. In solution, we expect to have greater  
13 availability.

14 DR. TEMPLE : But they also haven't seen  
15 large differences anyway with variable renal function  
16 and variable hepatic function.

17 DR. LIPICKY: But Abe is worried about  
18 double-strength grapefruit juice.

19 DR. BRAMER: The concentrated stuff.

20 DR. LIPICKY: Yes.

21 DR. BRAMER: I think your question about  
22 3A4 inhibition at the tip of the villus with

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1 grapefruit juice is also answered by the Erythromycin  
2 study .

3 DR. TEMPLE : Erythromycin, absolutely.  
4 Right. The Erythromycin should give you the  
5 approximate answer for grapefruit juice.

6 DR. LIPICKY: So now what is your worry,  
7 Abe?

8 DR. BRAMER : And there upon inhibition,  
9 you did see a doubling, a two-fold increase.

10 DR. THADANI: Yes. It could go to -- with  
11 other drugs, it could go much higher.

12 DR. TEMPLE: Doubling isn't 20-fold, but  
13 it is doubling.

14 DR. THADANI: You have the IV drug, right?  
15 You have the intravenous drug?

16 DR. BRAMER: I am sorry?

17 DR. THADANI: You have the drug in IV  
18 form?

19 DR. BRAMER: No, we do not.

20 DR. THADANI: You don't have it? Okay.

21 DR. BRAMER: We made attempts to make an  
22 IV formulation. The problem with this drug is its

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1 volubility. Japan and the United States took treat  
2 efforts to try to make an IV formulation. And the  
3 best we could come up with was an IV suspension, which  
4 we felt wasn't safe to give to humans.

5 DR. TEMPLE : I mean, the current  
6 recommendation is you are suggesting that people have  
7 the dose in various settings, and that is not  
8 unreasonable. I think a deficiency still is the lack  
9 of information so far about the active metabolize.  
10 Because halving the dose might not make any sense. It  
11 is not clear that those things are terribly worrisome.

12 DR. BRAMER: We do have metabolize data.  
13 I would like to say that when we look at Erythromycin  
14 as an example, we do see impact of 13015 and 13213.  
15 And therefore, we do have those pathways well  
16 characterized. And those are the only circulating  
17 analytes in plasma. So I do want to remind you that  
18 we do understand the metabolism of this drug.

19 DR. TEMPLE : And the active metabolize  
20 goes down?

21 DR. BRAMER : And the active metabolize  
22 definitely goes down --

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1 DR. TEMPLE: And the parent goes up. So  
2 it would be conservative, I suppose you would argue,  
3 to cut the dose down?

4 DR. BRAMER: Correct.

5 CHAIRPERSON PACKER: I think the committee  
6 -- I will look around -- would encourage the  
7 discussions between the sponsor and the division as to  
8 what additional information might be required on  
9 interactions to satisfy a regulatory need to provide  
10 adequate labeling information that would be  
11 incorporated into labeling. All right. We will move  
12 on to question 10. There has been a slight  
13 modification of question 10. Question 10 is really  
14 positioned to ask if there are deficiencies in the  
15 data base which the committee might consider to be  
16 fatal to' approval. With Ray's permission, I will  
17 eliminate question 10A, because I don't think any of  
18 us know the answer to it. And what I want to do is  
19 substitute for 10A the following question. The  
20 question is, is the lack of data -- is the present  
21 data base on the use of this drug concomitantly with  
22 anti-platelet drugs so insufficient that you would be

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1 reluctant to recommend approval? The second is, do  
2 you need a better estimate of the effective mortality  
3 before you recommend approval? Let me rephrase the  
4 first one. Do you need better data on concomitant  
5 therapy of this drug and anti-platelet drugs to  
6 recommend approval? And the second question is do you  
7 need a better estimate of the mortality effect to  
8 recommend approval? so question 10A is do you need  
9 more data on the interaction with anti-platelet drugs  
10 to recommend approval? We will take that question  
11 first. And before even -- JoAnn, I will ask you to  
12 begin, but these two questions are so important that  
13 after you vote on this, I do want to open it up for  
14 discussion. Go ahead. First is do you need  
15 additional data on the interactions with anti-platelet  
16 drugs to recommend approval?

17 DR. LINDENFELD: I think that there is  
18 probably enough data with aspirin to recommend  
19 approval and to get some post-marketing data with  
20 aspirin. But I think in order to -- and I think I  
21 could approve it with the caveat that we do not know  
22 what the interactions are with clopidogrel or

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1 ticlopodine. so I think the data is adequate, yes,  
2 for aspirin, and I would be willing to approve it.  
3 But somewhere it would have to say that we have no  
4 idea what the benefits are with ticlopodine or  
5 clopidogrel or the adverse events. We would have to  
6 make that quite clear.

7 CHAIRPERSON PACKER: Okay. JoAnn, before  
8 taking this around, if you recommended that -- I think  
9 what you are saying is that you do not think that the  
10 presentation limitation on data base would be an  
11 impediment for you in terms of looking favorable on  
12 approval. But if you were to actually say that you  
13 didn't know if clopidogrel or other anti-platelet  
14 drugs were widespread use, that would give or could  
15 give any physician that read the package insert some  
16 pause. My sense is that that is your intent.

17 DR. LINDENFELD: That is right. Except no  
18 one reads them.

19 CHAIRPERSON PACKER: Okay. Udho, we are  
20 going to go down the line on this. So, Ileana, the  
21 question is are you -- do you think the present -- do  
22 you need more data on the interaction with anti-

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1 platelet drugs before recommending approval?

2 DR. PINA: Let me just say that I don't  
3 think most physicians read package inserts. So I  
4 would have to rely on the marketing people to make  
5 that point very clear when the drug is being detailed  
6 should it be approved. so the answer is, no, I would  
7 not need more data for approval. However, I think  
8 that the warning has got to be there. Not because of  
9 interactions but because of bleeding, particularly  
10 with clopidogrel. Because I think the use is going to  
11 skyrocket in the next few months in most patients with  
12 vascular disease, even whether indicated or not. I  
13 think we are going to see it.

14 CHAIRPERSON PACKER: Okay. Ileana, just  
15 for the record, it really is a labeling issue and not  
16 so much whether physicians read labels or not. But if  
17 it is not in the labeling, then those who are involved  
18 in marketing won't be compelled to convey that  
19 information.

20 DR. PINA: I think it should be in the  
21 labeling.

22 CHAIRPERSON PACKER: Okay. Lem?

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1 DR. MOYE: Well, I think that it is one  
2 thing to say that we don't have the information. But  
3 then the question becomes what do you do without the  
4 information. And I am loathe to recommending approval  
5 in the absence of information. Information we must  
6 have before we make the recommendations. I am  
7 uncomfortable with voting for approval for a drug  
8 hoping that I am right. I want to be able to vote for  
9 approval knowing I am right, and I can't know it  
10 unless I have seen the authoritative data which  
11 demonstrates after rigorous scrutiny what the possible  
12 relationship is between clopidogrel and the drug at  
13 issue here. So I say in the absence of the  
14 information, I vote that it is impossible to vote for  
15 approval for this drug. And that before we can vote  
16 approval -- not vote for approval but vote approval --  
17 we must have the information from the sponsor about  
18 the potential interaction here.

19 CHAIRPERSON PACKER: Alan, you can comment  
20 although you can't vote.

21 DR. HIRSCH: I am comfortable with that.  
22 I think that we do need more information regarding the



1 clopidogrel/cilostazol interrelationship, probably  
2 both in-vitro as well as in-vivo, although I concede  
3 the current data with aspirin is adequate for me to  
4 let labeling do its magic or not magic trick.

5 CHAIRPERSON PACKER: So for you it would  
6 not --

7 DR. HIRSCH: It doesn't inhibit me from  
8 moving to labeling and bringing it to market.

9 CHAIRPERSON PACKER: Okay. Udho?

10 DR. THADANI: When we discussed the  
11 aspirin use at the last FDA meeting before you were on  
12 board, the weakest link was in peripheral vascular  
13 disease. But when I see the patients, all of my  
14 patients have peripheral vascular disease and coronary  
15 artery disease. So they are on aspirin. So given the  
16 two studies, one is comfortable. But the question  
17 will be patients with peripheral vascular disease are  
18 going to be put on clopidogrel because it has just  
19 been approved. You are talking about morbidity and  
20 mortality data. Somebody might end up on three anti-  
21 platelet agents. I would really like to see  
22 interactions in terms of safety data before I feel

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1 comfortable to say -- or there should be a black box  
2 in the warning labeling that there is no data. But I  
3 think I would like to see more data before going ahead  
4 and feeling secure that it should be used.

5 CHAIRPERSON PACKER: Okay. So your vote,  
6 if I am reading it --

7 DR. THADANI: For clopidogrel especially.  
8 I would like to see more data.

9 CHAIRPERSON PACKER: Okay. So YOU would  
10 like to see more data before recommending approval?

11 DR. THADANI: On the safety issues.

12 CHAIRPERSON PACKER: I understand. I  
13 think my understanding, Lem, is that your concerns  
14 were safety and efficacy? Because Udho I think is  
15 primarily saying safety.

16 DR. MOYE: My opinion is for both counts,  
17 safety and efficacy.

18 CHAIRPERSON PACKER: Okay. So far, just  
19 to summarize, Ileana would not consider it a block to  
20 approval, but would like to have it in labeling. Lem  
21 says he would like to see data on efficacy and safety  
22 before approval. Udho says he would like to see data

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1 on safety before approval. Tom?

2 DR. GRABOYS: I don't think we can depend  
3 on the labeling and I think we need to have full  
4 information before we let this drug loose.

5 CHAIRPERSON PACKER: So this is safety and  
6 efficacy?

7 DR. GRABOYS: Yes.

8 CHAIRPERSON PACKER: I am sorry?

9 DR. GRABOYS: Safety.

10 CHAIRPERSON PACKER: Safety. Okay.

11 DR. TEMPLE: Milton, can I just be sure?  
12 There has been a hint that maybe the aspirin data  
13 would be informative about platelet interactions in  
14 general. What are people saying? They need  
15 clopidogrel data or better aspirin data or better  
16 analysis of the aspirin data? We need to be clear on  
17 that, I think, as we go along here.

18 DR. THADANI: All of the above.

19 DR. TEMPLE : And also what would -- is  
20 this mostly about bleeding episodes? Is there  
21 anything else? Is it just bleeding episodes?

22 DR. THADANI: In addition to that, I think

1 there is a hint of excessive mortality here, 1.3.  
2 Whether we buy it or not. That is a different issue.

3 CHAIRPERSON PACKER: A separate issue.

4 DR. TEMPLE: Wait a minute. No, I mean  
5 the question I am asking about the platelet problem.  
6 The platelet problem. You can't get into the  
7 mortality problem. That is about bleeding. I just  
8 want to be sure we understand what we are being told.  
9 It is about bleeding. Aspirin would or would not  
10 substitute for specific data on clopidogrel. I think  
11 those need to be addressed as we go down the row.

12 CHAIRPERSON PACKER: Bob, I think the --  
13 what I would like to do is have the committee vote and  
14 then get a sense, no matter how they voted, of the  
15 specific answers to your question. Because *even* those  
16 who would vote one way or another would probably want  
17 it to be incorporated into labeling regardless, and  
18 then the question is what data do you need. So let's  
19 go through the vote. So the question is do you need  
20 more data before approval? If yes, is it efficacy and  
21 safety or just safety? Cindy?

22 DR. GRINES : I am not at all concerned

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1 about bleeding. I think that they have done studies  
2 with aspirin. I don't see that there has been any  
3 bleeding in their serious adverse events. And we  
4 routinely give ticlod and aspirin and aspirin and  
5 clopidogrel totally off label. So I am not at all  
6 concerned about that. What I do think we need more  
7 studies on is a combination of this drug with other  
8 vasodilators, which I see as a much bigger potential  
9 problem.

10 CHAIRPERSON PACKER: And you would be --  
11 you think that that is necessary before approval?

12 DR. GRINES: Or a requirement to perform  
13 a study after approval for safety issues.

14 CHAIRPERSON PACKER: Okay. If your  
15 feeling is the second, we will address that in  
16 question 12. But I think what you are saying is that  
17 your answer to this is that you do not need additional  
18 data prior to approval on the anti-platelet  
19 interaction?

20 DR. GRINES: Correct.

21 CHAIRPERSON PACKER: Okay. John?

22 DR. DIMARCO : I think clopidogrel data

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1 would be interesting, but I don't think it would have  
2 to be required for approval.

3 CHAIRPERSON PACKER: Okay. JoAnn? The  
4 question is a little bit different than the one you  
5 answered. So maybe you should vote formally.

6 DR. LINDENFELD: I don't think the lack of  
7 data -- I think the drug should be approved without  
8 additional data, but I would like to see more safety  
9 data on clopidogrel. And without that I would like to  
10 see clear labeling that we don't know the safety  
11 issues.

12 CHAIRPERSON PACKER: Marv?

13 DR. KONSTAM : I would not require more  
14 data on this subject before approval. But I would  
15 like to see a mandate for additional data following  
16 approval. Let me say I am uncomfortable about this  
17 point because I think that there is going to be  
18 widespread use of the agent on top of other anti-  
19 platelet agents, and I would raise questions on both  
20 sides. I would raise questions about the bleeding,  
21 although I am not super concerned about it. But I  
22 would like to see some effort done to answer the

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1 question. And I would like to see evidence for  
2 efficacy, specifically on top of clopidogrel. I would  
3 like to see that done. The reason that I am  
4 permissive of approval prior to the acquisition of  
5 that data really stems from the very impressive  
6 efficacy data set without anything else out there  
7 comparable at this point in time. And so for those  
8 reasons, I am pushed not to delay approval based on  
9 these concerns. But I think the concerns are real,  
10 and I would like to see a mandate for more than just  
11 labeling, but for acquisition of additional data  
12 following approval.

13 CHAIRPERSON PACKER: Now , Marv -- I am  
14 sorry, Ray?

15 DR. LIPICKY: Well, just one other  
16 question and I will just ask Marv. I don't want to go  
17 back through everybody. What kind of efficacy are you  
18 thinking about? The efficacy of walking distance or  
19 the efficacy of saving life that clopidogrel has?

20 DR. KONSTAM: No, no, no. The efficacy of  
21 walking distance. I am not --

22 DR. LIPICKY: You are not worried about

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1 doing away with clopidogrel's effects?

2 DR. KONSTAM: I am sorry?

3 DR. LIPICKY: You are not worried about  
4 doing away with clopidogrel's effects?

5 DR. KONSTAM: I am not sure what you are  
6 asking?

7 DR. LIPICKY: Fine.

8 DR. KONSTAM: The way I would design it,  
9 I would design it as this drug on top of background  
10 therapy with clopidogrel.

11 DR. LIPICKY: Right. But are you worried  
12 that clopidogrel has exercise tolerance effects that  
13 have never been measured and consequently it would do  
14 no good to add this drug?

15 DR. KONSTAM: Yes. Exactly. You said it.  
16 That is the question.

17 DR. LIPICKY: I see.

18 CHAIRPERSON PACKER: Okay, we are just  
19 going to -- before we talk to -- I am just going to  
20 ask Rob. Joan just needs to get the vote right.  
21 Those -- we just want to make sure we have got the  
22 record straight. Those who would withhold -- need

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1 data before approval -- Ileana, you said you need data  
2 before approval?

3 DR. PINA: No.

4 CHAIRPERSON PACKER: No. I am sorry,  
5 those who said they needed data before approval were  
6 Lem, Udho, and Tom, is that right? Okay, good. Okay,  
7 Rob?

8 DR. CALIFF: I would hope that -- there  
9 are a certain number of patients that were on aspirin  
10 in one of the studies. And as Cindy has pointed out  
11 with regard to bleeding, we are bombarding patients  
12 with so much more platelet inhibition that this stuff  
13 does that I am not really particularly worried, and I  
14 would hope that just going back to that data set would  
15 answer the safety question within a reasonable realm  
16 for the aspirin combination. I think whether the drug  
17 is looked at on top of clopidogrel is really a  
18 question for the sponsor in a competitive way.  
19 Because I would think an astute peripheral vascular  
20 physician would be loathe to add this to clopidogrel  
21 until there was some evidence that it really added  
22 something and didn't create a problem. But I don't

1 think that ought to be a requirement for getting  
2 approval. I would think it would be a smart thing to  
3 do in terms of improving the competitive position.

4 CHAIRPERSON PACKER: Okay. My own vote,  
5 and I must say that I have waxed -- I have gone back  
6 and forth on this one. I take, I think, both Rob and  
7 Cindy's point that we have cardiologists commonly  
8 throw a lot more combinations of drugs with anti-  
9 platelet effects on patients without any problems than  
10 might exist in this case. But I guess I -- if there  
11 were to be a reasonable chance that in the hands of  
12 primary care physicians a combination of this drug and  
13 clopidogrel would be bad, the last thing I would like  
14 to do is to know that a year from now after there are  
15 25 reports of hemorrhage. My sense is that it would  
16 be pretty easy to get that experiential data quickly.

17 DR. CALIFF: One thing I forgot to  
18 mention. I also agree with Cindy. Just from the  
19 perspective you mentioned, I am much more worried  
20 about vasodilators than I am about anti-platelet  
21 effect. And it sounds as if in all the trials that  
22 people on vasodilators were systematically excluded

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1 from the studies. This drug is a vasodilators. There  
2 is experience with blood pressure not necessarily  
3 going up and with heart rate going up -- a lot of  
4 people with ischemic heart disease. So there are a  
5 lot of concerns that I think need to be reflected  
6 seriously by the committee.

7 CHAIRPERSON PACKER: I guess I do need to  
8 formally vote, and my formal vote would be that I  
9 wouldn't see it as a bar to approval, but I really  
10 would like to see the labeling made clear that there  
11 is no information on the use concomitantly with  
12 clopidogrel. I think we need to let physicians know  
13 that.

14 DR. FORBES : Could I just make a  
15 clarification? I have heard this comment twice.  
16 Actually, we did not exclude vasodilators and we did  
17 not exclude nitrates. We withheld nitrates the  
18 morning of exercise. In other words, if patients were  
19 having angina -- if they were to that point where they  
20 were having angina before they were coming in --

21 DR. THADANI: We are talking about anti-  
22 platelet agents at the moment.

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1 DR. FORBES: Pardon me?

2 DR. THADANI: We are talking about  
3 clopidogrel at the moment.

4 DR. FORBES: Yes, but the vasodilator  
5 comment has come up twice now. And we can't tell you  
6 how many patients were on what vasodilators and how  
7 many were on them. So I just want to be real clear  
8 that we did not exclude those drugs.

9 DR. THADANI: Milton, if I could make one  
10 comment on the anti-platelet agent. I realize, Cindy,  
11 I do the same. We are aggressive with them. But  
12 those patients are under observation. And I have seen  
13 patient's hemoglobin dropping from 14 to 7 on oral  
14 agents. So I am not sure that we can be absolutely  
15 sure that the two anti-platelet agents are okay. This  
16 patient had no bleeding problem. We saw him on  
17 routine test and his hemoglobin was 14. This was an  
18 oral 2B3A. So I think that those are under protocol  
19 and we are watching that. And to give an open blanket  
20 statement that three anti-platelet agents can be used  
21 in all patients, I think I would be very reluctant on  
22 that.

1 DR. GRINES : I think there is a huge  
2 difference between an oral 2B3A, which is under  
3 investigation, compared to a drug which has as far as  
4 I can tell no bleeding complications at all.

5 DR. THADANI: But we don't have any data  
6 on citocloripine plus this plus aspirin. There are  
7 different mechanisms of action, so we really don't  
8 know.

9 DR. GRINES: Right. But we routinely --  
10 there are hundreds of thousands of patients every year  
11 in this country just getting stunts and the routine  
12 treatment is ticline and aspirin.

13 DR. THADANI: For four weeks.

14 DR. GRINES: For four weeks, right.

15 CHAIRPERSON PACKER: Okay. Bob, before  
16 you comment, I think the sense that the committee has  
17 is that by a 7 to 3 vote, they would not view the lack  
18 of information as an impediment to approval, but they  
19 think such information is very important and that the  
20 labeling should make clear if the drug is approved  
21 that at the present time that information is not  
22 available.

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1 DR. TEMPLE : Right. That is what I  
2 actually want to ask you about and to the particular  
3 comment that Ray stated. The numbers were going by  
4 fast, but it sounded like there were something like  
5 500 or 600 patients who had gotten aspirin  
6 concomitantly with the drug. That gives you at least  
7 some assurance about intracranial hemorrhage. The  
8 only intracranial hemorrhage I am aware of is someone  
9 who got TPA. So that looks pretty clean so far. Are  
10 you saying that even if someone had a fairly  
11 substantial aspirin experience that you would still  
12 have a very strong statement about clopidogrel? And  
13 there are many other drugs coming along or already out  
14 there that affect platelets. Is this a matter of  
15 establishing for once that the combination with an  
16 anti-platelet drug is okay, or do you really think  
17 that as new drugs come along you have to keep doing  
18 it? And I thought what Cindy said matters a little  
19 bit. I mean, there doesn't seem to be any real effect  
20 here. How far does this go? I also note that people  
21 were excluded from NSAIDS, which I would say is more  
22 troubling than all the other exclusions since

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1 everybody uses them so much.

2 DR. THADANI: Bob , on the clopidogrel  
3 data, if I remember correctly, there was no  
4 combination group. They compared to aspirin, but  
5 there was never aspirin plus clopidogrel. So we don't  
6 have safety data on a combination of aspirin plus  
7 clopidogrel. Remind me if I am wrong. But I do not  
8 -- unless my memory is --

9 DR. TEMPLE: No. But as somebody has  
10 said, we have three -- I don't know how many hundred  
11 million people have gotten aspirin with ticlopinine.

12 DR. THADANI: I realize that. But suppose  
13 a patient goes on both and then a third drug?

14 DR. TEMPLE : I am asking a different  
15 question. Is this a matter of principle that you need  
16 to know how the drug when added to a drug with  
17 platelet activity works, or is it particularly  
18 clopidogrel that there needs to be data on? What  
19 Milton said made me think that it was the latter, and  
20 I guess I had thought that it was the former and that  
21 people thought that aspirin data would provide the  
22 kind of reassurance -- if there were enough of it

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1 would provide the kind of reassurance you are talking  
2 about. But maybe I am wrong in thinking that.

3 DR. THADANI: It is a moving target  
4 because clopidogrel is going to be used more. That is  
5 why we want the data.

6 DR. TEMPLE : And there will be an oral  
7 2B3A inhibitor one of these days fairly soon too. So  
8 what -- is this a principle or do you have to sort of  
9 study each drug?

10 DR. THADANI: It is a principle. It  
11 should be a principle and a safety issue.

12 DR. TEMPLE: Say again?

13 DR. THADANI: It should be a principle and  
14 a safety issue. If I am going to use a drug, I want  
15 to know there is no increased bleeding in clinical  
16 practice.

17 DR. TEMPLE: Okay. Never mind.

18 DR. KONSTAM: Bob, there is the efficacy  
19 question too, though. There is a question of whether  
20 or not it is effective on top of clopidogrel.

21 DR. TEMPLE : Yes, that is a different  
22 question.

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1 DR. LIPICKY: Why do you think that that  
2 would be a question? Is there any reason for that?

3 DR. KONSTAM: Sure.

4 DR. LIPICKY: What?

5 DR. KONSTAM: Because since we don't know  
6 the mechanism of action of this agent --

7 DR. LIPICKY: Well, you know it was  
8 effective on top of that aspirin.

9 DR. KONSTAM: But clopidogrel is a more  
10 potent anti-platelet agent than aspirin.

11 DR. LIPICKY: And how does --

12 DR. KONSTAM: And how do we know that?

13 DR. LIPICKY: Well because patients were  
14 on aspirin in these placebo-controlled trials.

15 DR. KONSTAM: 500.

16 DR. LIPICKY: Yes, right.

17 CHAIRPERSON PACKER: We have not seen --  
18 the sponsor will obtain at some subsequent point in  
19 time a subgroup analysis of efficacy of aspirin versus  
20 non-aspirin patients. We have not seen that. Maybe  
21 we will now.

22 DR. KAZEMPOUR: Yes. We conducted the

1 aspirin and no aspirin study, and the result is that  
2 -- I can read the data for you. For the placebo arm  
3 first, the mean walking distance was 13 percent with  
4 aspirin. Without aspirin, it was 15 percent. So it  
5 was 15 percent versus 13 percent. And then looking at  
6 the 100 mg with aspirin is 39 percent and 100 mg  
7 without aspirin is 30 percent.

8 CHAIRPERSON PACKER: 30 percent is the  
9 last one?

10 DR. KAZEMPOUR: 30 percent. So with  
11 aspirin, it was more efficacious within the range.  
12 But the placebo was no difference between aspirin and  
13 no aspirin.

14 DR. CALIFF: I think that is helpful. The  
15 sample size for that was?

16 DR. KAZEMPOUR: The sample size for the  
17 100 mg with aspirin was 178. Without aspirin, the 100  
18 mg was 720. And the placebo with aspirin was 150 and  
19 without aspirin was 754.

20 DR. KONSTAM : You know maybe the  
21 peripheral vascular disease experts in this room can  
22 tell me that this is absolutely impossible. But I

1 would still -- since we don't know the mechanism of  
2 action of this drug, I think in my mind it is  
3 conceivable that the anti-platelet action of this drug  
4 is a major contributor to it. I think clopidogrel is  
5 a more potent anti-platelet agent than aspirin. And  
6 furthermore, although we have some background  
7 information -- we have some information about a small  
8 subset of patients that had some -- that had a check  
9 box somewhere that they were on aspirin, but that is  
10 not the same as really asking the question in a  
11 systematic way, does this agent add to clopidogrel.  
12 So I would just say that. Now if somebody wants to  
13 say there really is no reason to raise that question,  
14 I would defer.

15 DR. THADANI: So your aspirin data is only  
16 on 178 patients?

17 DR. KAZEMPOUR: The one that we have, yes.  
18 For the 100 mg, yes.

19 DR. THADANI: Yes, with the drug. But we  
20 were told it is about 700 or 800 patients and that is  
21 not true.

22 DR. KAZEMPOUR: We had study 96202. In

1 that one, **people** could take aspirin.

2 DR. THADANI: But in controlled studies,  
3 you only had 178 patients, is that correct?

4 DR. KAZEMPOUR: 96202 is also a controlled  
5 study . But here we looked at all 8 studies that we  
6 had.

7 DR. THADANI: Oh, the one you showed  
8 earlier. The 8 studies you showed earlier.

9 DR. KAZEMPOUR: The 8 studies.

10 CHAIRPERSON PACKER: Dr. Hiatt?

11 DR. HIATT: Just briefly. there is very  
12 little data on pure anti-platelet effects on treadmill  
13 performance and walking distance. There are the three  
14 trials **on ticlopendine** that show very modest effects.  
15 Nothing like you have seen today. I have made  
16 proposals to other sponsors to look at 2B3A receptors  
17 and all that in this particular endpoint. But right  
18 now there is no signal with aspirin and there is very  
19 marginal signal with **ticlopedine**. And if you want to  
20 explain the benefit this drug purely on its **anti-**  
21 **platelet** effects, I think it is a weak argument.

22 DR. KAZEMPOUR: I would like to clarify

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1 one more point. I only mentioned 100 mg. The 178  
2 that I mentioned was only 100 mg. If you add 50 mg to  
3 it, you **add** 125 to that, which the effect was in the  
4 same direction. I focused only on 100 mg.

5 CHAIRPERSON PACKER: And you should  
6 probably include the placebo taking aspirin as a  
7 comparator.

8 DR. KAZEMPOUR: If you include that, then  
9 it will be about 400.

10 CHAIRPERSON PACKER: You have to because  
11 your treatment effect is going to be placebo  
12 corrected.

13 DR. KAZEMPOUR: Exactly. The treadmill  
14 effects are placebo corrected and baseline corrected.

15 DR. LINDENFELD: I think one reason we  
16 **would** like to see just a little more data on  
17 **clopidogrel** is this question of **ticlopedine** and  
18 **cilostazol** in Japan causing gastric hemorrhage. We  
19 don't **have** any data, but it is mentioned a couple of  
20 times. And it is mentioned so specifically that I  
21 have a little concern about it.

22 CHAIRPERSON PACKER: Okay. I think we

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1 have sent the FDA a clear signal on this. Again, the  
2 majority vote of 7 to 3 is to suggest that this is not  
3 an impediment to approval. The second component of  
4 this question is the present estimate of the mortality  
5 effect. Do you need a better estimate before  
6 recommending approval? The same concept. Is the lack  
7 of mortality data worrisome enough that you would not  
8 recommend approval? And, JoAnn, why don't we start  
9 with you and then we will open it up for discussion.

10 DR. LINDENFELD: I think it is worrisome  
11 enough **not** to recommend approval. I think that  
12 although these are not heart failure patients and that  
13 is where we have mortality data, this is a drug that  
14 increases mortality in those patients and several  
15 different types of drugs which have contractility and  
16 heart rate effects just like this drug. And I think  
17 that although the risk of these patients was low, I  
18 think as has been mentioned before, Rob mentioned it,  
19 I think this will be used in some patients with more  
20 risk factors, and I would like to be able to tell the  
21 patients that I have some idea of what the mortality  
22 effect is.

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1 CHAIRPERSON PACKER: JoAnn, before we open  
2 this up for discussion, there used to be a time in the  
3 development of drugs for heart failure that if a  
4 sponsor came in with trials of 3 to 6 months in  
5 duration and that is all, no long-term studies, they  
6 could get approval. Now that would be very unlikely.  
7 Right now much longer term data is generally required  
8 of any new drug for the treatment of heart failure.  
9 Throughout the discussion with the FDA, the sponsor  
10 was given the impression -- I think this is true --  
11 that the way the drugs were to be developed for the  
12 treatment of intermittent **claudication** resembled the  
13 way that drugs would be approved for the treatment of  
14 heart failure 10 years ago. By your answer, you are  
15 suggesting that the criteria for the approval of drugs  
16 for intermittent **claudication** should now resemble the  
17 kind of data base we require for drugs for heart  
18 failure. Is that correct?

19 DR. LINDENFELD: Not exactly. I wouldn't  
20 be adverse to that, but I think that at least where we  
21 have a drug that we know increases mortality in a  
22 certain subset of the population which may overlap

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1 here a little bit, in that setting, yes, I think I  
2 would need to have that. When we know that this drug  
3 increases mortality several different times in several  
4 different studies. Not in the same population.

5 CHAIRPERSON PACKER: Okay. Actually --  
6 yes, Ray?

7 DR. LIPICKY: Could I just ask -- I  
8 understand that there are a couple of drugs in this  
9 class, maybe it is three or four, that have been  
10 associated with long-term oral use and in placebo  
11 controlled trials in patients with heart failure have  
12 been associated with having an adverse **clinical**  
13 outcome. Do you -- those drugs in those diseases were  
14 being used at the maximum tolerated doses, were being  
15 used in association with Digitalis, were being used in  
16 association with diuretics, and were being used in  
17 association with other drugs also in the treatment of  
18 heart failure. So that what is it that makes you  
19 think **that** that experience is able to be translated  
20 and that now that is an expectation when this is at  
21 **another** dose, it is clearly, **clearly, clearly**, I will  
22 say, although I recognize I am exaggerating, at a dose

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1 that is less than will increase contractile force and  
2 decrease cyclic AMP in the heart -- yes.

3 CHAIRPERSON PACKER: **No.**

4 DR. LIPICKY: Why do you say that?

5 CHAIRPERSON PACKER: Based on the rabbit  
6 data?

7 DR. LIPICKY: Yes.

8 CHAIRPERSON PACKER: **So?**

9 DR. LIPICKY: **So.**

10 CHAIRPERSON PACKER: We are not rabbits.

11 DR. LIPICKY: Do you know something  
12 different?

13 CHAIRPERSON PACKER: We are not rabbits.

14 DR. LIPICKY: No. I am just saying -- I  
15 said I was exaggerating. But it looked as though that  
16 was at a very low concentration. so what is it -- I  
17 just want to know why you are so sure that the other  
18 phosphodiesterase experiences in heart failure is  
19 translatable to any other patient population in any  
20 other setting with any other concomitant medications?

21 DR. LINDENFELD: Well, I don't think I am  
22 sure at all, but I would feel a whole lot more

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1 comfortable here if these similar types of drugs  
2 hadn't increased mortality.

3 DR. LIPICKY: I understand.

4 DR. LINDENFELD: I am not sure it  
5 translates it, but it makes me much more --

6 DR. LIPICKY: But you are asking for proof  
7 that it does not.

8 DR. CALIFF: But wait a minute. You  
9 demand this .00125 for whether somebody can walk a  
10 little further on the treadmill. I mean how unsure do  
11 you need to be about something like whether somebody  
12 lives or dies?

13 DR. LIPICKY: Well, I would be willing to  
14 -- I would be willing to say I am willing to approve  
15 this drug even if it increases the mortality by 1.3.  
16 And therefore, that is just a number and that doesn't  
17 matter. So it isn't clear to me exactly why one would  
18 argue I must know the number before I can decide about  
19 approval. Because then that excludes approval.

20 CHAIRPERSON PACKER: Ray, before -- this  
21 can get very interesting. Just let me make sure. You  
22 said **you** would approve a drug if it increased

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1 mortality -- if you knew -- knew -- it **would** be a big  
2 study to know -- that it increased mortality by 30  
3 percent.

4 DR. LIPICKY: Right.

5 CHAIRPERSON PACKER: Would you approve a  
6 drug if you knew it increased mortality by 200  
7 percent?

8 DR. LIPICKY: Well, that might be a little  
9 harder, **but** I would still make the same argument and  
10 let me make it now. And that is it is not up to you  
11 to say to doctors and patients that that is a risk  
12 that no one must ever take. It is up to the doctor  
13 and the patient to make the decision whether that is  
14 a risk that they want to take and not up to you 11  
15 people to say I will not allow you to take a risk like  
16 that.

17 DR. GRABOYS : It is our responsibility,  
18 though , **to** have guidelines for how we are going to  
19 then convey this kind of information to the physician,  
20 and then the physician and the patient will deal with  
21 that.

22 DR. LIPICKY: Well, fine. That is another

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1 issue. I am just saying I don't think it is -- I  
2 **don't** think I would like to see whether I could make  
3 that choice lay in your hands at this instance.

4 DR. CALIFF: You are doing something --  
5 you turned **me** off here. Maybe it is on purpose. But  
6 consider basically what you are doing is saying we are  
7 not going to ever have this information and so we will  
8 deprive the patient and doctor of ever being able to  
9 make that choice.

10 DR. LIPICKY: **No.**

11 DR. CALIFF: The choice they are making is  
12 I am going to take the drug in the absence of any  
13 knowledge about whether it may harm me.

14 DR. LIPICKY: **No.** I am saying that at  
15 this point in time one could say I have a point  
16 estimate and it looks bad. I realize it is not  
17 informative and that it isn't really a decision, but  
18 that is the most adverse thing you could say. So that  
19 I don't have to have a highly honed specific point  
20 estimate. so I know it is 1.31 plus or minus .05. I  
21 can consider approving it on the basis of this. It  
22 would have to have very bad labeling and say it has an

1 adverse effect on mortality. That all drugs known in  
2 this class have an adverse effect on mortality and  
3 that you don't know if people who are on **clopidogrel**,  
4 whether **they** will bleed to death, et cetera, et  
5 cetera. But that none of those things preclude the  
6 consideration of approval. What you are voting on now  
7 is you don't know a number and you are saying because  
8 I don't know that number, it precludes my even  
9 considering approving it. I have to know that number  
10 with more precision.

11 CHAIRPERSON PACKER: Marv?

12 DR. KONSTAM: I would just like to chime  
13 in with Ray for a second and take it another point.  
14 Which is let's just take the milrinone signal. Let's  
15 take the signal from milrinone in Class III and IV  
16 heart failure as an item that is raising this concern.  
17 Okay, well that was a 28 percent increased mortality  
18 in a **group** of patients with Class III or IV heart  
19 failure with all of the concomitant medications that  
20 Ray points out. Now it turns out that that turns out  
21 to be very similar to the point estimate of the 1.3 to  
22 1 that we see here. But as Dr. Borer points out, that

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1 is the difference between in the case of **milrinone**  
2 going up I don't know what it was -- from 20 percent  
3 to 30 percent one year mortality or more than that --  
4 as opposed to going from 2 percent to 2.6 percent. So  
5 I don't think all -- number one, I don't think **all**  
6 potential **28** percent increases immortality are alike.  
7 And with this background of 2 percent mortality per  
8 year in this population, it is much less concerning  
9 than if you had a background mortality of 20 or 30  
10 percent. So that is one point.

11 The second point is I think we cannot look  
12 at this question in a vacuum from the efficacy  
13 question. What was the known efficacy of **milrinone** in  
14 heart failure relative to other available therapies?  
15 Here we are seeing a debilitating condition for which  
16 we have heard from experts in the field that there is  
17 nothing else out there for these patients. Now I  
18 think that that has to be factored in. There is going  
19 to be a risk in this decision, but this is a risk  
20 being taken in the background of I might say an  
21 efficacy, data set that is better than any that I have  
22 seen in my two years on the panel and a drug in

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1 isolation, where there is nothing comparable to it  
2 that we know of. So I think for those reasons, I  
3 think it is not -- I mean, I get accepting of the  
4 signal that we see there and don't necessarily need to  
5 be as rigorous as I might be under the other  
6 circumstances.

7 CHAIRPERSON PACKER: And Marv, just to try  
8 to elucidate this. The reason for making the  
9 distinction here is not because you do not share  
10 JoAnn's concerns, because I think from everything you  
11 have said you do. It is because of the fact that you  
12 are factoring in a risk to benefit relationship which  
13 states that there are not -- maybe no other drugs or  
14 very little, and there is a benefit as opposed to  
15 **milrinone** where there was no benefit. I guess the  
16 analogous situation would be to take a look at  
17 examples where there have been drugs which there has  
18 been a benefit but also an increased risk like  
19 flosequinine.

20 DR. KONSTAM: Right. That is one point.

21 DR. TEMPLE: No, that is not correct.  
22 Flosequinine had no benefit after three months. **That**

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1 is an important part of why we won't agree.

2 CHAIRPERSON PACKER: That is a correct  
3 statement.

4 DR. KONSTAM : So there are two points.  
5 One is the clear and unique, at this point, benefit of  
6 this drug. And two is the very, very low relatively  
7 to the Class III and IV heart failure population --  
8 relatively much less background incidence. So that  
9 the theoretical 30 percent, if we picked it, would  
10 have a much less overall impact.

11 CHAIRPERSON PACKER: But let me just have  
12 you complete the thought here. I think that  
13 everything you are saying -- it goes from 2 to 2.6,  
14 what can you say. But the point estimate here is  
15 unbelievably coarse and does not preclude an increase  
16 of 100, 200, 300 percent, probably even more. Wou ld  
17 our equations change if you went from 2 percent to 6  
18 percent?

19 DR. KONSTAM : Yes, of course it would.  
20 But what Ray is asking is, I think, what is the signal  
21 that is making us raise this concern in this case with  
22 this drug in this population. And the signal that is



1 making us raise the concern is the milrinone and  
2 anoxinone and flosequinine data in heart failure. So  
3 I think if that is the signal that is making us raise  
4 the concern, then we really have to analyze what the  
5 differences are in this circumstance compared to that  
6 circumstance. And I think that the differences are so  
7 huge that I don't see a specific reason why we would  
8 be that concerned in the background of the strong  
9 efficacy that is here. I mean that is really the way  
10 I would frame it.

11 DR. THADANI: When you are saying  
12 differences are huge, if you take the heart failure  
13 population and all the similar classes of drugs, 50  
14 percent of the patients have coronary artery disease.  
15 So the increased death is a mixture of whatever  
16 reason, but the underlying disease which killed them  
17 could be sudden death or not necessarily worsening of  
18 heart failure. So that if they have got underlying  
19 coronary artery disease and you see some signal that  
20 this might be adversely effecting mortality, in the  
21 absence of a large trial, one feels very uncomfortable  
22 that you could be harming the patient as far as that

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1 is concerned. so I think the fact that you are saying  
2 they are Class II, III, or IV failure, the underlying  
3 pathophysiology on those patients also is coronary  
4 artery disease. And possibly they could die because  
5 you are increasing whatever the mechanism is that is  
6 there.

7 DR. KONSTAM: The two differences, **Udho**,  
8 that I am pointing out are one is the background  
9 mortality to risk, and two is the strong efficacy  
10 signal that we have.

11 DR. THADANI: But say you've got a **65-**  
12 year-old male who could walk 400 meters and he could  
13 walk another block and you tell him I can give you a  
14 drug that you can walk one more block, but there is a  
15 chance you might drop dead say 30 percent more. Is  
16 the patient going to take it? Or am I going to even  
17 give him the drug?

18 DR. HIRSCH: Can I try that one? Can I  
19 try what Marv is trying to say here for one minute?  
20 Sort of the last ditch effort here before the PAD  
21 expert runs. There have been at least three  
22 international meetings where the PAD community has sat

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1 for days on end talking about the drug approval  
2 process, and we have hashed this same question of do  
3 we learn from these past analogies, for example of PDE  
4 inhibitors and heart failure, do we learn anew in a  
5 new disease. I just want to recapitulate what Marv  
6 said.

7           Again, whereas there are these class  
8 effects that we are all aware of in our community,  
9 this is a different disease with a different  
10 background. We don't have the same degree of LV  
11 dysfunction, so you cannot extrapolate one set of  
12 worries. We don't want to have patients die, but you  
13 can't make that extrapolation entirely. The second  
14 point again, there are no other therapeutic options.  
15 To a certain extent, this is an orphan disease where  
16 there are not pharmacotherapies that have been  
17 effective. Looking for perfection, the life-saving,  
18 symptom-ameliorating drug is not going to happen for  
19 the first few drugs that come to market. If you  
20 expect that to be the gold standard, you can just I  
21 think personally not expect therapies to come down the  
22 road.

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1 DR. LIPICKY: Just one other small point  
2 I would like to make. And that is if you are using  
3 the congestive heart failure phosphodiesterase  
4 inhibitor stuff as **the** reason for your suspicion, you  
5 have pretty good point estimates of what the excess  
6 mortality might be. So there isn't any reason to  
7 speculate **if** that is the bias you are bringing to this  
8 about having 500 percent increases. Unless you want  
9 to impose other strange things upon something that you  
10 don't know anything about.

11 DR. HIRSCH: But it is imperative that we  
12 have better point estimates. I don't want anybody to  
13 take from this that we are satisfied with these wide  
14 confidence intervals. That can't be the standard for  
15 the future."

16 CHAIRPERSON PACKER: Bob?

17 DR. TEMPLE : If **people** are **just** non-  
18 specifically worried, that is, because they don't have  
19 the answer, that is one thing. If **people** are **focusing**  
20 on this so-called point estimate, that is really an  
21 abomination. There is no point estimate here. This  
22 is absolute nothing. If you look at the actual cases,

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1 very few of them are candidates even for having been  
2 drug-related. So be worried as a non-specific matter.  
3 That makes sense. But not because of that 1.3. That  
4 is absurd. But I need to make a point. If you look  
5 at the number of people who had sudden death, I **didn't**  
6 see anybody -- there might have been one person who  
7 might have had progressive heart failure. If **you** look  
8 at the **number** of people who had sudden death, you need  
9 to think about what size study could be done to answer  
10 this question, and it will not be small. I am  
11 thinking 10,000 or 20,000 or that neighborhood to get  
12 the answer to this question.

13 DR. KONSTAM : Well, I don't think that  
14 would be necessary. I mean I would like to see us  
15 commit ourselves philosophically at any rate to what  
16 -- the question I asked Jeff, which is, well, okay  
17 what **level** of increased mortality would we tolerate  
18 given the efficacy magnitude that we have here. And  
19 I don't -- and my own answer would be it would be much  
20 more than the 1.3.

21 DR. TEMPLE : Well, the 1.3 is what  
22 happened in the susceptible population with the bad

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1 drug. That is our model. That was what **milrinone** did  
2 in that population that has bad heart failure. So why  
3 would you think it would be more than that in these  
4 people who don't? so you want to rule out a 1.3  
5 percent risk with a population that has virtually --  
6 well as **we** just saw, there are 1,000 patients here.  
7 It is not zero. It has a very low risk of these  
8 events. And I think one has to think about what the  
9 numbers are going to be. I can't do that in my head,  
10 but probably Lloyd can or Lem can. It is a pretty big  
11 study we are talking about here.

12 CHAIRPERSON PACKER: Yes, Bob. I do want  
13 to make 'clear that I don't think anybody on this  
14 committee **is** concerned about this issue because of the  
15 observed point estimate. That would be absurd.

16 DR. TEMPLE: I just wanted to make sure.

17 CHAIRPERSON PACKER: Yes. None of this  
18 discussion would be taking place had there not been  
19 the prior experience with phosphodiesterase inhibitors  
20 and heart failure period. If there had been no  
21 previous experience -- well, Rob will modify that  
22 slightly perhaps. But if there had been no previous

1 experience, this 1.3 estimate would have gotten no  
2 discussion today.

3 DR. TEMPLE: Well, it still deserves no  
4 discussion, but the general question does.

5 CHAIRPERSON PACKER: Right.

6 DR. TEMPLE: But it is worth remembering.  
7 The **milrinone** study, you know the numbers. What did  
8 that have, 500 people in it? 400?

9 CHAIRPERSON PACKER: Milrinone? 1080.

10 DR. TEMPLE: 1080. But there were three  
11 groups, right?

12 CHAIRPERSON PACKER: No, two.

13 DR. TEMPLE : Okay. So in a study with  
14 1,000 people, you were able to pull this out in fairly  
15 short order.

16 CHAIRPERSON PACKER: But that had a high  
17 event rate.

18 DR. TEMPLE : But they had a very high  
19 event rate. This has a very low event rate. And as I  
20 said, I looked at the cases. Very few of them are  
21 candidate events. Most of them are noise -- tumors  
22 and post-infarction stuff. So that the place that

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1 might be susceptible is a very, very low event rate.  
2 So one has to just cogitate with that -- with what the  
3 actual number is too.

4 CHAIRPERSON PACKER: Abe?

5 DR. KARKOWSKI: Dr. Majuk did a  
6 statistical analysis of what the study sizes are.  
7 They are in the report. To rule out the size that you  
8 see here, you need 20,000 patients. To rule out a  
9 doubling, you need about 2,000. To rule out a 50  
10 percent increase, you need about 8,000 patients.

11 CHAIRPERSON PACKER: Okay, Rob?

12 DR. CALIFF: This kind of -- I know I am  
13 **obsessive** about this issue. But just to try to give  
14 you some idea of why I personally lose sleep over  
15 approving drugs for chronic diseases that have  
16 associated reasonable mortality rates. If we take the  
17 numbers that were given to us, 8 million people in the  
18 United States, 4 million symptomatic, and if this  
19 treatment is as good as it looks and it really does  
20 look good, you would hope all 4 million would get it.  
21 But if only 2 million got it and I think the best  
22 estimate in the real world of the underlying mortality

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1 is probably about 4 percent. Whenever you do a trial  
2 where you require a treadmill test, you get a select  
3 population and the mortality is lower. The ages are  
4 lower. We know we have an aging population. So the  
5 people with **claudication** are not fairly represented by  
6 the trials. And that is not a fault of the trials.  
7 It is just inevitable. They were good trials. So in  
8 those 2 million people, we will have about 80,000  
9 deaths this year. And even if there is a .3 relative  
10 increase, and I am not picking that number just  
11 because it came out of the studies. It is the  
12 previous relative effect of this class of drugs. That  
13 is an extra 24,000 deaths. I don't think that is a  
14 trivial issue to be concerned about. And also I don't  
15 think for me, as everybody knows, it is not specific  
16 to this class of drugs. This mortality rate is  
17 comparable to many kinds of cancer. And we certainly  
18 would accept cancer drugs that improved quality of  
19 life even **if** they didn't effect mortality, but we  
20 wouldn't think about not looking at mortality in  
21 cancer trials. So 2,000 to 4,000 patients given the  
22 drug or not given it, everything else has been taken

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1 care of, I think, in this application. We know the  
2 drug works for symptoms. I don't regard that as  
3 something that is onerous for a Population of 8  
4 million potential people in the market or whatever you  
5 want to call it.

6 DR. KONSTAM: But Rob, to get that level  
7 of effect that you are surmising in your calculation,  
8 we need not a study of 2,000. We need a study of  
9 20,000.

10 DR. CALIFF : Okay. So let's compromise  
11 and let's say --

12 DR. KONSTAM: 10,000.

13 DR. CALIFF: No. Let's say 4,000 to 5,000,  
14 which would exclude the doubling.

15 DR. KONSTAM : But you don't have any  
16 reason to suspect an increase in mortality of that  
17 level based on any available data.

18 DR. CALIFF: I would suspect an increase  
19 in mortality in any vase-active drug.

20 DR. KONSTAM: At what level? A doubling?

21 DR. CALIFF: I don't know. We are talking  
22 about a chronic disease in which people die as a major

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1 manifestation of the disease. We are not talking  
2 about pain relief for a few minutes and then someone  
3 having a procedure. I just think having an idea of  
4 safety with regard to the most important endpoint in  
5 the disease is important. Now the sponsor here is  
6 caught in a historical glitch, I hope, which I think  
7 we ought **to** deal with in a practical way.

8 DR. LIPICKY: I am not sure that is true.  
9 Because I am not sure I agree with the reasoning that  
10 you are laying out.

11 DR. CALIFF: I am sure you don't.

12 DR. LIPICKY: Okay. The number of deaths  
13 that **would** occur as a consequence of the incidence of  
14 deaths due 'co the disease doesn't influence me any at  
15 all. The relative risk to an individual is what ought  
16 to be the consideration, not the total number of  
17 bodies that come up. If you are interested in the  
18 patient, you are interested in that person, not in the  
19 nation's problems with burials. So it is the relative  
20 risk and it isn't really dependent upon the absolute  
21 incidence of death or anything on that order.

22 Two, from an **approvability** point of view,

1 I **don't** disagree that it would be important to get a  
2 reasonable estimate of what those effects are. But  
3 from an **approvability** point of view, one could approve  
4 this drug **because** of the concerns with the most  
5 adverse relative risk that one could think of. And  
6 then it could be removed by a post-marketing study.  
7 If in fact one wanted to remove it. And this is --  
8 the thing that puzzles me is the aspect of even under  
9 worst case scenarios, I think people might elect to do  
10 this and it might be better than the worst case  
11 scenario.

12 DR. CALIFF: The problem is unless it is  
13 explicitly dealt with, the patients never hear the  
14 worst case scenario.

15 DR. LIPICKY: Well, but that --

16 DR. CALIFF: And if you had a package  
17 insert or a patient insert that said you need to know  
18 that our best estimate based on prior knowledge in the  
19 absence of any reasonable evidence is that there is a  
20 30 percent higher chance that you will die if you take  
21 this drug, and that by the way you --

22 DR. LIPICKY: Well, that is easy to do.

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1 DR. CALIFF: Yes.

2 DR. LIPICKY: You can do that.

3 DR. CALIFF: But it is not very often  
4 done.

5 DR. LIPICKY: Well, but we can. It is not  
6 hard to do. If that is the concern. It is sort of  
7 where to put these things prioritized and what the  
8 real concerns are and the basis of the concerns.

9 CHAIRPERSON PACKER: Okay. Let's call for  
10 a vote. And anyone can say anything they want as they  
11 are voting. I think we have had a pretty full  
12 discussion of all the issues. The question to the  
13 committee is do you think that the -- do you think  
14 that you would -- well, I am trying to vote yes or no  
15 parallel to the time, but I think it is not -- do you  
16 need a better estimate of mortality effect before  
17 recommending approval. Ileana, we will begin with you  
18 again.

19 DR. PINA: Sharing everyone's concerns,  
20 but looking at the numbers that we have, no.

21 CHAIRPERSON PACKER: Okay. so no, that  
22 means that -- just so we make sure because it is a

1 little bit confusing.

2 DR. PINA: It means, no, that I don't need  
3 any more mortality data right now.

4 CHAIRPERSON PACKER: Okay. I would ask  
5 each one of you to simply say what it is and then say  
6 what it means just so that we are not confused.  
7 Because no frequently means no approval. Here it  
8 means no need for any additional data prior to  
9 approval.

10 DR. PINA: No need for any additional.

11 CHAIRPERSON PACKER: Okay. Good. Lem?

12 DR. MOYE: Yes. I think we do need a  
13 better estimate of mortality. We have absolutely --  
14 just a paucity of data post-6 months. And with the  
15 concerns that have been raised within the 6-month data  
16 base, I just am extremely uncomfortable drawing any  
17 conclusion about long-term consequences of exposure to  
18 this therapy.

19 CHAIRPERSON PACKER: Udho?

20 DR. THADANI: My answer is yes, I would  
21 like to see more data on the safety issue that the  
22 drug is not going to kill patients over the long run.

1 CHAIRPERSON PACKER: Tom?

2 DR. GRABOYS: Yes, need more data.

3 CHAIRPERSON PACKER: Cindy?

4 DR. GRINES: I would like more data, but  
5 not necessarily before approval.

6 CHAIRPERSON PACKER: John?

7 DR. DIMARCO : Yes, I would like to see  
8 more data. Primarily, I think, because the patients  
9 I see have heart failure or arrhythmias and angina and  
10 by a way a little **claudication**. And I think that is  
11 a different population than we are looking here where  
12 **claudication** is really their dominant syndrome. But  
13 I don't -- I can't imagine how labeling can keep it  
14 from being used in that other population where we have  
15 a lot of concerns.

16 DR. LIPICKY: But, John, why would anyone  
17 give someone a drug to relieve their claudication if  
18 they **don't claudicate**?

19 DR. DIMARCO : No, they do have  
20 **claudication**, but they also have heart failure and  
21 angina and other things and they have been excluded  
22 from these trials. But if it is out there, **people**

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1 will use it in those populations. And I think it  
2 would be very hard to label it not to use it in the  
3 typical patient with **claudication** that a cardiologist  
4 **s e e s**. And that **may** be different than somebody in a  
5 peripheral arterial disease clinic.

6 DR. THADANI: In real experience, most of  
7 the patients I see in cardiology also have  
8 **claudication**. Maybe one is more than the other. So  
9 if you have it in the open, you are going to use the  
10 drug. Because they also have coronary disease and  
11 they might have MI. When you see the patient --

12 DR. LIPICKY: I understand. But how do  
13 you know whether -- how do you even know they have  
14 angina if they are regularly processed as  
15 **claudication**?

16 DR. THADANI: When my patients are in the  
17 coronary care unit, they come with unstable angina.  
18 You talk to them and they also have coronary disease.  
19 And when you talk to them about what happened before  
20 that, they said well my leg hurts. And when you do a  
21 **doppler** study, they have both diseases. So I think it  
22 is not that **clearcut** as in this patient defined

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1 population.

2 DR. LIPICKY: But you **wouldn't** put them on  
3 this drug in the coronary care unit.

4 DR. THADANI: No, no, but when **they go**  
5 out .

6 DR. LIPICKY: Six months later. And if  
7 they are still exercise limited by **claudication**, you  
8 might use this drug.

9 DR. THADANI: No, no. They might have a  
10 one-year history of stable, intermittent **claudication**,  
11 and then they have unstable angina episodes. Some of  
12 them have stable angina episodes. So it is not that  
13 **clearcut**.

14 DR. LIPICKY: Life is tough, but I am not  
15 sure why you would be thinking you are going to give  
16 a patient who doesn't have **claudication** as the  
17 limiting symptom this drug.

18 DR. THADANI: I think it is not as  
19 clearcut **as** the drug trials are making out here in  
20 real practice -- at least in my judgment.

21 DR. TEMPLE: What is the answer to Ray's  
22 question? Why would you give someone who has heart

1 failure and can't exercise this drug?

2 DR. THADANI: We have more patients with  
3 a combination of coronary artery disease and  
4 intermittent **claudication**.

5 DR. LIPICKY: I understand.

6 DR. TEMPLE: I am sorry. The people in  
7 the trials had coronary artery disease. But if they  
8 had so much angina that they had a chest **pain**  
9 endpoint, then they couldn't get in a trial. So they  
10 had to have claudication as their endpoint. That is  
11 who got in the trial. Why, as Ray says, **would** You  
12 give someone who didn't have **claudication** in the  
13 course of their lives, who couldn't exercise enough to  
14 achieve **claudication**, why would you give them this  
15 drug? Sort of non-specific --

16 DR. THADANI: Sometimes they have both  
17 problems.

18 DR. LIPICKY: How can they?

19 DR. THADANI: You walk and you've got a  
20 little bit of leg pain, but you also have chest pain.

21 DR. LIPICKY: Do you alternate?

22 DR. THADANI: Sure you could. I mean, if

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1 you keep them walking, some people do.

2 DR. TEMPLE: The people you are worried  
3 about are the people with ventricular dysfunction,  
4 right?

5 DR. THADANI: Sure.

6 DR. TEMPLE: Okay. That is the particular  
7 group. Now why would they be on this drug if they  
8 can't exercise?

9 DR. THADANI: If you took say 100 patients  
10 with coronary artery disease, some have good LV  
11 function and some of them have ejection fractions  
12 below 40. Unless you measure, you are not going to  
13 know.

14 DR. TEMPLE: Yes, but EF below 40, they  
15 are in these trials.

16 DR. THADANI: We don't know. We have no  
17 idea.

18 DR. TEMPLE: Well, why would they be out?

19 DR. THADANI: Because they didn't measure  
20 it. I don't know. What you are suggesting is  
21 information which is not there. They have not  
22 provided it to me.

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1 DR. TEMPLE: Yes. Can I make my level of  
2 concern clear? I don't believe anybody is going to do  
3 a 20,000 patient trial. And therefore people will  
4 continue to use **Trental**, a drug with exactly the same  
5 concern that **you** already have because it is a  
6 phosphodiesterase inhibitor too. And there will not  
7 be any long-term study of that drug because nobody has  
8 to do a long-term study. So that is what you've got.

9 DR. THADANI: But surely this drug looks  
10 so good on profile on its anti-platelet effect --

11 DR. TEMPLE : Yes. And they will just  
12 spend five years doing a 20,000 patient trial. Sure  
13 they will.

14 DR. THADANI: I realize that. But it has  
15 got an excellent profile of anti-platelet effect.

16 DR. TEMPLE: Yes, I know. And it is so  
17 good they will spend --

18 DR. THADANI: So they should be able to do  
19 a trial and prove how good the drug is.

20 DR. TEMPLE: It is not -- you know, they  
21 have to answer for themselves. It seems very  
22 unlikely, and you haven't asked them, whether they are

1 going to randomize 20,000 patients into a several year  
2 trial. But it doesn't seem too likely and I don't  
3 know whether we are supposed to make decisions based  
4 on that anyway. But you are setting a standard for  
5 symptomatic treatments. Now I -- it certainly is true  
6 that the standard is set here because of a concern  
7 about a particular class of drugs. I understand that.  
8 And that is perfectly legitimate and something to  
9 worry about. But you are setting a standard that  
10 requires a level of assurance that is very high. I  
11 was making a list of all the things you don't know.  
12 You don't know whether any drug for arthritis  
13 increases the risk for death by 1.3. You **don't** know  
14 that for any antihistamine. You **don't** know it for any  
15 vitamin supplement, and there is plenty of reason to  
16 worry about at least one of them. You don't know it  
17 for **pentoxifyline**. You don't know it for any drug now  
18 used for angina. I understand that many people are  
19 very interested in this and it is good meat for public  
20 discussion. But this is very unusual and you should  
21 be very conscious of what you are saying here. It  
22 says no symptomatic treatments. If there is any

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1 reason **for** concern, and you can always think of reason  
2 for concern, no symptomatic treatments without  
3 mortality data, which for low risk individuals means  
4 very, very large studies.

5 DR. **CALIFF**: Wait a minute. That is not  
6 what is being said. I think the concern is in  
7 diseases that have a relatively high mortality as a  
8 background. Chronic therapies that could affect the  
9 underlying disease process should have some evidence.  
10 And I think if you look at precedent setting, instead  
11 of doing 10 exercise trials, why not do two good  
12 exercise trials and do a simple look at what the  
13 underlying major morbid events are. I bet the cost of  
14 those would be just about the same.

15 DR. **LIPICKY**: That is true, but they  
16 didn't.

17 DR. **CALIFF**: All right. So we have got  
18 two things. One is the precedent of what is  
19 desirable. And the other is how do you deal with a  
20 particular case.

21 DR. **MOYE**: And we can certainly express  
22 our opinions about the research program with which we

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1 are presented.

2 DR. LIPICKY: Sure.

3 DR. MOYE: Now what they have done with  
4 reasonable advice was to do 8 trials looking at  
5 exercise tolerance.

6 DR. LIPICKY: Well, I wouldn't say  
7 reasonable advice, but all right.

8 DR. MOYE: Well, advice for looking at  
9 exercise tolerance. And unbeknownst to them and  
10 unbeknownst to anybody else, this is the data that  
11 they have. Now there have been concerns that have  
12 been raised in 1998. If these concerns had been  
13 raised 10 years ago, I guess our response would have  
14 been different. But in 1998, our concerns are  
15 sufficiently elevated that we -- some of us feel more  
16 comfortable requiring more data at a higher quality  
17 level. And I just continue to be uncomfortable with  
18 the idea of, well, you know you didn't require this  
19 data for a drug that you didn't review actually a few  
20 years ago. So why shouldn't we have the same low bar  
21 in 1998? I mean certainly our standards can evolve as  
22 the technology evolves and as the clinical trial

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1 methodology evolves.

2 DR. TEMPLE : They can, and you need to  
3 think about it. But you also, as a committee, need to  
4 think about ~~whethe~~ the incentives to develop drugs of  
5 certain kinds will persist. You don't have to worry  
6 about that. We have to worry about that. But it is  
7 not a matter of indifference. I am not sure actually  
8 you can **get** 20,000 people into a large simple trial in  
9 this condition. I don't know if that is true at all.

10 DR. CALIFF: You keep saying 20,000, Bob.  
11 Your own staff didn't say it would take a 20,000  
12 person trial to do this.

13 DR. TEMPLE: For 1.3 it does, Rob. That  
14 is the hypothesis.

15 DR. LIPICKY: For 1.3 it does.

16 DR. TEMPLE: Why would I want to rule out  
17 a two-fold increase when in the population that was  
18 most at risk it was only 1.25.

19 DR. CALIFF: Because as a general matter  
20 of policy, you ought to show in chronic diseases with  
21 high mortality with treatments that effect the  
22 underlying disease process that you are not doing a

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1 substantial level of harm.

2 DR. TEMPLE : That is a very important  
3 statement, Bob. So you are saying it actually has  
4 nothing to do with the previous experience with  
5 phosphodiesterase. It is a general principle, which  
6 is what I originally thought it was.

7 DR. CALIFF : To me it is a general  
8 principle.

9 DR. LIPICKY: But it doesn't contain all  
10 of the biases that everyone else is coming from. It  
11 is a general principle of developing a new drug, and  
12 it isn't because this is a phosphodiesterase  
13 inhibitor?

14 DR. CALIFF: That just adds a little extra  
15 level of concern from the usual. I mean I will be the  
16 first to admit that these are tough issues. But  
17 wouldn't you feel badly if there was an adverse  
18 effect, and we have had several examples of that and  
19 it makes you worry,

20 DR. LIPICKY: No, I would not.

21 DR. CALIFF: You wouldn't?

22 DR. LIPICKY: Because in fact this has a

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1 very distinct advantage and I would be willing to try  
2 to write a label that says -- and include a patient  
3 packet insert that says there is up to whatever you  
4 want it to name, a 50 percent increase in the  
5 probabilities of your dying, and you will get two  
6 blocks worth of benefit. Do you want to take this  
7 drug? And that is the risk/benefit and the  
8 **approvability** assessment, and it kind of makes me  
9 wonder why you think that you have a principle -- not  
10 you personally -- that allows you to take that  
11 decision making process out of the hands of the doctor  
12 and the patient.

13 DR. CALIFF: So all you need to write the  
14 label that you wanted to write is about a 4,000  
15 patient study --

16 DR. LIPICKY: I have got it already. I  
17 don't **need** any more.

18 DR. CALIFF: Oh, you've got it?

19 DR. LIPICKY: Sure I do. I will bring the  
20 phosphodiesterase congestive heart failure stuff to  
21 bear. That is what everyone else is doing except you,  
22 and I have got a real good point estimate from that.

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1       Granted, it is in a different population.

2                   DR. CALIFF :    You were just arguing you  
3       wouldn't extrapolate from that.  Now you are arguing  
4       that you would.

5                   DR. LIPICKY: No, I am saying `

6                   DR. TEMPLE:  You would express that as a  
7       worst case.

8                   DR. LIPICKY:  I am expressing that as a  
9       worst case.  And I am not -- and I would reject the  
10      notion that based on that experience you could expect  
11      things like 100 or 200 or 300 or 400 percent increases  
12      in mortality in this patient population.  So I would  
13      accept that as the worst case.  I would say I have got  
14      my best estimate.  That labeling could be gotten rid  
15      of by doing a good mortality trial that says, no, it  
16      isn't the case in this patient population.  Even when  
17      we include people with a little bit of rest pain and  
18      a little bit of gangrene and so on and so forth.

19                  DR. THADANI:  Ray, one other issue I think  
20      you have to -- we have been made to believe there are  
21      no alternatives.  There are alternatives available.  
22      All the vascular surgery patients don't like it, but

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1 the recent publication on several hundred patients, if  
2 you just give a beta blockade and do the surgery on  
3 peripheral vascular disease, the mortality is pretty  
4 low .

5 DR. LIPICKY: How many publications, Udho?

6 DR. THADANI: There is only one  
7 publication.

8 DR. LIPICKY: Aha, you've got 8 here.

9 DR. THADANI: I realize that. But the  
10 mortality in that number --

11 DR. LIPICKY: So you are offering one  
12 published **study** as an alternative? Come on. Be real.

13 DR. THADANI: No, I realize there is no --  
14 there **are** about 300 patients, but the **mortality** is  
15 less than .5. So I think there are other alternatives  
16 available before you are going to increase the  
17 mortality double and tell the patient you may die. If  
18 I **am** a physician, I can tell the patient what  
19 alternatives are there. The patient can decide which  
20 he wants to'take. I will buy that. But you can't say  
21 that if you can walk 500 meters and if I **am** going to  
22 tell him that his chance of dying is more, I **would**

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1 really like to see the data. We are not addressing  
2 the issue that it is not effective. I think we are  
3 agreeing it is effective. We are just uncomfortable  
4 with the safety issues. And I think that has to be  
5 taken into perspective.

6 DR. CALIFF: Milton, actually if Ray could  
7 really write a label so that every patient would be  
8 informed and make the choice that he described in an  
9 informed manner, I would be pretty happy.

10 DR. TEMPLE : We could have patient  
11 labeling. We could have, at your recommendation,  
12 labeling to the patient that lays out what is known  
13 about drugs of a related class.

14 DR. LIPICKY: Sure. But I don't know that  
15 the other stipulation we made of really an informed  
16 consent **could** be guaranteed any better than you can  
17 guarantee an informed consent in the clinical trial.

18 DR. TEMPLE: Well, I don't know about --  
19 informed consent is problematical. But getting  
20 labeling to patients so that they can discuss it and  
21 have to discuss it in some sense with their physician  
22 is possible. I just wanted to dilate on something

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1 else. What we are hearing here is concern about  
2 uncertainty. And nobody likes any degree of  
3 uncertainty. And heaven knows we are as sympathetic  
4 with that as anybody else. But one still has to ask  
5 how much one can rule out uncertainty. For example,  
6 there has just been a recent meta-analysis that raises  
7 the question of whether beta blockers as  
8 antihypertensives are useful. Now you may find that  
9 stunning, but the fact is there are not a lot of  
10 studies that show that beta blockers are useful, and  
11 here we sit and we live with this right now. We have  
12 all kinds of recommendations to use that as a first or  
13 second therapy, and boom, there is some uncertainty  
14 about it. That is fairly stunning. We still don't  
15 know for sure whether lowering the blood pressure  
16 below 90 is important to -- okay, people are looking,  
17 but the data aren't there yet. We could make a list  
18 of 100 things that are deserving of attention and that  
19 we would like to know the answer to and that are all  
20 completely legitimate. And the question here that we  
21 are talking about is how much ruling out of  
22 uncertainty must one do in each of these settings. I

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1 was giving my list of all the things we don't know  
2 because one of the uncertainties are that the many  
3 drugs we use chronically we don't have good mortality  
4 data for them and it isn't easy to figure out how to  
5 get it. Epidemiologic methods I think in my  
6 experience are not very good at very low risks -- 1.3  
7 and stuff like that. They give you the wrong answer.  
8 So the question is what do you do in that case. And  
9 that is what everybody is really grappling with. How  
10 far do you go and what price do you pay.

11 CHAIRPERSON PACKER: Bob, I guess the  
12 basis here is not uncertainty as much as it is a  
13 history of having been burned a lot with these drugs.  
14 But let me ask a question.

15 DR. TEMPLE: We weren't burned. We got  
16 the right answer. They weren't approved.

17 CHAIRPERSON PACKER: I understand. The  
18 question is can you describe a little bit more to us  
19 about what a patient handout means?

20 DR. TEMPLE: Well, sure. We have or are  
21 close to having -- we have always had authority to  
22 require patient labeling when that was considered

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1 important to the proper use of the drug. The early  
2 model was oral contraceptives in which the labeling  
3 for patients was a virtual textbook of methods of  
4 contraception. It really put the patient into the  
5 decision about deciding what method to use. That is  
6 easier to conceive of in contraceptives than it is  
7 here, but with some effort one could perhaps do it.  
8 If there were thought to be a legitimate set of  
9 choices to present to patients like here this  
10 increases your exercise tolerance but it is closely  
11 related to a class of drugs that in a different  
12 setting caused this and such and we can't be sure that  
13 that risk isn't here, one could try to write those  
14 things out doing it as much in lay language as you can  
15 without losing meaning, and one could -- the **company**  
16 could agree and we could insist that that labeling be  
17 provided to every person who got the package. You can  
18 have what is called unit of use packaging, so that  
19 every person who gets the drug has to **get** that  
20 labeling with it.

21 CHAIRPERSON PACKER: And the labeling  
22 comes from the pharmacist?

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1 DR. TEMPLE: The labeling is attached to  
2 the package. The only sure way to get labeling to  
3 patients is to include it as part of the package.  
4 That is not common in the United States, but it is the  
5 normal way drugs are distributed throughout much of  
6 the rest **of** the world. So that can be done. It is  
7 done for most oral contraceptives. It is done for  
8 Halcyon. Where you really want people to have it, you  
9 attach it to the package. And then they always get it  
10 and it **is** attached to the package, so they can't throw  
11 it away.

12 CHAIRPERSON PACKER: Okay. Bob, can I  
13 make the following recommendation? Because I guess  
14 the concept of patient -- of a patient handout may or  
15 may not assuage the concerns of the committee. Could  
16 we do the following? We are just in the middle of a  
17 vote. If we could complete the vote with the premise  
18 that we will take the vote again with the  
19 consideration of a patient label. Would that be  
20 satisfactory?

21 DR. TEMPLE: Your call. Sure.

22 CHAIRPERSON PACKER: Yes? Okay. We

1 already heard JoAnn vote. The question is the same  
2 question; do you need a better estimate of mortality  
3 effect before recommending approval of the drug. And  
4 again, this is what might be called under conventional  
5 circumstances, I guess, because we are going to take  
6 another vote. Marv?

7 DR. KONSTAM : I will vote, no, I don't  
8 seek other information and basically I am very  
9 influenced by the balance of the very strong efficacy  
10 data set coupled with the fact that I think the  
11 concern that is raised stems from the heart failure  
12 population. I would, in addition to whatever we come  
13 to with regard to patient information, I would hope to  
14 see a specific warning with regard to patients with  
15 concomitant heart failure. And I guess my comment to  
16 Bob with regard to the interchange that he had with  
17 Udho before is that I think it is not an ideal world  
18 and **there** are patients with heart failure and  
19 peripheral vascular disease, and it is not so **clear**  
20 that patients with limiting heart failure would not be  
21 receiving this drug. So I would expect some warning  
22 with regard to using the drug in patients with heart

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1 failure.

2 CHAIRPERSON PACKER: I understand the  
3 sponsor has actually proposed on its own to  
4 contraindicate the drug in heart failure. That is a  
5 pretty strong warning. So that would be consistent  
6 with your view on this. I just wanted to complete  
7 this vote because we are going to take another one  
8 based on the package insert concept. Rob, under what  
9 might be called conventional circumstances, do YOU  
10 need a better estimate before recommending approval?

11 DR. CALIFF: If nothing else was going to  
12 be done in the future, I would say yes. I need more.

13 CHAIRPERSON PACKER: Okay. And I would  
14 vote yes as well. That would make for 7 versus 3.  
15 And now the question is whether the committee would  
16 reconsider that vote if the patient was handed  
17 together with the drug a piece of paper that would say  
18 everything that we are worried about and that  
19 wordsmithing could occur between the agency and the  
20 sponsor. Something which is not commonly done. The  
21 question is would we be reassured if that label -- if  
22 that patient label sufficiently highlighted the risks

1 that we are concerned about with this class of drugs.  
2 So the question is would you change your vote -- and  
3 this will only apply to those people who voted yes.  
4 Would you change your vote if the prerequisite for  
5 approval was a patient insert. And let me see, who  
6 voted no? We will begin with Lem.

7 DR. MOYE: I don't think we need a fancy  
8 label or a patient insert. I think we need the data.  
9 So I am not changing my vote.

10 CHAIRPERSON PACKER: Udho?

11 DR. THADANI: I second that. I am not  
12 going to change my vote.

13 DR. GRABOYS: I will third it. I won't  
14 change my vote. I think it would create chaos in the  
15 physician/patient relationship.

16 CHAIRPERSON PACKER: John?

17 DR. DIMARCO : I actually think that  
18 appropriate labeling and accepting the  
19 contraindication for heart failure patients. Then if  
20 we are sure that that is very prominent, then I think  
21 that we could relax my prior request for information  
22 before approval.

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1 CHAIRPERSON PACKER: I mean, we are  
2 talking about a patient handout essentially. Because  
3 if it is a package insert, nobody will read it.

4 DR. DIMARCO : That is exactly right.  
5 Something that both the doctor and the patient read.

6 CHAIRPERSON PACKER: Right. Okay, JoAnn?

7 DR. LINDENFELD: Yes, I would change my  
8 vote. The important thing here, I think, is that it  
9 is a drug for people who have a severe illness. And  
10 as long as we can be as certain as we can be that the  
11 patients understand what the risks are, then I would  
12 change and say we ought to go ahead and approve it if  
13 we can do that.

14 CHAIRPERSON PACKER: Bob?

15 DR. CALIFF: I would change, but I would  
16 want two things. One is a patient handout and the  
17 second is a commitment to collect one-year mortality  
18 data, and I would only require three pieces of  
19 information. Did the patient take the drug or  
20 placebo. Was the patient dead or alive. And I guess  
21 the third is a couple of things. The functional part  
22 of the SF-36, which would get the longer term efficacy

1 data and answer the mortality question.

2 CHAIRPERSON PACKER: And I guess I would  
3 change **my** vote as well, but it would be conditional  
4 pretty much on the same criteria that Rob has  
5 outlined, including a patient handout, a formal  
6 mortality experience with some long-term efficacy  
7 data. That vote is 7 to 3. Marv **doesn't** have to  
8 because he was comfortable with the conventional  
9 route. Okay, can I ask -- yes?

10 DR. TEMPLE: Just one thing about the last  
11 couple of points. What relative risk -- what risk  
12 increase is this study that they are to be asked to do  
13 to rule out?

14 DR. THADANI: 20,000 patients?

15 DR. TEMPLE: Well, you can't say the size  
16 really. But how big an increase are we looking at  
17 here trying to rule out?

18 DR. CALIFF: This is a compromise between  
19 level of uncertainty, which we would all like to be  
20 certain, as you said, but we can't be. I would say  
21 something like 50 percent increase. Maybe 75 percent.  
22 I would have to see the practicality of the sample

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1 size.

2 DR. TEMPLE: Okay. But we are now talking  
3 about a risk larger than the risk that triggered this  
4 concern in the first place. This is sort of a general  
5 statement now.

6 DR. CALIFF: That is for you. For me, I am  
7 always concerned about chronic diseases.

8 DR. TEMPLE : That is what I am saying.  
9 Your concern is really unrelated to the fact that this  
10 is a phosphodiesterase inhibitor. It is what you feel  
11 ought to be known about a drug for chronic treatment.

12 DR. CALIFF: Right.

13 CHAIRPERSON PACKER: Bob, I think there is  
14 actually -- can I fashion a compromise that I think  
15 both you and Rob will be happy with? That may be the  
16 first time this ever happens.

17 DR. TEMPLE: wow , give it a whack.

18 CHAIRPERSON PACKER: I think what Rob is  
19 saying is he wants to rule out a 75 percent or  
20 whatever increase in risk of death. Remember in the  
21 Promise trial and in many other trials, the point  
22 estimate was 1.28, but the right-sided confidence

1 interval was up to about 1.7 or 1.75. So to rule out  
2 a 75 percent increase in mortality, you are not  
3 talking about the point estimate. You are talking  
4 about **the right-sided** confidence interval. I think  
5 you are. How else would you be able to rule it out.  
6 So you are actually talking about exactly the same  
7 thing. His right-sided confidence interval at 1.75 is  
8 similar to your point estimate, which is approximately  
9 the same as the point estimate for the existing data  
10 base for PDE inhibitors. Is that logical?

11 DR. TEMPLE: It is logical. I just want  
12 to be sure we know what advice we are getting. I  
13 understand Rob quite well, I think, which is that any  
14 drug for chronic use ought to have a mortality data  
15 base that rules out making things worse. This is just  
16 an example of it, but it is not because of anything  
17 specific about it. Other people, I think, are  
18 concerned mostly because this is related to a class of  
19 drugs that was a problem in several other settings.  
20 Those are two different theories of why you need more  
21 data **with** different implications. I am not sure we  
22 can finish the conversation now. But it is worth

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1 taking note of.

2 CHAIRPERSON PACKER: They are not mutually  
3 exclusive.

4 DR. TEMPLE: No. But they have a lot to  
5 do with how big the study has to be. Because I see  
6 what you are saying about the confidence interval and  
7 maybe that blends them a little. But we need to think  
8 about that.

9 CHAIRPERSON PACKER: Okay. Can I -- in  
10 looking **over**, I would propose skipping question 11  
11 because I don't think there is an answer.

12 DR. LIPICKY: Fine.

13 CHAIRPERSON PACKER: And question number  
14 12, the committee has actually answered every single  
15 one of **these** questions already. The committee has  
16 said that -- and let me just -- I will summarize this  
17 quickly and make sure that everyone agrees that they  
18 might feel comfortable with a highly conditional  
19 approval which would involve both a patient handout as  
20 well as a mortality trial. That the regimen that  
21 would be recommended, as JoAnn mentioned before, would  
22 be 50 to 100 mg bid. That the committee was actually

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split **on** quality of life. So I think the agency needs to sort of use its own judgment here. That we have been clear about the mortality issue. We were not persuaded that the labeling should say anything about superiority of **cilostazol** and **Trental**. That we think a post-marketing mortality trial is indicated if you are going **to** approve it. That enzyme interaction studies are needed but probably post-marketing or **pre-**marketing depending on your judgment and depending on the specific question. And I think that is it.

DR. LIPICKY: Just one clarification. You said up **to** 100 **mg**. You didn't mean 150?

CHAIRPERSON PACKER: I think JoAnn -- I think I **am** summarizing it correctly. The sponsor is not requesting 150 bid.

DR. LIPICKY: It doesn't matter what they are requesting.

CHAIRPERSON PACKER: She was uncomfortable with the increase in adverse reactions to the 150 bid. Also , I think everyone on the committee --

DR. LIPICKY: Do you mean the 15 percent increase in headaches?

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1                   CHAIRPERSON PACKER : I think everyone on  
2 the committee would say at this particular point in  
3 time if there were increased -- if we are worried  
4 about an increase in mortality at 100 bid, we are  
5 really going to be worried about an increase in  
6 mortality at 150 bid, especially since that regimen is  
7 associated with an increase in the heart rate of 10  
8 beats per minute.

9                   DR. LIPICKY: Fine.

10                  CHAIRPERSON PACKER: Okay. Any other  
11 comments? Disagreements? We are adjourned.

12                  (Whereupon, at 6:30 p.m., the meeting was  
13 concluded.)

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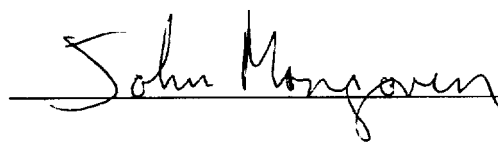
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C E R T I F I C A T E

This is to certify that the foregoing transcript in  
the matter of:           CARDIOVASCULAR AND RENAL DRUGS  
                              ADVISORY COMMITTEE  
  
                              85TH MEETING

Before:                    FOOD AND DRUG ADMINISTRATION  
Date:                      JULY 9, 1998  
Place:                     BETHESDA, MARYLAND

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



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