U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

85TH MEETING

Thursday
July 9, 1998

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

AGENDA

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

8:58 a.m.

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?

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

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, not withstanding 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

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

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

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

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

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

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

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

of' cilostazol. Cilostazol is a dihydral qinolinon derivative with a molecular weight of 369.47. This compound is a phosphodiesterase inhibitor. Its pharmacological profile includes anti-platelet activity, anti-thrombotic activity, vasodilation, and inhibition of vascular smooth muscle cell proliferation. In addition, cilostazol decreases triglycerides and increases HDL cholesterol levels.

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

In the United States, Otsuka America

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

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

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

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

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

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

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

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

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

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

DR. KARKOWSKI: Correct.

CHAIRPERSON PACKER: Okay. Terrific.

DR. LIPICKY: If that study is really

critical to your decision making.

CHAIRPERSON PACKER: Okay.

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

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

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

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

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

DR. TEMPLE: Okay.

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

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

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

still the status of those questions at the present time?

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

CHAIRPERSON PACKER: Okay. Thank you.

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

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

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

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

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

from the preclinical pharmacology studies into perspective.

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

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

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

cells.

Cilostazol also inhibits vascular smooth muscle cell proliferation in a concentration-dependent fashion. These effects were observed over the concentration range of 1:30 micromolar. Other PDE_3 specific inhibitors such as amrinone and non-specific inhibitors such as IBMX have limited effects in this model. Evidence of these effects were also noted in clinical trials of restenosis following percutaneous coronary interventions. In separate studies involving stinting and atherectomy procedures, there was a trend towards improvement in the rate of restenosis.

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

significant changes in LDL cholesterol levels, the ratio of APO-Al to APO-B changed in a favorable fashion.

Like other drugs which inhibit PDE_3, cilostazol exhibits similar trends in cardiovascular hemodynamics in isolated organ and whole animal models. These effects include increased heart rate, coronary blood flow, contractility, and others that I have listed on the slide. They are likely due to elevated intracellular cyclic AMP and cardiac myocytes and coronary vascular smooth muscle cells.

With the original NDA submission, OAPIdid not know the effects of cilostazol on cyclic AMP levels in cardiac myocytes. Additional experiments have been conducted to determine these levels and how the findings relate to other PDE_3 specific inhibitors. These results are now available. They were provided to the FDA this past week. And with the permission of the Chair, we would like to display these results today.

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

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

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

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

the cilostazol or the milrinone groups.

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

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

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

DR. LINDENFELD: In relation to comparison to milrinone, do you have any comparisons to any of the other PDE_3 inhibitors in any of these same preparations?

DR. CILLA: No. We don't have amrinone or other PDE_3 inhibitors in these models at this time. These studies were literally conducted with in the last two to three weeks.

DR. LINDENFELD: And this is a clinical question, in all of the data, cilostazol increases heart rate both by EKG and helter. Can you give us some idea of how that relates to clinical studies of the other PDE_3? Although I know they are different diseases, are these heart rate increases different or what -- or similar?

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

DR. LINDENFELD: Sure. Can you relate in other studies of PDE_3 inhibitors heart rate increases? Does it increase more or less? I know they are different patient populations, but there is a substantial dose-related increase here.

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

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

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

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

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

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

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

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

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

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

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

DR. LINDENFELD: I think that is my questions. Or one other question -- again, this may come later. But you referred to a trend to improvements in coronary stinting, but in our packet the data wasn't considered evaluable or wasn't evaluated., is that correct? I can't remember who reviewed that. But the coronary stinting data was not --

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

DR. LINDENFELD: Okay.

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

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

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

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

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

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

DR. PINA: Okay.

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

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

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

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

DR. CILLA: Yes.

DR. THADANI: That is okay.

CHAIRPERSON PACKER: Tom?

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

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

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

CHAIRPERSON PACKER: John?

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

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

CHAIRPERSON PACKER: Marv?

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

DR. CILLA: Sure.

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

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

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

DR. KONSTAM: But you showed milrinone.

DR. CILLA : I am sorry, with milrinone. I apologize.

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

DR. CILLA: Right now what we are doing with this particular data is to suggest that PDE_3

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

DR. LINDENFELD: In that same vein, do the other PDE_3 inhibitors have substantial metabolizes that are active? Just to try to compare these two.

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

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

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

CHAIRPERSON PACKER: Dr. Karkowski?

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

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

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

DR. CILLA: Yes.

CHAIRPERSON PACKER: Why did you choose the rabbit?

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

cardiovascular industry. So we wanted to look at that particular model. We would always prefer to use human tissue for studies, and that is why we looked specifically at human platelet cyclic AMP levels as w e l l .

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

DR. CILLA: We were specifically interested in comparing 2 PDE_3 inhibitors within a species. So if you look within a species, the comparison we felt was reasonable.

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

DR. CILLA: I understand.

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

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

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

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

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

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

DR. LIPICKY: But you are surmising that.

CHAIRPERSON PACKER: No, that has been

done.

DR. LIPICKY: I see. Okay.

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

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

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

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

DR. CILLA: Our purpose simply was to look at the difference in PDE_3 inhibitors. We feel that the safety of cilostazol really comes from our tremendous safety data base which will be discussed later.

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

DR. CILLA: Yes. I think the implication is that PDE_3 inhibitors are not all the same. That you must look at the different tissues in which you are seeing the results to determine their various effects. For instance, we have more effects on vasodilatation than other PDE_3 specific inhibitors. I am probably not the person to answer your question on the safety margin.

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

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

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

DR. CILLA: Right.

DR. CALIFF: Okay.

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

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

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

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

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

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

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

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

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

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

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

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

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

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.

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

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

experience doing this, measuring oxygen uptake, the peak VO_2 values for these patients are around 10 to 15 ml per kilogram per minute, which is not unlike the peak $V0_2$ for Class III heart failure. Different pathophysiology but very similar impairment in peak exercise performance. So the point here is that this is not a trivial symptom. This actually has significant ramifications to daily activity.

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

large population clinical trials.

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

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

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

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

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

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

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

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

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

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

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

physical functioning scores are markedly impaired in both patients with congestive heart failure and in claudication, not unlike the peak $V0_2$ data, a marked impairment in that domain. But it is also important to emphasize that these patients are not impaired across the entire range of functions because their mental health and their social functioning scores are quite normal. so a therapy guided against treating claudicants would be designed to improve physical function but not to improve mental health.

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

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

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

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

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

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

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

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

CHAIRPERSON PACKER: We will begin the questions with JoAnn.

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

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

So I think that we shouldn't just think

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

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

DR. HIATT: In terms of mechanism?

DR. LINDENFELD: Yes.

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

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

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

DR. HIATT: Correct.

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

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

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

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

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

DR. LINDENFELD: Okay.

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

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

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

CHAIRPERSON PACKER: Udho?

DR. THADANI: I agree with you that the treadmill is a more objective testing. We have been doing it in angina for a long time. If you modify the protocol -- 1 think one of the reasons you modify is because if you have a constant speed, you have to wait forever in some patients and they don't qualify for

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

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

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

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

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

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

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

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

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

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

DR. HIATT: Right.

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

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

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

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

DR. HIATT: Right.

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

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

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

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

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

CHAIRPERSON PACKER: Bob Temple and then Alan Hirsch.

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

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

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

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

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

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

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

DR. HIATT: Clopidogrel?

DR. TEMPLE: Yes.

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

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

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

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

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

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

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

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

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

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

CHAIRPERSON PACKER: Let's see, Ray?

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

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

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

need to discuss it now.

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

DR. LIPICKY: Yes.

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

DR. LIPICKY: Well, two had aspirin.

CHAIRPERSON PACKER: What is that?

DR. LIPICKY: Two had aspirin. Two had aspirin.

CHAIRPERSON PACKER: Yes. Okay, Alan?

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

efficacy, I am always interested in mechanisms. So I want to come back one more time from your perspective and look at potential PDE mechanisms and claudication and ask how it relates to other PAD data you are aware of. so, for example, cilostazol or PDE_3 inhibitor might improve cardiac output or inotropy. Is there experience with other animal or human data that suggests that increased cardiac output and supply to the muscle improves walking distance?

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

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

DR. HIATT: Right.

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

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

DR. HIATT: Not well shown.

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

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

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

DR. HIATT: Correct.

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

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

DR. HIRSCH: I am leading you on.

DR. HIATT: Ticlopedine as an anti-

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

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

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

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

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

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

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

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

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

DR. LINDENFELD: Is there any data?

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

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

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

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

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

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

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

DR. HIRSCH: That is why I am here.

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

CHAIRPERSON PACKER: I understand.

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

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

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

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

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

DR. TEMPLE: I think that was my point.

CHAIRPERSON PACKER: But that --

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

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

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

CHAIRPERSON PACKER: Lem?

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

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

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

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

relief at two years.

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

CHAIRPERSON PACKER: Ileana?

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

DR. HIATT: That is an interesting question. If you take a heart failure patient to $V0_2$ max, or I would probably say more correctly peak $V0_2$, the RER values are always very high -- 1.1 or 1.2.

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

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

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

fairly significant reduction due to a very different mechanism.

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

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

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

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

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

CHAIRPERSON PACKER: I want to ask you about how this committee should define quality of life in these patients. Quality of life has become a buzz word, a buzz word which many sponsors are interested in having incorporated in their labeling because they be 1 ieve it provides them with certain commercial advantages. But the question is what is a measurement of quality of life in a patient with intermittent claudication. The analogies that you have made with heart failure is actually really, I think, not only valid but very interesting. Because as in claudication, there is a discrepancy between hemodynamics and symptoms or exercise performance, and there may or may not be a relationship between

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

DR. HIATT: Correct.

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

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

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

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

CHAIRPERSON PACKER : Yes.

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

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

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

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

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

probably a little less relevant.

CHAIRPERSON PACKER: Bob?

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

CHAIRPERSON PACKER: No, Bob --

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

DR. HIATT: Right.

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

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

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

DR. HIATT: You bet.

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. CALIFF: The question is I am trying

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

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

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

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

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

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

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

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

DR. CALIFF: Okay. Thanks.

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

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

CHAIRPERSON PACKER: Thank you.

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

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

presentation.

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

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

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

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

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

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

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

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

The baseline demographics and medical

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

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

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

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

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

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

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

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

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

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

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

package insert.

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

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

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

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

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

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

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

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

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

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

treated patients were able to move into the next stage.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Additionally, patients receiving cilostazol 100 mg walked significantly farther than patients receiving placebo regardless of the concomitant use of beta or calcium channel blockers, the presence of diabetes, and the duration of their

peripheral arterial disease upon screening.

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

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

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

In addition to the physical dimensions of

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

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

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

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

CHAIRPERSON PACKER : I am sorry?

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

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

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

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

DR. FORBES: Sorry about that.

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

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

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

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

DR. FORBES: It is the same.

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

DR. FORBES: That is correct.

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

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

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

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

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

DR. LINDENFELD: Or just an approximate

percentage.

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

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

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

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

DR. FORBES: We did not look at that.

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

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

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

CHAIRPERSON PACKER: Just get closer.

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

aspirin and 1,170 were not.

DR. LINDENFELD: Okay. So about the same.

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

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

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

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

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

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

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

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

CHAIRPERSON PACKER: Okay.

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

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

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

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

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

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

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

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

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

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

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

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

CHAIRPERSON PACKER: Lem, let me just -- 1 guess I will just comment last on this. I am not certain, first of all, how many investigators read the statistical. analysis of their protocols, I am sorry to say.

DR. MOYE: I am speechless.

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

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

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

DR. JIN: We only assigned the worst rank

to the patient with no post-baseline measurement.

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

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

CHAIRPERSON PACKER: I see. If yOU assigned the worst rank to the people who dropped out, the trial would fail?

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

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

DR. JIN: Yes.

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

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

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

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

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

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

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

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

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

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

DR. TEMPLE: I think that is debatable.

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

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

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

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

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

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

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

DR. FORBES: 94301?

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

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

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

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

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

DR. THADANI: Yes. I am just -- the other issue is when you log transform. I know it is a statistically valid way to get away with the noise in the baseline. The graphs you showed showed a very marked improvement -- you know you are talking about 60 or 80 meters. And yet the statistics reveal if you look at the median values on -- the absolute values, most of the trials -- 1 don't know if you have seen it or not -- but in front of us show an improvement of 20 meters rather than 60 or 70, with the exception of one trial. In pivotal trial 2192202, the 100 mg improvement in absolute median change is 25.5 meters rather than 60 or 80, which is far less than when you

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

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

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

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

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

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

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

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

CHAIRPERSON PACKER: Lloyd, just introduce yourself.

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

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

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

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

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

CHAIRPERSON PACKER: Ray?

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

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

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

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

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

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

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

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

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

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

DR. KAZEMPOUR: For quality of life and

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

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

CHAIRPERSON PACKER: Rob?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. FORBES: That is correct.

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

DR. FORBES: Yes.

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

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

DR. CALIFF: Okay.

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

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

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

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

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

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

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

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

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

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

CHAIRPERSON PACKER: Lem, do you have a comment?

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

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

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

DR. LIPICKY: It is a whole other topic.

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

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

CHAIRPERSON PACKER: You have seen both work?

DR. LIPICKY: Yes.

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

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

CHAIRPERSON PACKER: Okay.

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

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

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

CHAIRPERSON PACKER: Bob?

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

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

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

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

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

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

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

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

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

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

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

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

DR. LIPICKY: Yes.

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

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

DR. KARKOWSKI: Milton?

CHAIRPERSON PACKER: Go ahead.

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

comfortable with that outcome.

CHAIRPERSON PACKER: Maybe we should ask and we cculd find that out.

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

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

DR. FORBES: Actually --

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

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

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

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

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

CHAIRPERSON PACKER: Let's see, we will -- hold on a second. Ray, I think you had a different topic. Let's try that.

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

CHAIRPERSON PACKER: Does anyone have any -- Bob?

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

CHAIRPERSON PACKER: Abe?

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

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

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

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

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

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

CHAIRPERSON PACKER: Why don't we do this. Let us, if we can -- 1 just want to make sure that members of the committee who have not had a chance to

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

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

CHAIRPERSON PACKER: Absolutely.

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

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

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

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

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

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

DR. FORBES: Absolutely.

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

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

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

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

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

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

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

I would like to see the data.

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

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

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

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

DR. HIRSCH: Thanks.

CHAIRPERSON PACKER: Udho?

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

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

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

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

DR. FORBES: That is correct.

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

DR. FORBES : That is correct.

DR. THADANI: so if you carry forward, I

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

DR. FORBES: That is correct.

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

DR. FORBES: Yes, there is.

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

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

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

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

DR. THADANI: Yes.

DR. FORBES: Okay. We actually did a couple of things. The first was we measured the resting ankle brachial index. And not every trial is significant, but there are three trials, I believe, that are actually statistically significant showing the ABI increases with cilostazol treatment relative to placebo. Now the increases, you may say are they clinically relevant? The changes that we are seeing in an ankle brachial index -- 1 told you the baseline value is 0.64 -- we are seeing something around the

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

CHAIRPERSON PACKER: Tom? Cindy?

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

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

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

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

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

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

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

DR. GRINES: Okay.

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

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

increase. And I wondered if you felt that --

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

DR. FORBES: Yes, actually.

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

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

DR. FORBES : That is correct.

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

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

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

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

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

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

CHAIRPERSON PACKER: Bob?

DR. FORBES: Do you have a specific question?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

statistically significant using conventional analyses in those three trials.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. LIPICKY: Right.

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

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

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

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

CHAIRPERSON PACKER: No. My understanding

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

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

it.

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

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

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

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

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

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

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

CHAIRPERSON PACKER: Ray I think has a

direct response.

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

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

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

DR. LIPICKY: I understand.

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

DR. LIPICKY: I haven't.

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

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

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

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

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

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

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

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

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

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

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

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

DR. LIPICKY: Well, I wanted to change the

subject an hour ago. It is a relatively simple question, I think, and maybe it will come up later. But as I looked at your slide 02, which was the dropouts before the first post-randomization measurement, the sort of average number of people that missed their first post-randomization measurement was 6.6, and it ranged from 17 percent to 4 percent or something on that order. And the reasons that are given for dropouts and for side effects and so on are things like headache and diarrhea. It doesn't quite fit to me that that number of patients would drop out between the time that they are randomized to the time of the first post-randomization test measurement if they are all stable PAD and the worst thing that happens to them is they get headache and diarrhea. How did -- how come? Or do you think I am nuts?

DR. FORBES: No, no.

CHAIRPERSON PACKER: It wasn't supposed to be two questions.

DR. FORBES: Can I have back-up slide N-15? Let's see if this answers your questions or at least augments it. Can you move me to N-17, please?

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

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

is a big number, 173.

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

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

DR. FORBES: That is everybody.

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

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

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

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

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

CHAIRPERSON PACKER: I am just saying that

we have seen --

DR. LIPICKY: So maybe this will come up.

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

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

CHAIRPERSON PACKER: And in fact, why don't we hold -- 1 am sure you will talk about this in safety.

DR. LIPICKY: Okay.

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

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

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

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

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 'chose symptoms on the SF-36 because it is not measured at the tine 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

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

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

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

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

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

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

1:45 p.m.

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

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

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

CHAIRPERSON PACKER: Well, there are two separate issues. One is an issue of what happens to patients after they drop out because YOU want to maintain the concept of an intention to treat analysis. I guess I am more concerned about the specific issue that was raised before the break, which is one of the -- 1 think it is our general perception that quality of life instruments incorporate into them not only the benefits that can accrue from therapy, but the adverse side effects that can be caused by drugs. And somehow there is a question or questions

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

DR. WARE: Right.

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

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

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

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

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

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

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

CHAIRPERSON PACKER: All the usual things, right.

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

CHAIRPERSON PACKER: Yes, Bob?

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

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

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

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

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

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

DR. TEMPLE : Because physical things mostly do.

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

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

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

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

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

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

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

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

CHAIRPERSON PACKER: One, they are not equally distributed.

DR. WARE: Then we should be concerned.

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

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

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

CHAIRPERSON PACKER: Yes, Milt?

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

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

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

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

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

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

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

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

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

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

DR. KONSTAM: No, it doesn't.

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

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

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

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

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

CHAIRPERSON PACKER: No.

DR. LIPICKY: Yes.

CHAIRPERSON PACKER: No.

DR. LIPICKY: Yes.

CHAIRPERSON PACKER: No.

DR. LIPICKY: Yes.

DR. THADANI: Let's vote.

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

CHAIRPERSON PACKER: Tom?

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

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

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

CHAIRPERSON PACKER: It is clear -- it is

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

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

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

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

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

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

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

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

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

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

DR. THADANI: SO, Bob, YOU had a severe headache --

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

the other.

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

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

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

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

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

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

CHAIRPERSON PACKER: Rob and then Ray.

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

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

CHAIRPERSON PACKER: Ray?

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

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

DR. CALIFF: Yes.

DR. LIPICKY: Okay.

CHAIRPERSON PACKER: Let's proceed with safety.

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

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

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

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

The most frequently reported adverse events were headache, diarrhea, and abnormal stools at

32, 17, and 14 percent respectively in the total population. Other AE's in this population are shown in decreasing incidence here and on the next slide. A complete list of the adverse events is found in your briefing packet. All of these adverse events were generally reported as mild to moderate in severity.

Data on discontinuation of study medication due to adverse events is presented here. The mild to moderate nature of the adverse events is reflected in the need to increase the reporting sensitivity to greater than or equal to 1 percent. Had we left the threshold at 3 percent, only headache would have remained in the chart. Discontinuations for other adverse events ranged from 1 to 1.1 percent.

Serious adverse events were defined according to FDA criteria. The incidence of adverse events versus serious adverse events is shown here. The incidence of SAE'S decreased within each treatment group. For an overall comparison of 13 percent in cilostazol total, 12 percent in placebo, and 14 percent in the pentoxifyline group. For any individual event defined as serious, the incidence was

low and did not exceed 2 percent in the total cilostazol group. Based upon the underlying disease, intermittent claudication, patients are expected to have an increased risk of cardiovascular adverse events. We will explore these further.

In addition to the adverse event reports, a question was raised and we also had looked into the metabolism of cilostazol and its potential interactions with concomitant medications. We agree this is important information to appropriately label the product. I would therefore like to take a minute and ask Dr. Steven Bramer to present this critical data and respond to the question that was raised earlier today.

DR. BRAMER: Good afternoon. My name is Steven Bramer, and I am the director of pharmacokinetics and pharmacodynamics and metabolism for Otsuka. I would like to present a brief overview of drug metabolism and drug/drug interactions. We have been communicating with the FDA regarding these issues, and this afternoon I would like to address the questions they have posed.

We have carried out numerous studies in order to understand cilostazol's absorption, distribution, metabolism, and excretion in humans. Cilostazol's disposition in plasma was well-characterized by single dose and multiple dose pharmacokinetic studies in normal volunteers and in patients with peripheral arterial disease. Carbon-14 labeled cilostazol masked balance studies identified metabolizes and routes of excretion. Only cilostazol and three of its metabolizes were found circulating in the plasma and warrant further exploration. These are OPC-13015, OPC-13213, and OPC-13217.

In-vitro experiments involving recombinant DNA, abbreviated cDNA, and human liver microsomes identified the cytochrome P450 isozymes responsible for the metabolism of cilostazol and its metabolizes. Cilostazol's metabolism has been well-characterized. Based on the chemical structure in non-clinical results, there are possibly 11 expected metabolizes of cilostazol. However, the human carbon-14 labeled cilostazol Study revealed only two metabolizes found circulating in plasma -- OPC-13015 and OPC-13213. A

third metabolize, OPC-13217, was only found in trace concentrations. These metabolizes were at 28 percent and 9 percent of cilostazol's systemic exposure. Cytochrome P450, abbreviated CYP, isozymes are a clinical. concern regarding drug/drug interactions. Cilostazol's metabolism is primarily by CYP3A4 and to a lesser extent by CYP2C19, and even to a lesser extent by CYP182.

We have studied the inhibition of cilostazol's metabolism clinically by probe drugs known to inhibit specific cytochrome P450 isozymes. Erythromycin, an inhibitor of CYP3A4 , increased cilostazol systemic exposure measured by AUC and Cmax by 73 percent and 47 percent respectively. Also omeprazole, inhibitor of CYP2C19, increased cilostazol AUC and Cmax by 26 percent and 18 percent respectively. CDNA data suggested that CYP2D6 may be involved in the metabolism of cilostazol. However, quinidine, a very important inhibitor of CYP2D6, had no impact on the metabolism of cilostazol. These findings are consistent with in-vitro metabolism studies.

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 1 iver 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 CYS3A4.

I would like to discuss the appropriateness of our war friend to detect CYP3A4

inhibition. 20 percent metabolism of R-warfarin by CYP 3.84 is based on a point estimate from one paper published by Bill Treger.

Interaction with diltiazem and fluconazole results in greater than 20 percent and 52 percent decrease in R-warfarin clearance. KI, the concentration necessary to cause 50 percent inhibition of CYP3A4 shown here in parenthesis for diltiazem and for fluconazole. Keep in mind the smaller the KI, the more potent the inhibitor. Please note that diltiazem is an inhibitor of CYP3A4 and increases cilostazol concentrations as agrees with the microsomal data. Our analytical assay had a sensitivity of 3 nanograms per ml versus the previous referenced studies which had an assay sensitivity of 100 nanograms per ml. Our study had greater than 80 percent power to detect a 9 percent difference in R-warfarin clearance and an alpha equal to .05. In addition, the microsomal data shows that cilostazol is not an inhibitor of CYP3A4 or any of the other isozymes.

R-warfarin is a weak substrate of CYP3A4, and several published results that have shown

previously have shown that inhibition of CYP3A4 leads to increased R-warfarin concentrations. To test the losses on its metabolize effects on CYP3A4, the impact of R-warfarin concentrations were assessed. If cilostazol and its metabolizes inhibited CYP3A4, R-warfarin concentrations would have increased. However, cilostazol and its metabolizes had no effect on R-warfarin concentrations and thus do not inhibit CYP3A4 .

The metabolism of cilostazol has been well characterized. The plasma concentrations of cilostazol are increased by drugs that are inhibitors of CYP3A4 and CYP2C19. Cilostazol does not inhibit cytochrome P450 isozymes as shown by the CYP3A4 example. We recommend a dose adjustment when co-administering cilostazol with inhibitors of CYP3A4 and CYP2C19.

We have discussed phase 1 drug/drug interaction studies listed on the slide. Additional analyses were carried out on the phase 3 population data where we looked at the safety profile of cilostazol coadministered with other medications.

Shown here are the most frequent type of conmeds administered during our phase 3 trials. As you can see, there is a large number of individuals that were exposed to calcium channel blockers, beta blockers, nitrovasodilators, beta-selective agonists, vasodilators, the ACE inhibitors, Digoxin, and H1 receptor antagonists. Drugs that fall into these categories are either P450 substrates or could be P45 inhibitors.

Shown here is the list of CYP3A4 inhibitors coadministered during our phase 3 trials. Our analysis showed a 50 percent increase in cilostazol concentrations upon coadministering diltiaze-m. However, there are no remarkable differences in the adverse event profiles as shown on the next slide.

We have looked at the type, incidence, and severity of adverse events and found coadministration with diltiazem to be well tolerated. There were no greater incidence of serious adverse events contributable to coadministration with diltiazem.

Shown here are the five most frequent

adverse events associated with cilostazol. There were no greater incidence of headaches, diarrhea, and abnormal stools. Compared to on or off conmed and compared to placebo, there appears to be a slight trend for an increased incidence of palpitations and dizziness.

A similar approach to the data is shown here following coadministration of cilostazol with P450 inhibitors as a group. There was no greater incidence of serious adverse events in patients taking P450 inhibitors. There appeared to be a slightly greater incidence of palpitations upon coadministering these drugs. Therefore, caution is recommended when coadministering CYP3A4 inhibitors with cilostazol. That concludes my presentation.

CHAIRPERSON PACKER: I know we are going to go over more safety data, but I just wanted to find out if the committee had any specific questions on the pharmacokinetics. JoAnn?

DR. LINDENFELD: I just didn't understand. The R-warfarin data, what model was that in? How was that done?

DR. BRAMER: I am sorry, I couldn't hear your question.

DR. LINDENFELD: The R-warfarin, what model system was that? I missed that. You showed that R-warfarin levels did not increase --

DR. BRAMER: R-warfarin is metabolized by CYP3A4 .

DR. LINDENFELD: Right. But tell me how that was done, just the mechanics of that quickly. Normal volunteers?

DR. BRAMER: Oh, it was basically, we had a priming dose of warfarin and then we had a single dose pharmacokinetic profile of warfarin. We gave cilostazol, multiple dosing for a period of time, and then we looked at the R-warfarin pharmacokinetic profile again. So we compared R-warfarin before and after multiple dosing of cilostazol.

CHAIRPERSON PACKER: Bob?

DR. TEMPLE : One of the metabolizes is active and is maybe five times as potent or something like that?

DR. BRAMER: Correct. OPC .

DR. TEMPLE: So if you think that and it is 9 percent of the total, then it is responsible for something like half the activity. What happens to that in the presence of Erythromycin, or actually it would be more interesting to know what happens in the presence of ketoconozol, which I guess you don't have.

DR. BRAMER : We -- obviously -- we have looked at the metabolizes, OPC13015 and OPC13213 and cilostazol in all the drug/drug interaction studies -- diltiazem, Erythromycin, omeprazol, and quinidine. And therefore, as expected, upon coadministration of omeprazol as an example, which inhibits the 2C19 pathway, we had increased concentrations of cilostazol and decreased concentrations of OPC13213. That metabolize by that particular pathway. Similar results were observed as you inhibit 3A4. OPC13015 is formed by the 3A4 pathway. And therefore, cilostazol concentration is increased and there was not a change in OPC13015 concentrations.

DR. TEMPLE : Right. But you were also recommending decreasing the dose in the presence of certain things that increased the parent. But those

might decrease the metabolize. So it is not so clear that that is good advice.

DR. BRAMER: Actually, our recommendation was based upon a 73 percent increase in AUC. So what I recommended was a dose adjustment or starting dose of 50 mg, just based on comparison of AUC values.

DR. TEMPLE: But that is just AUC for the parent. It doesn't take into account the AUC for the metabolize, which may be responsible for half the activity. Maybe you are just being cautious, but that doesn't necessarily seem like it is so obvious.

DR. BRAMER: No, actually we were just being cautious.

DR. THADANI: A couple of questions. You give the drug concentration or metabolize concentration of your drug. What happens to the other drug concentrations such as diltiazem or other drugs?

DR. BRAMER : To answer your question, based on the microsomal data that Dr. Flockhart performed, which he is in the audience, we knew the pathways of metabolism of cilostazol. And therefore, we used probe drugs -- Erythromycin, which is a

mechanism based or suicide inhibitor of 3A4, a very potent inhibitor, and we looked at the concentrations at steady state of Erythromycin. Therefore, we expect Erythromycin to have an impact on cilostazol and not vice versa based on the science. The same logic was followed for the other drug/drug interactions.

DR. THADANI: Have you any data on statins? Because in peripheral vascular disease, a lot of patients have dislipidemia. And is there any interaction with statins, which is also through 3A4?

DR. BRAMER : There is the potential for drug/drug interactions with other substrates of 3A4. But as far as looking at inhibitors of 3A4 or the other isozymes, we do not feel that there is any safety concerns.

DR. THADANI: Is there assurance without having data or do you think you need data or are you pretty sure there will be no interaction?

DR. BRAMER : Actually, I feel very confident that we know the interactions because we chose very potent inhibitors. As I mentioned before, quinidine is a very potent inhibitor of 2D6 .

Erythromycin is a suicide inhibitor of 3A4. And quinidine is also a potent inhibitor of 2C19. So based on understanding the metabolism, I feel fairly confident in making recommendations with inhibitors.

DR. THADANI: And other issues on safety, I don't know if somebody else is going to discuss about the QTC issue. Is somebody else going to deal with that?

DR. BRAMER: Dr. Ingenito will address the QTC issue if necessary.

DR. THADANI: Okay. There is some -- obviously the heart rate goes up. You correct it different- ways, as you have told. Looking at the helter data, one of the difficulties you run into --

CHAIRPERSON PACKER: We have not heard the rest of the safety presentation, right?

DR. THADANI: All right.

CHAIRPERSON PACKER: So hold. I leana?

DR. PINA: My question was similar. It was about the statins. I know you know the concomitant therapy on the group of patients. Were there a lot of patients on statins? Because that is not mentioned.

You have got calcium blockers, you have got beta blockers.

DR. BRAMER: Yes, give me one moment and I will answer your question.

DR. PINA: It is a population that I would expect that many of them would be on statins.

DR. BRAMER: Of the entire population, 29 percent were on lipid-lowering agents which are predominantly the statins.

DR. THADANI: Which ones? Can you define which statins or no?

DR. BRAMER: I can give you a list of the statins if you like.

DR. TEMPLE: Only two of them are susceptible.

DR. THADANI: Yes, the lovostatin.

CHAIRPERSON PACKER: Bob?

DR. BRAMER: That was lovostatin, sinstatin, prevastatin, flustatin, and toravastatin.

DR. TEMPLE: But you don't actually have blood level measurements of those. You just know that they were given together and that nothing -- nobody

had rabdomyelysis, say.

DR. BRAMER: Correct.

DR. TEMPLE: You have not done any actual in-vivo studies to look at interaction with drugs that are metabolized by say 3A4? You have deduced that from in-vitro studies in which you say you didn't see any inhibition of that pathway at relevant concentrations, is that correct?

DR. BRAMER: No. Let me correct that assumption. Because we have -- again, we understand inhibition of other drugs and their effects on cilostazol by looking at the Erythromycin study and the omeprazol study --

DR. TEMPLE: No, no. That is not what I am asking. Did you test for the inhibition of drugs that are metabolized by the 3A4 pathway like cisopride or synthestatin or something like that? And I think the answer was no, you did that in-vitro.

DR. BRAMER : Well, no. We have the R-warfariri study to show. R-warfarin is a weak substrate of 3A4. And therefore, in addition to the microsomal work which supports that cilostazol is not

an inhibitor of 3A4 or other isozymes.

DR. TEMPLE: Okay. I guess I don't have data in mind to know what you would expect from a serious inhibitor of 3A4 on R-warfarin. Do you know?

DR. BRAMER: Take diltiazem as an example.

DR. TEMPLE: No, no. Take a really good inhibitor. Take ketoconazol.

DR. BRAMER : Ketoconazol is -- actually diltiazem is a very potent inhibitor of 3A4, more potent than ketoconazol. Ketoconazol is a broad-based inhibitor.

DR. TEMPLE: No, no. That is not correct.

DR. BRAMER: Diltiazem is a very specific inhibitor for 3A4 and its metabolizes are a specific inhibitor of 3A4.

DR. TEMPLE: I am sorry, the antifungal cause virtually 100 percent inhibition of that pathway. You can't get more potent than that. I mean I am speaking about data on trefenadine and things like that. But Erythromycin is not nearly as good an inhibitor as they are. Now I can't speak to R-warfarin because I haven't seen those data. But the

usual 3A4 pathways, the ones that get you in trouble, I don't think diltiazem is nearly as strong on those, although it is a partial inhibitor.

DR. BRAMER : You mentioned ketoconazol. I did make reference --

DR. TEMPLE : There are other people who know these things.

DR. BRAMER : You mentioned ketoconazol. I did make reference to fluconazol, where we did see a 52 percent change in R-warfarin concentrations or clearance.

DR. TEMPLE: Okay. Fluconazol is not as good an inhibitor of 3A4 as itriconazol and ketoconazol, but it is something of an inhibitor.

DR. BRAMER : I would like to ask Dr. Flockhart to address this issue.

DR. FLOCKHART: Just to try and state it clearly, Bob. The clinical study that is being done has not been done with the statins that you described. The clinical study that has been done is giving racemic warfarin and then measuring the R-warfarin as a result. Now the precedents there are that -- there

are four -- ketoconazol, Erythromycin, itriconazol, and diltiazem, all of which have effects on R-warfarin. From an in-vitro studies perspective, about 20 to 30 percent of R-warfarin metabolism is by that route. It is by 3A. It is also metabolized by cytochrome P451A2 and some by 2C9. So it is not an ideal probe for 3A. But having said that, the answer to your question is if YOU use a high octane 3A inhibitor, you reduce the clearance of R-warfarin using ketoconazol or Erythromycin by about 50 percent. If you use diltiazem, it is about 20 to 30 percent, reflecting the fact that it is a weaker entity.

DR. TEMPLE: so that is not a really great probe for the capacity --

DR. FLOCKHART: It is not a perfect probe, but major league inhibitors -- big guns, the ones you get scared about, the ones that you guys all have on your warnings -- change it 40 to 50 percent. Weaker ones do. And in this study, cilostazol didn't change the R-warfarin at all.

DR. TEMPLE : Yes, that sounds somewhat reassuring. But if you wanted to have the most

sensitive test of whether it could inhibit it, you would pick synthestatin, which goes up a nice 20-fold with --

DR. FLOCKHART: That would be the most sensitive.

DR. TEMPLE: You don't have to fool around with 30 percent.

DR. FLOCKHART: Right.

DR. TEMPLE: 2000 percent.

DR. FLOCKHART: Right.

DR. TEMPLE: Okay. So there is that and then there is also in-vitro data that make you feel that you need much more of the parent to get any inhibition, and that is why you think it is not going to inhibit that pathway much.

DR. FLOCKHART: I think the simple answer to the question is we don't absolutely know, but it seems very unlikely based on the in-vitro data which requires pretty high concentrations of cilostazol to inhibit 3A. In a setting I would point out -- and this is a very important point -- in exactly the same conditions where one does see inhibition by cilostazol

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

reasons for its great potency is although in vitro, it is very specific and you use a very, very low concentration, in-vivo when it is given at 100 mg or 200 mg by mouth twice a day, it is a pleomorphic inhibitor. It becomes a significant useful inhibitor of 2C19 and of 2C9, some of the flavin monostatin agents as well. Here we were going to figure out specifically if we nailed 3A what change we would get. And the size of the changes in the studies you report, Erythromycin universally is lower, but it is not always that big a difference. Often it is half as effective, for example, in the trefenadine studies as ketoconazol. So I think we were going for a more specific scientific answer to the question rather than the huge size effect. But we did have data that suggests that you are not looking at huge numbers here. Because you are not looking at a 14 to 24 change in the AUC like you are with trefenadine.

DR. TEMPLE: And it also could be that the metabolize goes down instead of up.

DR. FLOCKHART: Exactly. A very good point. A very good point.

DR. TEMPLE : As a kind of protection, I suppose.

DR. FLOCKHART: Whatever the mechanism of the drug is. But it is possible its efficacy could be somewhat decreased by a decrease in the metabolize.

DR. THADANI: You showed the palpitation incident goes higher on diltiazem.

DR. BRAMER: Correct.

DR. THADANI: What happened to the heart rate? Do you have any data? Because we heard that the drug can increase heart rate by 5 or 6 beats. I saw the sample size is very large, so I presume that is from open label studies, the data you showed. Have you any idea of the heart rate you should expect if you are on diltiazem? Will it go up to 20 beats or 15 beats or what?

DR. BRAMER: No. Actually we did not see that subpopulation have a heart rate increase greater than what we have seen with the rest of the population that were not on diltiazem.

DR. THADANI: You expect the heart rate will go up if they are complaining of palpitations,

though . In the 11 persons who had palpitations, the heart rate could be 20 or 30. I am just curious. You have no data on that?

DR. BRAMER : As to why the heart rate increases?

DR. THADANI: No, no. Actual heart rate data. All you said is symptoms of patients. Did the physicians look at the heart rate on patients who complained of palpitations?

DR. BRAMER: We -- actually there is -- we have looked at this data base, and we didn't see anything with these conmeds that would lead us to have a greater increase in heart rate.

CHAIRPERSON PACKER: Okay. Can we go on with the rest of the -- hold on one second. Can we go on with the rest of the presentation? In saying that, let me say that because of certain limitations in terms of the availability of this room, it really is critical that we begin the questions no later than 3:15. And that means that we have to get through the committee questions on the safety issues. So if I could ask you to proceed with the safety issues, but

for the sake of time YOU can skip some of the narratives which I see are coming up and we can hopefully get through much of this. Because I am sure the committee has some questions on the slides which are coming up.

DR. INGENITO: Very good. If I may take one second to clarify a point earlier about cilostazol pharmacology. Quickly, Dr. Califf had asked about the relevance of our in-vitro PDE_3 comparative studies. And clearly we have not fully defined the effects of cilostazol and its metabolizes on PDE_3 activity ***or*** the clinical implications of such activity. The reason we showed you the study was to suggest, as your following discussion also implied, that different PDE_3 inhibitors can differ in their effects on specific tissues even if they are similar to others. And therefore, while PDE_3 inhibition raises legitimate concerns, we can't necessarily draw specific inferences about the clinical effect merely from the presence of the inhibition. That was the only purpose in demonstrating that.

CHAIRPERSON PACKER: Nor can you provide

reassurance from the data that you showed.

DR. INGENITO: Yes. The safety of cilostazol will be further examined in the target population through ECG, helter, cardiovascular morbidity, a review of cardiovascular mortality and all cause mortality as well as a brief review of the laboratory data.

Evaluation of the ECG parameters showed the PR interval and QRS interval as decreasing, and the QT interval also showing a decrease with the heart rate having an average 7 beat per minute increase. And as you can see, a dose-dependent increase across the three dose groups.

I have not included here the QTC information. However, I would be happy to do so if you would like. It was summarized in the briefing packet. would you like me to go into that, Mr. Chairman?

CHAIRPERSON PACKER: Yes.

DR. INGENITO: May I have back-up slide H-29? The patient population used in these clinical trials was evaluated at baseline prior to study drug

treatment. They were evaluated for the model which allowed the most accurate QT correction. I would like to emphasize that this was prior to study drug treatment. This figure shows that at baseline, again prior to any treatment, Bazett's model had a slope of 6.5 milliseconds for each 10 beat increase in heart rate. We have been aware that cilostazol produces an increase in heart rate, and this model may therefore overestimate the QTC.

If we look at other accepted models -- we reviewed Fredericias correction and found that it may underestimate the QTC as the slope of the line decreases with the increasing heart rate.

Linear regression as a correction for QT versus heart rate appeared to give the most accurate correction when evaluated prior to drug treatment.

To summarize the QTC data, we see that by the three methods in the cilostazol total group, a modest increase of 5.2 milliseconds if you use Bazett's, a decrease of 1.8 milliseconds by Fredericias, and a change of . 1 milliseconds using the linear regression.

Please return to core slide 11. In addition, we conducted 24-hour helter monitoring in two protocols, 92202 and 95201. We evaluated the increase in ventricular premature beats per hour according to published criteria. The percent of patients meeting this criteria was 4.4 percent in the cilostazol group versus 1.2 percent in the placebo group, producing a non-significant P value of .3. We also examined non-sustained ventricular tachycardia. Patients were evaluated for meeting the criteria of both new or increased non-sustained V-tat. Out of the cilostazol patients who had a baseline and post-baseline helter, 12.8 percent met the criteria. out of the placebo patients, 7.1 percent met the criteria. This gave a P value of .2. However, it was noted that in 18 of the 23 patients who had either new or increased non-sustained ventricular tachycardia on cilostazol and who had more than one helter, in 14 of the 18 patients, the presence of new or increased non-sustained V-tat was not replicated in both helter monitors on drug. In 5 out of 6 patients in the placebo group, the same finding of lack of replication

of the increase was noted. The data suggests that spontaneous variability may in part explain these findings. However, a direct effect of cilostazol cannot be excluded.

We searched the data base for two cases of sustained ventricular tachycardia. These are described in the narratives presented here. One case of sustained VT was on cilostazol 150 mg, and the second case was identified in our data base on placebo, both patients having a similar case history.

We further evaluated adverse event reports of arrhythmia and possibly related events through the phase 3 trials. If we looked at reports of ventricular tachycardia, you see .4 percent cilostazol and .3 percent placebo. V-fib .1 percent in both groups. Syncope is .7 in cilostazol and .5 in placebo. Convulsions, none in cilostazol and .2 in placebo. And for atrial fibrillation reports, .9 in cilostazol and .7 in placebo, and 1.7 in pentoxifyline.

Cardiovascular morbidity, that is, non-fatal myocardial infarctions and strokes revealed no

difference in the incidence between the cilostazol and the placebo groups, being at 1.2 percent for MIs and .5 percent for strokes.

Cardiovascular and all-cause mortality are presented here. To date this represents the largest data base of controlled clinical trials for intermittent claudication. The cardiovascular mortality incidence is .6 percent in the total cilostazol group, .5 percent for placebo, and was .6 percent in pentoxifyline.

If I may clarify a few of the points on these slides that were reasons. These were listed by the investigator as the cause of death. In the ventricular fibrillation, this patient was status post coronary bypass surgery and was off drug for 8 days. Kidney failure you see here as a cardiovascular event was listed. The patient underwent bypass surgery and subsequent complications were renal failure and then ventricular fibrillation. And in the angina cases listed as mortality, one case was status post bypass surgery, and the other case was a patient who had reported to his physician angina and was evaluated and

found to have obstructions, refused PTCA, went home and discontinued medication and died two days later.

If we include other events, we find that the mortality is .8 percent in the total cilostazol group, .7 percent for placebo, and .6 percent in the pentoxifyline group.

To summarize our review of laboratory data, lipid parameters were the only significantly different laboratory measurements between cilostazol and placebo-treated patients. As an example, an increase of 10 percent in HDL and a decrease in triglycerides of 30 percent was observed in study 93201. I list this particular study because lipid changes were prespecified as an endpoint. However, this was reflective of our other clinical trials.

In conclusion, cilostazol has extensive clinical exposure. The adverse events we saw were manageable, tolerable, and had comparable profiles in patients on cilostazol plus or minus various concomitant' medications. No significant lab abnormalities associated with cilostazol were observed, and the all cause mortality and

cardiovascular morbidity in the target population appeared comparable to placebo. Questions, sir?

CHAIRPERSON PACKER: We will begin with JoAnn.

DR. LINDENFELD: Let me start -- I want to come back to mortality, but just start with bleeding. It is mentioned a number of times in the reviews that both ticlopedine and warfarin are not allowed to be used in Japan with this drug because of an excess of gastric hemorrhages. Can you give us some idea of what the data is there?

DR. INGENITO: When we talked to our colleagues, our understanding is that it was more of a precautionary measure rather than having strict adverse event data showing an increased or dose effect with those two drugs.

" DR. LINDENFELD: Okay. And you have about -- as I understand it, about 1,000 patients who have also taken aspirin along with cilostazol?

DR. INGENITO: Yes.

DR. LUCEY : And there is no excess bleeding or problem there?

DR. INGENITO: No, there is not. And I can actually provide you with the percentages.

DR. LINDENFELD: How about just the percentages. It is probably not enough numbers to be significant.

DR. INGENITO: Well, what we did was -- because you are correct. There were not enough numbers if you just looked at hemorrhage as an event. So we actually -- if I may have back-up E-16 just to show you how we tried to evaluate this. We combined a number of COSTART terms. We took a lot of the terms which would code to various hemorrhages. This is the list of what we combined in our data base in order to get a significant number of patients who might have some form of hemorrhage. So we tried to take a conservative approach to this. And if I can go to slide E-18. Based upon that compilation of hemorrhage, when we looked at the total cilostazol, we had the rate on aspirin being 8 percent versus 6.9 percent off aspirin and placebo is 12 percent versus 4.9. So we did not see an increase in hemorrhage for those patients on aspirin versus off within the data

base.

DR. LINDENFELD: Okay. And you have seen -- I know you showed your own mortality data, but I think you have probably seen Dr. Rodin's FDA analysis of mortality based on patient exposure, and although not significant, it shows a disturbing trend for increasing mortality with increased dose. Can you just comment on that a little bit or tell me if you agree or disagree with that?

DR. INGENITO: Sure. If we go back to the core slide on mortality and look at that slide for you. I think the difference that causes the appearance of a dose response -- you are referring to the .7, .9, and 1.1. In the overall incidence of events, this percentage is made up of one patient. So when we look at it in terms of crude incidence, you are seeing only one patient reflected there.

DR. LINDENFELD: Maybe we can get Dr. Rodin to comment on this. Because his point estimates really -- although the confidence intervals are wide, go up with increasing doses.

DR. RODIN: Dr. Rodin, FDA Cardio-Renal.

1 would have to check my report here for a second, but I know we have been in constant communication, so any discrepancies have had to have come up and been spoken of. One thing to check on is whether we are dealing with the same total sample sizes because the data did continue to accrue over time. I will need -- I will look . But I know we have had enough conversations that any discrepancies should be well on your mind. But I will look but perhaps you can address it.

DR. LINDENFELD: Well, I think page 138 of your report.

DR. RODIN: Okay.

DR. LINDENFELD: Because I think this will be an important point. Although this is not statistically significant and again the confidence intervals a're wide. There is exposure, adjusted rate, placebo 1.9, 50 mg bid, 1.58, 100 mg 2.63, 150 mg 6.3. Again, not significant -- not even close, but maybe we could just have some comment about that.

DR. KAZEMPOUR: May I add the comment. The rates that you just mentioned are PEY adjusted, but the ones that you see over there are proportions.

So there is a difference between those that you just mentioned because they are PEY adjusted.

DR. LINDENFELD: But they were adjusted because there was less exposure to cilostazol than in the placebo, is that right?

DR. KAZEMPOUR: In a controlled trial, they are parallel. But if you multiply them by about somewhere around 3. something -- because we run them for about a four month trial on average. They are 6 months, but if you multiply them, you will get about the same increase. Because you are multiplying the difference that you observe over there between .7 and .8. When you multiply by about 4, you will get the same differences that you just mentioned.

DR. LINDENFELD: I guess what I am looking for is some reason not to be disturbed a little bit by this in a drug that has similar characteristics of others that increase mortality.

DR. INGENITO: In actuality, as Dr. Kazempour stated, the PEYs are similar as mean exposure per patient. It comes out to be approximately four months for both groups when you

take it across the whole cilostazol population.

CHAIRPERSON PACKER: Dr. Rodin?

DR. RODIN: The best I can do right now unless you can identify a specific discrepancy for me to focus further on, I can describe my analysis. The sponsors produced this analysis for me. I know the dates. The confidence intervals are only shown in my analysis and not here. Is that a concern? Are these conference intervals correct? What is the discrepancy that is of concern here?

DR. CALIFF: You show a relative risk of 1.3, which is not huge.

CHAIRPERSON PACKER: Maybe I need to ask everyone to tell me what they are asking. Because I am -- I think that the -- 1 don't think that anyone is saying that there is a difference between what the sponsor is showing and what the FDA review has shown. So I don't think we are looking for an explanation or an outline of any discrepancies. I think that what everyone is saying is pretty much the same thing, which is that at the lowest dose the observed incidence is 0.7 and then it goes to 0.9 and then it

is 1.1, and that is not statistically significant. Is there any additional comment on that is the only question. I don't think we need to pursue whether there are discrepancies. Whether there are or not, you can settle later on.

DR. LIPICKY: But there are none. Those are exactly the same numbers. Someone may have written down that that looks like a dose response, and if they did, they shouldn't have.

CHAIRPERSON PACKER: Maybe I should ask the question just to follow-up from JoAnn in a different way. The point estimate that can be calculated from the data with very wide confidence intervals is a relative risk of 1.3?

DR. INGENITO: The relative risk is -- on the overall mortality?

CHAIRPERSON PACKER: Overall.

DR. INGENITO: Overall mortality relative risk, the difference is 1.3.

CHAIRPERSON PACKER: Okay. Now I guess we have to remind ourselves that as opposed to most controlled trials which come up with point estimates

of mortality where all patients are followed for death until the end of the planned duration of therapy. The mortality data we have here is not for the intended duration of -- original intended duration of therapy. This is on therapy plus 30 days.

DR. INGENITO: We also followed the patients and accounted for all but 2 patients for the intended therapy duration.

CHAIRPERSON PACKER: Okay. And that has a point estimate of 1.3?

DR. INGENITO: Yes, sir.

CHAIRPERSON PACKER: Okay. Do you find that -- I understand this has huge confidence intervals that go probably as far as this room, but I guess I need to ask you do you find that reassuring, worrisome, or uninformative?

DR. INGENITO: I think when we look at the overall number of events, which is small, and we look at the confidence intervals there and we compare it to patients who have crossed over from placebo into open label and we follow our open label trial, which we followed patients there at 2, 4, 6, 8, 18, 20 -- every

12 weeks after. So they are followed quite often in the open label and we are finding that the relative rate is staying fairly constant. I find that to have some reassurance.

CHAIRPERSON PACKER: Let me maybe ask the question a different way.

DR. INGENITO: Okay.

CHAIRPERSON PACKER: The most interpretable data on mortality is data that has a control group. If you look at the data that you have where you have a parallel control and YOU look at death, you come out with a point estimate of 1.3 with very, very wide confidence intervals. Do you find that to be worrisome, reassuring, or uninformative? Can you conclude anything from that?

DR. INGENITO: My conclusion is that I think we are certainly dealing with a phosphodiesterase inhibitor which has a ne9ative history in patients with severe heart failure. And we as a sponsor agree that cilostazol should be contraindicated in patients with heart failure. In absolute terms, I think the point estimates suggest

that the mortality in our target population may be greater than placebo by a small amount with a wide confidence interval. Based upon the benefit that you have seen in the previous presentations and understanding of the disease, it would be reasonable and not imprudent to, given the limited alternatives available --

CHAIRPERSON PACKER: I am sorry, I am not asking for a risk/benefit assessment.

DR. INGENITO: Okay.

CHAIRPERSON PACKER: I just want to know whether you think a point estimate of 1.3 with extremely wide confidence intervals is reassuring, worrisome, or uninformative. In other words, have you learned anything from a total of 20 events with confidence intervals that include the possibility of a 20-fold increase in mortality? What are the confidence intervals on the 1.3? I mean with 20 events, they are going to be huge confidence intervals. I mean what I -- I think most of the time when we look at a small number of events, we conclude that we cannot conclude very much. And if you think

that the point estimate teaches you something, because you must believe that the point estimate teaches you something because you seem to be reassured that it is close to 1. Let me just stay that a point estimate of 1.3, if you believed it -- 1 don't know if I can possibly understand how one would believe it -- but if you believed that 1.3 were real, that would represent a 30 percent increase in mortality. And let me just remind you that in the Proms Study , milrinone, a phosphodiesterase inhibitor, was associated with a 28 percent increase in mortality.

DR. INGENITO: And yet we are separating or we are really looking at in the mortality rates there a difference of .1 percent or actually .15. So 1.5 events in 1,000 patients.

CHAIRPERSON PACKER: I think what you are saying is that you don't think it tells us very much.

DR. LIPICKY: Right. I think he is saying it is not informative.

CHAIRPERSON PACKER : It is not informative. That is fine.

DR. FISHER: Can I make a comment. This

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_3 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

suggested, and it is uninformative for that. There just aren't enough events.

CHAIRPERSON PACKER: Yes, I think the most important point is when you have very little data, you can reach very few conclusions.

DR. CALIFF: Right. But there is a critical issue which is does the underlying event rate represent what is going to happen if this drug is turned loose on people with claudication. Because if it does, then although it is uninformative as to the true relative risk, it is pretty informative that there is not a whole lot to worry about. If this was really the true underlying event rate. But if the underlying event rate in the population of interest in the real world is much higher and you have the same sort of modest concern about relative risk, it is a different issue.

DR. FISHER: Yes, I would agree with that. But I would suggest that YOU get on to Jeff's talk because for one thing, we are really tight for time. And then he will address these issues from his point of view and then you can debate it. It comes up in

the questions again, of course, too.

CHAIRPERSON PACKER: Lem, did you have a question'?

DR. MOYE: Just briefly. How many adverse events post-6 months follow-up come from a double blind placebo-controlled environment?

DR. INGENITO: I didn't hear your question.

DR. MOYE: How many adverse events post-6 months follow-up come from a double blind placebo-controlled environment?

DR. INGENITO: Post-6 months?

DR. MOYE: Post-6 months.

DR. INGENITO: From the double blind placebo-controlled?

DR. MOYE: Yes.

DR. INGENITO: The longest trials were six months and then we actively tried to collect any adverse events within 30 days after.

DR. MOYE: 30 days afterwards. Okay.

DR. INGENITO: 30 days after, yes.

DR. MOYE: But the issue on the table that

we will eventually have to address is not six months plus 30 day label. It is long term label, isn't that correct?

DR. INGENITO: Yes.

DR. MOYE: Okay. So I really am concerned about this issue of uninformative. I mean I agree that saying anything about a rate of 1.1 or 1.3 is uninformative. But I think we do have to have some information about potential long-term sequelae if we are providing a long-term label. I mean we are talking about chronic therapy here, and we don't have any information that I have been able to discern dealing with long-term consequences, of the 8 trials that were done, which has to be a record in somebody's book. Of the 8 trials that were done, not one looks at long-term issues, yet we are looking at long-term labeling.

DR. LIPICKY: But you never have that data, Lem, for almost anything.

DR. MOYE: I know, and I am never happy.

DR. LIPICKY: Right. I understand. So that is fine.

DR. THADANI: Also one of the issues is you wouldn't say the risk ratio is 1.3 to 1. A lot of these patients with peripheral vascular disease have cardio disease. And when you throw it in the open market, some of them are going to have asymptomatic LV dysfunction. And that might be more prone to problems as has been previously reported with this class of drugs. So I think one can't be reassured when you are going to throw it in the open population of which way it is going to go. So does one need a trial of 20,000 patients to address this? That is a different issue. Perhaps your drug looks so good and if it also affects platelet function maybe that is the way to go. But I think those are issues which have to be -- at least the committee members would like to be reassured of.

CHAIRPERSON PACKER: Bob?

DR. TEMPLE: One of the adverse consequences of the good instincts expressed repeatedly to look at all events is that we now see a bunch of deaths, some of which are not very plausible, and we don't even try to analyze the cause of death. Now I don't want to overdo that and say that you

should believe everything you think you see, but it does seem looking at them. One of them says accident. I mean I would like to know a little more, if a person was a passenger say, probably the drug didn't do it. Or some of them are called oncologic deaths. I would like to know a little more. You can die suddenly of a cardiovascular thing even though you have a cancer, but there may be something to learn from some of those and some of them are post-procedural deaths. so you could link that, I suppose, to the thing that led to the procedure, but that may not be the same as the things we are worried about when you are talking about a phosphodiesterase inhibitor. So I guess I would think you might want to say something and our people eventually might want to say something about the specific ways these people died because that may be relevant here.

CHAIRPERSON PACKER: Can we go on to another question that came up and could I ask the sponsor to have someone who knows more about the ways that one can correct for the QT interval to talk about the three methods? Because in taking a brief survey

of the committee, no one on the committee wanted to volunteer to discuss those three methods. So could someone do that briefly? I think it would be fair to say that some of us hadn't -- didn't even know there were three methods.

DR. MORGANROTH: My name is Joel Morganroth. The traditional method of correcting the QT interval, which is obviously dependent on heart rate, is to take that QT measurement and extrapolate it to what that QT duration would be at a heart rate of 60. In order to do that, you apply the 1929, which was when Dr. Bazett came up with this principle, and it is essentially a square root function. And that is what is traditionally programmed into almost all EKG machines and it is what everyone generally does.

As you saw from the slope of the graph that shows you what heart rate corrections would do at various heart rates, it is clear that when you become tachycardic that the Bazett formula is not very precise in extrapolating down to what that QT duration would be at a heart rate of 60. And so others like Dr. Fredericia from Europe said the best way to do it

is with his formula, which is a cubed root function, and when you do that, you essentially get the opposite effect. You get a slightly different correction that isn't as precise at high heart rates and may be better at slower heart rates.

The linear regression model essentially -- Sagi reported on this -- essentially takes a linear regression statistical approach against all heart rates over time, and you tend to get a better correction. It is a very complicated formula, so almost nobody uses it. And you saw the results of that slope was pretty flat.

This is an interesting drug because it does have an increase in heart rate that is fairly, I wouldn't say huge, but 7 beats per minute isn't small either. And it therefore affects the QT interval. And if you just look at the QT interval, you saw it actually decreases. So here is a drug that decreases the QT interval virtually at the heart rates that are seen in this study, which is averaged at a 7 beat per minute increase, and yet when you apply the traditional garden variety Bazett formula, you get

this small increase of 5 milliseconds. But when you use the other corrections, you get either a shorter QT interval by Fredericia or a no effect on the QT.

So we generally, having talked about this -- Dr. Ruskin, Dr. Moss, and myself and all having had different subsets of experiences with drugs and QT intervals -- sort of concluded that this doesn't appear to be an important issue relative to looking at depolarization issues and torsad du point and the usual things that you do with drugs that prolong the QT on the basis of the fact that at least two out of the three formulas seem not to show a prolonged QTC and even the one that is traditionally used didn't show very much of a QTC change.

DR. GRABOYS: Joel, are you going to be the spokesman for the company on this? Or who should I address.

DR. MORGANROTH: Well ask your question and I may or may not answer it.

DR. GRABOYS: Well, there is a couple of things. One is when I looked over this data, I was really upset that there was no preclinical

pharmacology at all. I mean, there was nothing on animal cardiograms. There was nothing on animal action potentials. So that there was really no background. If the company had presented some of that stuff, I think we could accept these mean data with a little more confidence. But what you are really looking at with these curves is you are just looking at the means and I don't see any data about how many -- I mean, we know this isn't sodalol. I mean, are there people in the group who had greater than 30 millisecond changes? Are there people who had greater than 60 millisecond changes? Those are the people who are likely to get torsad, and I don't care how you correct it if you want to look for those changes.

DR. MORGANROTH: I will say that when one looked at the categorical changes as I call them -- you know, greater than 20 percent or greater than 500 millisecond absolute when you didn't have that at baseline -- there was no signal of any QT depolarization effect. The only signal came on the mean whet? you used Bazett's up to 5 milliseconds. And I can't answer why in the preclinical they didn't do

this before they went into clinical. I guess at the time they started, it wasn't as routine to do that as it is now. And since they never saw anything in the clinical area and no one raised the issue, they didn't go back to do it would be my guess. But they could obviously be --

DR. GRABOYS: What are the actual data about changes over -- I mean, I thought someplace in the thing that they had -- almost everybody who had prolongations to greater than 500 were on drug. It was like 1.5 percent on drug and zero -- maybe, Arthur, you could report.

CHAIRPERSON PACKER: Maybe Art knows that data.

DR. MOSS: Dr. Moss. We looked at all of the QT interval data and particularly looked at all of the patients who were identified as having a QT interval as read as being greater than 500 milliseconds at any time, but in particular after drug initiation. There were 13 such patients. 12 of the 13 had either left bundle branch block or pacemaker, so that there turned out to be only one patient out of

the 13 that had modest QT prolongation. There is also no significant morphologic change in the repolarization. And I think because of the prior experience that they had with the drug where they had never identified Torsad or QT prolongation, that I suspect that that was why there were no animal studies. I came into this long after that, but I suspect that was the rationale.

DR. THADANI: On one of the slides they showed, I thought I saw several patients above 500 QTC .

DR. MOSS: They showed them around 560.

DR. THADANI: Yes. That is what I was interested in. You showed dots on one of the graphs of three corrected models and there were several patients above 500, somewhere around 560. So I know the drug is causing tachycardia. But is there any correlation of the three methods with actual Torsad, or is it only the Bazett's formula that has been evaluated in the past?

DR. MOSS : You mean unrelated to this study because there were --

DR. THADANI: No, say unrelated to this study . If you took all of the studies which have been published with prolonged QTC, most of the patient people have used corrected QTC. Now we are bringing in two new formulas. Is there any information on the clinical outcome of those new formulas versus the Bazett's?

DR. MOSS: No. The Bazett is the one most traditionally used here in the United States.

DR. THADANI: So we should rely on that?

DR. MOSS: And the linear regression was also an outgrowth of the Framingham study. The Fredericia tends to be used a little bit more frequently in Europe, but generally I would say 80 to 90 percent are still Bazett in all the published literature.

DR. THADANI: So if you took sodalol, quinidine, peparin --

DR. MOSS: It is all based on Bazett.

DR. THADANI: So that the others are superfluous. Are we camouflaging by showing other data when there is no data on that -- clinical outcome

data?

DR. MOSS : Well there is data on the length of the QT and the relationship.

DR. THADANI: I realize that, but no outcome data.

DR. MOSS: No outcome --

DR. THADANI: No outcome in Torsad terms?

DR. MOSS: Yes, there is unrelated to this study . If you want me to comment on it, I will be glad to. But fundamentally there is an exponential relationship between the length of the QT interval and the risk of developing Torsad, and this has been reported out in a meeting that Dr. Lipicky was at in Philadelphia several years ago. But that is the only information that we really have between QT prolongation by Bazett and Torsad.

DR. THADANI: Sure.

CHAIRPERSON PACKER: Maybe I can ask one question, Jeremy, before YOU start. Does anYone -- milrinone increased heart rate about 7 beats per minute in its trials. So a very similar increase is seen with this drug. But I never -- 1 guess I can't

remember that the issue of QT ever came up with milrinone. I assume that it just didn't. Was that because no one actually measured the QTC?

DR. L.PICKY: I think that is the case.

CHAIRPERSON PACKER: Okay.

DR. RUSKIN: Jeremy Ruskin. Just a brief comment. It is important to point out that there is still some debate about what is more significant clinically, the absolute QT or the QTC. And in fact in Europe, regulatory bodies are relying more on the absolute QT. So I don't pretend to have an answer to that, but it is important to point out that there is nothing sacrosanct about the QTC. And it is interesting that this drug, in terms of what happens when you give it to patients, is that the QT comes down -- the absolute QT interval shortens.

DR. THADANI: But if you are treating a patient -- say if I put a patient on a drug, I know absolute QT is important, but say QTC goes up to above 500, wouldn't you be worried and stop the drug in case the patient goes on some drug which causes bradycardia and induces Torsad? It may be at that point, but if

something happens.

DR. RUSKIN: Yes, I think I would. Other things being equal, I think I would be concerned about that.

CHAIRPERSON PACKER: Okay. Anybody else on the committee have any questions about safety? Alan?

DR. HIRSCH: One very quick question. I didn't see the blood pressure data presented. Whenever I see heart rate go up 5 to 7 beats a minute, I like to know the systolic and diastolic blood pressure response with a vasodilator. Do you have that data?

DR. INGENITO: There appeared to be a minimal decrease of approximately 6 mm of mercury, 3 to 5 mm in the systolic blood pressure and no change in the diastolic blood pressure in our population.

CHAIRPERSON PACKER: Does anyone else have any questions about safety? Why don't we go on to Dr. Borer's presentation. Jeff, I know you have lots of receptors for the time issue having been up here before and pressed for time. So we will ask you to do

the best you can.

DR. BORER : I will try to do that. I won't be able to present the formal comments that I have in the time that I think you have left, but let me see if I can give you an overview. First of all, the data show that cilostazol consistently results in greater activity tolerance than placebo. The magnitude is pretty impressive and I think that translates into a meaningful improvement in quality of life, not just a statistical improvement. But yOU know that the drug approvability isn't based on efficacy only, but on the relation between efficacy and safety for the intended use.

The reason I am talking about these things is that I chaired the data and safety monitoring committee and the event adjudication committee in blinded fashion for the two largest trials. So I didn't perform the studies, but I had an unusual window on the data and it may be useful for you to hear what I think about them.

I am not a peripheral vascular disease expert, so I needed to transform these data in some

way so I could understand them. And to do that, I used some of the ancillary analyses you have already heard. The two large trials that I was specifically monitoring are listed here. You have heard about them in great detail, and I don't want to go through the details again. The key point is that I come from New York and a typical city block in New York is 80 meters long. With an 80 meter block in that first big trial -- I am sorry, I will go back to it -- there was a one and a third block increase in walking distance, but it wasn't just one and a third blocks, it was one and a third blocks after placebo was subtracted on a treadmill that was at a constant uphill grade. Now using the usual METs relationship formulas that people in the field, which I am not, use, that treadmill grade made walking about three times more difficult than on flat ground. So if you use the usual transformations, on average that trial resulted in about a four block improvement in exercise tolerance if you are walking on the flat -- much less for some people but much more for some other people. You know, that is pretty good. And it was associated with the

quality of life improvement, et cetera.

The important point here is that that is enough walking to be able to get people to neighborhood stores in the city or from their cars to stores in a suburban shopping mall or rural shopping mall or to walk to their seats in a baseball stadium or to walk to their seats in a theater, even if they had to walk up a moderately steep hill to do it.

In the other trial, the improvement -- the other trial used a slightly different treadmill protocol. There was clearly an improvement. It was about a half a block on treadmill, more than placebo. Also a half a block more than pentoxifyline on the same ramp treadmill protocol. So there is some variation here, but again the improvement was clear and it was seen.

I don't think this kind of interstudy variability is surprising, particularly when we are talking symptom-based endpoints, but I was concerned about it and Rob Califf mentioned this and Udho Thadani mentioned this and I had thought about it too. So to evaluate the drug, I figured we had to look at

the variability. And for my own edification, I combined all the placebo control trials of at least 12 weeks duration, that is the phase 3 trials, to look at the average change in walking distance on the treadmill. Now remember in addition to any of the flaws that were mentioned about this kind of combination, nonetheless it should be a conservative analysis because the data suggests that on cilostazol walking distance continues to increase for at least the 24 weeks on the long studies, and several of these studies were shorter than that. Also, some treadmill protocols were vigorous and some were more vigorous. All involved exercise that was two to three times more difficult than walking on the flat. And as you heard, one trial, the 94301 here that was the European comparator of pentoxifyline and cilostazol, reported results based on tests in some cases that were taken as long as two weeks after the drug was stopped. And of course although I wouldn't make a big issue of this, the measurements were made at trough all other times. The drug effect plausibly might have been a little greater than at trough. SO, again, there are

reasons to consider this analysis to be conservative.

Despite these variations, when you combine the 8 trials, cilostazol 100 mg bid increased placebo corrected walking tolerance slightly more than three-quarters of a city block down here, walking on an uphill treadmill. If you make the transformation again based on METs differences, on a flat that would be about two blocks on average for all these trials, short and long or whatever, and some people did much less well in that but some did a lot, lot better.

The benefit was seen consistently across all the trials, even allowing for the usual intertrial variability that is usually a feature of these kinds of studies, and the data are supported by the quality of life measures which can be thought about the way John Ware discussed, and I certainly can't add to that. In practical terms, that sounds to me like a pretty solid benefit.

Nonetheless, for approvability, the exercise tolerance increase must not be offset unreasonably by safety concerns. And the concerns here need to be met head-on really. This drug, as we

have heard so many times today, like pentoxifyline but quantitatively different, has some PDE inhibiting activity. PDE inhibition in myocytes raises legitimate concerns in heart failure, but in this NDA, patients whose exercise tolerance was limited by heart failure were excluded from study, so that we could evaluate drug effect specifically on claudication relief. The result is that really we can't say anything about safety for patients with heart failure.

Also, cilostazol causes a dose-related increase in resting heart rate that you just heard about, and these two pharmacological effects raise the possibility of drug-related heart attack and sudden death, and the patient selection factor here limits the target population by circumscribing the group about which we can assess safety. On the other hand, the drug has pharmacologic effects like reduction of platelet aggregability, antithrombotic activity, vasodilation, HDL cholesterol increase, decrease in the smooth muscle mitogenesis, you heard about all of them, and in theory they could minimize cardiovascular events. So it seems to me that what we have to do is

to look at the data. This is the same problem that we commonly face when the focus of drug evaluation is symptom relief.

What we have to do is to measure the theoretical concerns against the actual data. Now if you consider the dossier in the context of NDA's of other drugs for exercise tolerance improvement in peripheral arterial disease, this program is really uniquely rich in placebo-controlled trial data. There are more than 2,700 patients observed from 12 to 24 weeks in placebo-controlled trials. Unfortunately, though, the patients with peripheral arterial as a group form a high risk population, as you heard, with a 20 to 30 percent five year mortality risk and major, major lifestyle limitations. But our population presents the same problem as many NDA's focused on symptom relief, that is, to enable evaluation of claudication relief. The study population was designed to include people who were limited specifically by claudication. The result is that morbid and lethal event rates were sufficiently low on cilostazol, on placebo, and on pentoxifyline that

statistical power just isn't sufficient to identify small intertreatment differences, even if they exist.

Nonetheless, these are the data. And despite the limitation in power to discriminate between drugs for different events, I think at least some plausible inferences can be drawn for the population for which the drug is targeted, which is the population that was studied. First, in absolute terms, the rates of mortality and infarction on the drug are low for the target population and they are comparable to those reported in the literature in similar populations. More importantly, these relatively "low rates of major problems have to be weighed against the relatively large improvement in activity tolerance.

Second, even though we lack the power to exclude differences rigorously at these event rates, there is no significant difference in mortality and in myocardial infarction among cilostazol, placebo, and pentoxifyline, and probably more importantly in absolute terms the differences are relatively small and seem at least reasonable for the benefit we

observed. Also, there is no difference in the rate of progression to vascular surgical procedures among the treatments and that wasn't discussed earlier. In fact, in the two largest trials for which I chaired the monitoring committee, there was a modest tendency to reduction in vascular operations for patients on cilostazol compared with placebo.

Now you know it is very hard to draw any conclusions based on performance or non-performance of a therapy as an outcome event. However, I think it is worth considering the surgical data for a minute because decisions to operate were made by investigators blinded to drug treatment and were made after development of arrest pain or early tissue devitalization. Now these are conditions universally accepted as indicators of drug failure. And as Bill Hiatt said, in this population vascular surgery isn't undertaken lightly and is seldom undertaken at all for claudication relief in the United States because perioperative risk is relatively high. So it is reassuring at least that claudication reduction with cilostazol wasn't associated with an excess in the

need for surgical procedures.

Finally, I think it is useful to look at the post-marketing data. No question, there is an important weakness here. Uncontrolled post-marketing observational data can be influenced by factors that confound interpretation and of which we are unaware. But at least it is reassuring that in 10 years of post-marketing experience involving more than 3,300 patients in formal surveillance studies, more than 7,000 other patients in pre-approval and post-approval trials, all drawn from more than 850,000 patients who have received the drug, no concerns about drug-related mortality have been raised. No regulatory body or evaluator has identified safety concerns that outweigh the benefits of cilostazol in patients with peripheral vascular disease.

In summary, it seems to me that cilostazol improves exercise capacity meaningfully and impressively. This benefit is apparent in patients with a disease that is severely debilitating and for which medical and even surgical alternatives are very limited. Mortality data need to be balanced against

efficacy, and these are relatively sparse in the NDA because of the modest rate of major untoward events in all the groups. Nonetheless, I believe that despite this limitation, which is common in NDA's for exercise tolerance improvement indications, the controlled trials and post-marketing experience taken together suggest that cilostazol is acceptably safe for its intended use. In the final analysis, I believe the benefits of the drug in the intended population outweigh the theoretical concerns that aren't borne out in the NDA studies, and as in most similar NDA's, that can't be rigorously evaluated without patient exposure of greater magnitude than usually is a part of an NDA for symptom relief. For these reasons, I believe approval of the drug is appropriate now with labeling that expresses the current knowledge about benefits and risks, and I hope as you consider the issues that you will agree with me.

CHAIRPERSON PACKER: Any specific questions tc Dr. Borer? Udho?

DR. THADANI: Dr. Borer, the data on the absolute meters, is that a median or mean value?

DR. BORER: Those were mean.

DR. THADANI: Because after you gave us -- 1 think if we have the light, I could see the page.

DR. BORER : Those are the mean values, Udho .

DR. THADANI: On page 23, I think when they give the median values, they are only about anywhere from 20 to 25, with the exception of one study which is 61.

DR. BORER: Right. These --

DR. THADANI: So that might translate into lesser if you mean those numbers.

DR. BORER: These are the mean values, not the median.

DR. THADANI: Rather than the median, okay.

DR. BORER: And the entire issue of which you use, of course, is open to some interpretation. You heard what Lloyd thought about the mean versus the median, and you may have other views of it. But I used the mean, which I thought was perhaps reasonably representative of the totality.

DR. THADANI: The other issue is the post-marketing data is mostly from Japan and the Pacific Islands, where the coronary artery incidence is not high. So how much reassurance one could get from where the coronary disease is not that prevalent, I am not sure, as opposed to other countries where the coronary artery disease is more prevalent. The post-marketing data may not be that accurate because they don't have many deaths.

DR. BORER: Yes, there is no question that one must interpret with great caution post-marketing data from anyplace, and I think your comment is absolutely right. Nonetheless, here are the data and they didn't show anything that was worrisome.

CHAIRPERSON PACKER: Marvin?

DR. KONSTAM: Jeff, I just wonder how far you could go in quantifying or quantitatively expressing your degree of comfort. And maybe this is the way Rob might ask this question. So given the efficacy, and I agree with YOU that it is pretty impressive efficacy. That is my view. Would you say in this population -- would you for example tolerate

a doubling of mortality? Or rather than my asking it in a leading way, what level of mortality increase would you tolerate, either in absolute terms or in percent terms, given the degree of efficacy that you see?

DR. BORER : That is, of course, the key question here. I have been thinking about that question ever since I saw the final data set. I don't think there is any right answer. But I will tell you what I personally believe. Let me begin by reminding you that these are very limited patients. They can't do the everyday things they want to do. They are dependent on other people. They have economic costs that most of us don't have. Even just to deal with survival issues. And currently there is a very limited armamentarium to deal with this. Now this drug seems to provide real and important benefits. It is not just a block of walking or two blocks of walking. In some people it is a lot more than that. But there are many, many benefits that you heard about today that alter in a beneficial way the way these people live that are possible with cilostazol and not

without it. And this kind of benefit allows people to be, I would think, self-reliant and to live with some dignity and to have some fun. Against these benefits, the risk seems to me reasonable and acceptable. Mortality and MI risk are low. That risk might prove to be higher on cilostazol. None of the data, as everybody has said, are sufficiently precise or stable alone for a final estimate. But let's take the worst case. If you take the point estimate for the time adjusted mortality risk, the 2.6 -- it is 2.57 now - but the 2.6 versus 1.9, that is about a 1.3 point estimate. Let's take that. What does that mean? You start from a 2 percent annual placebo risk. Let's think about a 65-year-old man, the average age of the people here, who can expect, Bill Hiatt told us, to have stable claudication for the next five years. So let's talk about the next five years. During the next five years, he would have one chance in 10 of dying before age 70 without drug and one and a third chances in 10 of dying with the drug worst case scenario. Now Rob suggested a doubling. Okay, one chance in 10 of dying within five years without the drug and two

chances in 10 of dying within five years with the drug. You know, in people who have to call on other people to help them get their food and to move about, I must say as a doctor I have no problem at all offering this trade-off to a patient as a rational and reasonable option. They might not choose to take it, but I think that many or even most would take the risk. And that is in a worst case sort of scenario, and there are other ways to deal with the data that might be more sympathetic, but no more accurate. so I think that the benefit of this drug outweighs the risks as well as we can assess them at this time. And I don't know if that absolutely answers your question, but that is the way I think about it.

DR. KONSTAM: So, let's see -- it sounds like if you say it is a baseline 4 percent mortality is what you are talking about -- 4 percent annual mortality. This population had about a 2 percent.

DR. BORER: Right.

DR. KONSTAM: But in the -- 1 guess saying 1 in 10 means 20 percent 5 year and meaning 4 percent per year is what you are talking about for the

baseline.

DR. BORER : Two percent per year would give you 20 percent in 10 years.

DR. KONSTAM: Ten years, sorry. Okay, sorry. Ten years. so 2 percent then -- it sounded like you said in your view, and this is just your view and maybe nobody else agrees with it, you would tolerate based on the efficacy that you see a doubling to 4 percent per year?

DR. BORER: That is right, to 4 percent per year. That is right.

DR. KONSTAM: Is that the limit? Is that as far as you would go?

DR. BORER: Well, no, it is not as far as I can go. But, you know, making a stab at a number is difficult for me. The way I derived this was to look at the numbers that were as close to real as I had them. And I said, okay, in this population that actually perhaps sustained this risk, did the benefit they achieved outweigh that risk. And the answer to me was plausibly yes. someone might choose no, but it is not irrational to choose yes. To pick another

number is just to be shooting at blanks. I picked these numbers out of the data.

CHAIRPERSON PACKER: Rob?

DR. CALIFF: This is really tough. Because as the day has gone on -- actually from looking at the original package, and the case is convincing about the clinical benefit, I agree with you . But the baseline data that I am seeing is not telling me that most of these people were having to get help to get to the grocery store. And I guess the big concern -- I would agree that if the whole population couldn't walk across the room and now they could live independently -- if it was that kind of a change, that sounds very exciting. But let's work at it the other way. You've said that you can't say anything about patients with heart failure. You have had a lot of experience over the years with this and you are in this position now of the really big overview. What would the label look like that would keep doctors and patients from inadvertently taking a risk which has been unquantified? Would you extend it to anyone with left ventricular dysfunction? Should

the label say if the doctor offers this to a patient, it is a horrible thing to do? I mean, we have drugs that have labels and most doctors never know what the labels say. In my poll of house staff in our institution, there is not a one that knows that oral hypoglycemic all have a label that says this drug may kill you. So just putting it in the label, seeing what has happened recently with some of the drugs that have been put out, seems like a worrisome thing. Sort of on the other side of what you are saying. Yes, if people are really completely disabled, the opportunity to help may be worth the risk. But just sort of saying that we didn't want to look at that population or that is not our target population so we are going to pick a low risk group where there is no chance that we will see that the drug could be harmful, that is what I see happening with most of these trials. And then we are left like we are today. Where would you -- what would the label read that would keep patients from being exposed?

DR. BORER: You raise a lot of crucial issues. Let me just say, though, that it is probably

not really fair to infer that the population was selected as low risk so you wouldn't see a problem. The population was selected because that was the population in which you could study claudication. People who are limited by something, it is not the same as claudication.

DR. CALIFF: But you would agree that if in the planning of the trials it had been the intent of those who planned it to understand the risk for cardiovascular events, that there would have been something else done besides just exercise studies? Is that true or not?

DR. BORER: Yes, of course it is true. If the intent of the development program was to understand the absolute magnitude of cardiac risk, then one would perform a study, if YOU wanted to get it done during the time of the NDA, involving an extraordinarily large population, which really hasn't been done before. It hasn't been one of the standards of evidence that has been employed and it is economically' -- you know, it is a tremendous burden. Now that doesn't -- 1 am not saying that it is wrong

in any way. But if it isn't the standard that has been applied and it entails a tremendous economic burden, you wouldn't undertake it unless there was a requirement to do it. Absent a tremendous population in a short period of time, you have to perform a study in a smaller population over a much longer period of time, which again entails a number of burdens that would be difficult. That doesn't mean that I wouldn't like to have those data and you wouldn't like to have those data. They aren't the data on which these kinds of decisions usually are based because they usually don't exist, which doesn't mean we wouldn't like to have them. However, in this population described in this way, I think we can be reasonably comfortable.

Now then we come to the more important point you are raising. How do you prevent other people from taking the drug, people who don't fall in the labeling restrictions, and I don't have an answer for that. The usual way that this is done is by putting a black box on the label and expecting that the detail people, et cetera, et cetera, will be very responsible in the way they present the drug to

doctors. Is that effective? Obviously it is not as effective as it might be. And do I have a remedy for that? No, I don't.

DR. LIPICKY: Just to be sure that the record is straight, the lack of a morbidity/mortality data base with this drug lays right at our feet, not at the company's feet. We did not say that that was required. And in fact, during the time -- and I understand none of this has any meaning. It doesn't change the circumstance. So I am not offering it. But I just want to be sure that the record is straight. So I am not offering it as an excuse or anything else. It is just so you know. And at the time that. the development program was going on, the adverse consequences of phosphodiesterase inhibitors was not known. And in fact, I am not sure why the people at the table think that the past experience with other phosphodiesterase inhibitors applies here. That is just the bias you are bringing.

DR. HIRSCH: Can I amplify that after you are done, Ray?

DR. LIPICKY: Yes.

DR. HIRSCH : Finish and let me continue with that. I want -- if I have any purpose for being here as sort of a PAD physician, I have to speak up now or forever hold my peace. This is not like the other markets -- again, heart failure that we are dealing with and other patient populations. I mean first of all, we just simply don't have confident mortality data. So we can debate and try, Rob, to try to put numbers on our confidence, but we are not going to be able to do it. The confidence limits are too wide to predict, number one.

Number two, again, like Dr. Lipicky just said, we have never asked for -- when I say we, I mean everybody in the PAD field including FDA -- have not asked for mortality data to antecede efficacy for symptom improvement. Now when you translate that to an unusual market -- this is PAD where patients face different choices. When we ask about risk/benefit ratios, what I see going on in the real world is patients doing not the SF-36 but the standard gamble. They are facing their physician and they have to ask the question, would you be willing to take this short-

term, let's say for a vascular surgical operation -- this short-term risk of an adverse outcome for this better risk of walking improvement? In other words, patients face these choices and they make their choices, and frankly in this population the patient is usually willing to take the choice to walk even facing a short-tern or cumulative risk of an adverse outcome or death. I think these patients know that they are not going to live forever and they are usually willing to make the choice. That is just an anecdote.

But without mortality data, these patients face other choices where again we don't have data, but they make the choice for efficacy. We tell patients who don't face vascular surgery that we don't have a medication to work and to exercise. And actually asking a patient with PAD with a coronary disease burden to undergo vigorous exercise in a program, which almost always in our country happens without monitoring or ST segment monitoring, is also asking the patient to take a risk, and the patient takes the risk. And frankly the patient is willing to because they get better.

The point is, I guess, to me when we ask the patients to take the gamble, the usually take it in favor of symptomatic improvement in this population. Now that is not heart failure where there are other modalities. You have diuretics, you have Digoxin, you have ACE inhibitors, and YOU have A2 antagonists and you have other choices. So in the lack of a marketplace -- again, I think we are looking at new drug approval -- we should be very careful when we do the efficacy/safety analysis to be careful to weigh efficacy. And if we don't have better mortality data, we can ask for that later. End of speech, I think.

DR. LIPICKY: But I want to add just one more comment to what he said before he says something. That is that if one could have elected say to do mortality trials and found that mortality was increased or decreased, but then one would not know if the patients felt better in a trial of that nature, right? So in fact many -- there are tradeoffs in all of the approaches to developing drugs. Morbidity and mortality trials, I suppose, one argues that if people

aren't in the hospital that they must be feeling better. I am not convinced that that is true, but I understand that one could argue that. So in the large scale real life morbidity and mortality trials, you have some kind of hardcore real clinical benefit, so to speak, that you can anchor to, but YOU don't know that people want to have that. You don't know that they are feeling any better or that their symptoms are any better or anything else.

DR. CALIFF: Well, but you are almost as bad as Milton in this unfair option in some of the ways that he has posed questions. I have already said that I think that the series of studies on symptoms -- this is a great series of studies, well performed and well presented. The issue for me is not either/or. The issue for me is that you've got 4 million people potentially eligible to take this drug and many of them have substantial comorbidities of the type that look to me like they were not included in this trial. We have an environment, particularly in the U.S. now, where most practitioners have 12 minutes to see a patient, and I think you have recently seen evidence

of what that can do in terms of people keeping things straight about what indications and contraindications and complexity of administering therapy can bring. And also to set the record straight, I am not saying that the lack of the data is the sponsor's fault. It is your fault.

DR. LIPICKY: Yes, I understand.

DR. CALIFF: But it doesn't relieve my anxiety about turning something loose in potentially 4 million people, which if it had a 30 percent increase in mortality and knowing the way things are done in practice in the U.S. today, the potential for harm that could be done that might be addressed by doing in addition to the symptomatic study a fairly simple study to just measure who lived and who died and the type of patients who are really going to be treated in practice. But I have said my piece.

CHAIRPERSON PACKER: As in many examples today, we are not going to resolve this. And, Bob, with your permission, I am really anxious to get on to the questions. I promised JoAnn that I would give her the last. word since she is the primary reviewer. We

have to get out of this room by 5:30. We have no alternative. Our lease expires. So, JoAnn?

DR. LINDENFELD: A quick question. Knowing that this is one of the few alternatives for these patients, we have said that they could walk a block and a third longer. But in the patients that were most limited, they had the least improvement. In a patient who could walk less than a block to start out with, what improvement might we have expected with this drug? It is not a block and a third. It is substantially less than that.

DR. BORER : Right. That is a very good question. I really can't answer that. What I can tell you is that the block and a third increase on the treadmill came from a block and a half baseline. So it is a substantial improvement on what was there. How many were less than a block I can't tell you.

CHAIRPERSON PACKER: All right. Thanks a lot . That concludes the sponsors presentation. While Jeff is returning to his seat, I guess both he and I are aware of data that blocks in New York are shorter than blocks almost anywhere else. There are 20 city

blocks to a mile in New York and an average of 10 city blocks to a mile almost anywhere else in the United States. The reasons for that are beyond the scope of today's meeting.

DR. GRABOYS: Doesn't it make a difference if you are going across town or uptown or downtown?

CHAIRPERSON PACKER: Yes, it makes a big difference.

DR. GRABOYS: So it depends which way.

CHAIRPERSON PACKER: It does. And that is true of most things in life. Okay. We will get right to the questions. The first questions deal with the analysis of exercise data including both absolute claudication distance and the initial claudication distance. We will turn to our primary reviewer and ask the first question. Actually, JoAnn, with your permission I will direct this to Lem. Lem, a logarithmic transformation was conducted on the analysis on the raw data. I know you have addressed this, but we need to just state it briefly because Joan needs it for the records. Was its use appropriate in this case?

DR. MOYE: I believe it was appropriate. I think that they went the additional required step of doing the analysis on the untransformed data and the results did not change.

CHAIRPERSON PACKER: Okay. Does anyone disagree? Question number 2, were the patients studied in the reported trials reasonably representative of American patients with intermittent claudication? Let's say this is the first example that I know of of a patriotic slant to a question. Usually we are not so country-specific in the way the questions are asked. JoAnn, what are your thoughts?

DR. LINDENFELD: I think these were reasonably representative. They were certainly, I think, a lower risk of a high risk subset in that they had no heart failure. We know that. But they also didn't have angina limiting their exercise capacityat all and in fact could be off Isordil. But I think they are reasonably representative.

CHAIRPERSON PACKER: Okay. Bob?

DR. TEMPLE : Well, I want to ask a question because this has come up a number of times,

especially in the form of Rob's concern that a different group of people would be included. Could people be specific about how they think this was a relatively low risk group? And I ask that because you obviously can't include people who don't get claudication. So the people with bad heart failure, they can't be in the trial and they wouldn't have heart claudication. So that is not it. So what else about this group is different? And I think that is relevant to how one might label the drug later, so we should pin that down.

DR. LINDENFELD: Well one thing I think might be low risk is that they could be taken off of Isordil. So that meant they didn't have a lot of angina I would think.

DR. THADANI: But a lot of patients had a previous MI, I think about 20 percent. They were smokers and there were other risk factors. If you take the general patient population of peripheral vascular disease, when I see the consults on those patients or do angina studies, some of them have both problems, but they can't go to angina because their

intermittent. claudication stops them first. And if you were to do a cardioangiogram or even a stress on these patients, a lot of them will have underlying CAD. The peripheral vascular disease correlates better than carotid. So although you are saying lower risk -- because the data base is only 3 to 6 months here. If you look at Creakey's study, he is talking about 20 percent mortality. I realize they are all-comers. so I don't think we can say low risk in mortality or morbidity terms from the data given.

DR. TEMPLE: Well, they had to be six months away from an MI, right?

DR. THADANI: Well, I realize that.

DR. TEMPLE: And they had to be some distance away from surgery. I mean, it would be helpful to pin down those aspects because labeling could conceivably reflect that in some way.

DR. HIRSCH: But Bob to make a point that they are not or they are representative, if you look at other major national studies, the mid-trial from the NIH, the McDermott's data from Northwestern recently, Capri even, really 70 percent or so of the

PAD patients out there who claudicate aren't coming to the doctor with coronary disease or heart failure. They are. like this.

DR. TEMPLE : Okay. Well, I am asking particularly because of what Rob has been saying. That when you make the drug available, all of a sudden the people who get the drug are going to be very different. And it is important to pin down in what ways. Because if you are really worried about it, you can -- you know, you can have a patient insert and put the patient in the loop too. So one could do that. So I think it is important to say what particular increased risk population one might worry about here. And I guess I am -- 1 don't understand how the heart failure population would be worried because they are not going to be able to claudicate. So it must be something else.

DR. THADANI: But , Bob, the heart failure population now -- the changing of heart failure is very different. You can have Class II failure with LV dysfunction or limited by walking 500 meters by 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 disrythmias.

DR. TEMPLE : Yes, but you can't be different because if you have limiting of those things, then you can't -- then you are not a claudicant, right?

CHAIRPERSON PACKER: Marv?

DR. KONSTAM: Well, I just was going to say that it seems that there is something different in terms of the differences in the mortality rates that we see here compared to what we are told is the ambient mortality rates in the population of patients. So it sounds like there is something different. And I don't know exactly what the answer is, Bob. I hear what you are saying from a logical perspective, but my suspicion is that in fact patients with heart failure, even though they were really limited by claudication, were in fact excluded. I mean that would be my suspicion . As to the type of ways that it was moved toward a lesser risk population. If you look at the percentage of patients who were in the studies who had heart failure, one might find that it was a lower population than the population out there with claudication who has heart failure.

DR. LIPICKY: What is the higher number that has been cited here?

DR. KONSTAM: I am sorry?

DR. LIPICKY: What is the higher mortality rate that has been cited here?

DR. KONSTAM: 4 percent.

DR. LIPICKY: In people who have six months worth of claudication stable and no accelerating, is that a correct number, 4 percent?

DR. KONSTAM: We can ask Dr. Hirsch that question.

DR. LIPICKY: I mean, are we dealing with the right thing? That is, is it not that patients who have stable claudication and only claudication as their symptomatology, and who have had it for at least six months. Is the rate that has been observed in these trials really different from the rate that one would see in a population characterized by that? Do we know that? Because people are assuming that we do and that the rate that was observed is very low.

DR. HIRSCH: I think they are different populations. The two best things I can think of are

the clopidogrel data set, where 60 Percent of the patients had had surgery and 40 percent were claudicants. so you can't necessarily take the 4 percent rate from them and apply that to the 2 percent rate here. And then you have to look at Creakey's mortality data, which includes asymptomatic to *very* severely symptomatic. So I think that this population is a little bit more narrowly defined.

DR. CALIFF: So is it that it is a population -- so what is the definition Of the population? Is it patients with stable claudication?

DR. HIATT: It is stable claudication who come into these kinds of trials. This is a representative mortality figure. But it may not represent the totality of PAD, which is probably --

DR. CALIFF: Okay. What is the difference that is contained in that phrase, "who come into these trials"? I mean, I guess that is what we are asking you to define.

DR. HIATT: Well, if we look at the natural history and you are looking just at stable claudication symptoms. Not unstable claudication.

Not severe PAD. Those patients have higher mortality rates. This population obviously has a lower mortality rate, about half of what you would expect.

DR. GRABOYS: So you are talking about a labeling that is going to define a very small segment of the population. These people are clinically stable. They don't have LV dysfunction. They may not be insulin-dependent diabetics. They may not be continued smokers. I mean this is --

DR. LIPICKY: No, they have diabetics here.

DR. HIATT: They have diabetes. They have lots of comorbid disease. But in fact, you wouldn't want to treat someone with a medication unless they had stable limiting claudication symptoms that were more severe than their heart failure symptoms or their angina.

CHAIRPERSON PACKER: It sounds as if -- I think what T hear is pretty much everyone saying the same thing, which is that were this committee to look at this drug favorably, we would look at this drug favorably in the patients who were studied, and the

patients who were studied were patients with stable claudication without angina or heart failure. Consequently, if further deliberations of this committee were to say that they felt comfortable with this, my guess is wording that describes something like this would be the wording that would appear in the indications section, that is, that one would -- this drug would be indicated in patients who had stable claudication without angina or heart failure.

DR. HIATT: That is not quite it.

DR. LIPICKY: It is for people whose exercise is limited by claudication.

CHAIRPERSON PACKER: Okay. That is fine.

DR. HIATT: It is that simple, with an ABI of less than .85.

CHAIRPERSON PACKER: Ileana?

DR. PINA: My only question with that population is in the studies, they had to be taken off -- and I think JoAnn said this too -- off their chronic nitrates. They could take sublingual and intermittent nitrates. And in the average population, the physicians that are going to give this, even if

they are stable claudicants, are not going to stop the anti-anginal agents. So the population may be a bit different. I am not that concerned about the heart failure patients because I don't think they are going to be in here. The real sick ones are not going to be in here. There may be some with asymptomatic left ventricular dysfunction or the Class I's or Class II's, and I am not that concerned about them. But the patients who would have angina, have their anti-anginal agents been stopped, and we don't know anything about that.

CHAIRPERSON PACKER: And there will be other opportunities to discuss this. But I think we -- I just want to ask the committee one question because there is one difference that no one in this committee has discussed yet with respect to question number 2, which is the anti-platelet use. Because we heard and we understand there is a changing paradigm here, but most of the patients in these trials were not taking anti-platelet drugs, and the impression we all have is that maybe the use of anti-platelet drugs in this patient population will increase and increase

dramatically because of their ability or at least the ability of one agent to affect the long-term outcome. so that is not -- there is some experience with aspirin, but most of the patients in this data base weren't taking anti-platelet drugs. So that is a difference in the population that is studied here from the population which is likely to be the tar9et population, even if that target population is described as exercise limited by claudication.

DR. THADANI: I think, Milton, that is a pertinent point. In the earlier discussion the clopidogrel issue was brought in. And since the drug has been approved only recently and improves outcome, one would presume even the PAD expert sitting next to me is going to prescribe that drug. And if you did, that patent is already on -- because that is the benefit. If a patient is on that and then if you give this drug, are you going to be able to show improvement in exercise?

CHAIRPERSON PACKER: That is not the question being asked. The only question being asked the committee in question number 2 is what are the

differences.

DR. THADANI: That might make a difference in the safety outcome.

CHAIRPERSON PACKER: A totally different question and we will discuss it later.

DR. THADANI: Okay. Then the question would co-me up too with triase down the road if you are eluding to that too. Because a lot of oral agents, at least in coronary artery disease going on at the moment, and if more cardiologists are going to use those, then if a patient is put on this, those are relevant. So the population could be different because of the background different therapy.

CHAIRPERSON PACKER: Okay. Bob?

DR. TEMPLE: Milton, filing for later discussion, one difference is it seems very likely that people with this disease will be on clopidogrel. We don't. know whether they are going to be on aspirin. This committee has concluded that aspirin is not useful in that setting, but they may very well be on clopidogrel So that is one difference.

CHAIRPERSON PACKER : That is the

difference I was highlighting.

DR. TEMPLE: Okay. I can't help saying I wouldn't have thought the difference was whether the drug worked in that population, it is whether people bleed, right? That is what we are worried about, if anything.

CHAIRPERSON PACKER: Yes. We are going to discuss this again, I promise. Question number 3, the clinical trials lasted for 12 to 24 weeks. Were these trials long enough for a study of this indication? Before I ask JoAnn to address this, let me ask Ray. There are lots of ways one can interpret this question. Is the intent of the division that this be a --

DR. LIPICKY: I think you can skip it. Because you have really discussed that business already.

CHAIRPERSON PACKER: That never stops us from discussing it more.

DR. LIPICKY: And it really was intended to raise the question of if you feel good for six months and then die in the seventh, is that good

enough. But you have gone through all of that business.

CHAIRPERSON PACKER: We have gone through all of that.

DR. LIPICKY: And is six months a long enough mortality trial? And we want to give you the chance to yive your milrinone experience all over again. So skip it.

CHAIRPERSON PACKER: Thank you. Question number 4 is a discussion of dropouts and the analysis of dropouts. The primary question that is being asked here is primarily on the exercise tolerance. I think that is a correct statement. Number 4 is focused on exercise tolerance and the question that arises -- hold on one second. I just want to make sure that my notes are right. It does focus on exercise tolerance, but in fact there is no subsequent place where -- no, actually we can pick it up in 7 on the secondary endpoints. So we will focus number 4 on exercise. And the first two-part question in number 4, are you satisfied that the dropout patients had been adequately accounted for? And then please go on and

answer, are the last observation carried forward analyses acceptable.

DR. LIPICKY: And one word answers can do.

DR. LINDENFELD: Yes and yes.

CHAIRPERSON PACKER: Does anyone disagree? Udho?

DR. THADANI: Just a concern regarding that some patients who really deteriorate and are carried forward with the same disease process. I think we eluded to that before. But accepting -- since everybody does it, we are going to accept it. But maybe in the future, it would be nice to look at patients who for some reason started getting resting leg pain and maybe different ways of doing it. So I agree with it as it is, but with a proviso.

CHAIRPERSON PACKER: I guess I would reiterate. I would underscore Udho's concern. I think that in this case, the last observation carried forward analyses are acceptable. But I have real concerns about relying on last observation carried forward analyses if there is a meaningful number of patients who drop out because of worsening of the

disease which is related to the primary endpoint being measured. And in those cases, I would feel uncomfortable with a last observation carried forward, but that is not pertinent to today's NDA. Bob?

DR. TEMPLE : Also, analyses were done. One a not too aggressive one that just attributed bad outcomes to everybody who dropped out and *one* that attributed bad outcomes only to the treated patients who dropped out, which is certainly the maxi-punishment. And the results in this case were still robust.

CHAIRPERSON PACKER: Of course all of these questions are a lot easier to answer because the P values were so small.

DR. TEMPLE: It really helps.

CHAIRPERSON PACKER: These questions would be a lot more interesting if the P values were borderline. I guess interesting isn't a really good word. Number 5, which if any of the trials showed that cilostazol is superior to placebo for the claimed indication? We have already discussed what that might be, what the sponsor is proposing. Which of any of

them failed to show superiority? So, JoAnn, I guess what is being asked is of the 8 placebo controlled trials, how many fall into a superiority category and how many do not? And if there are any that fall into -- if there are some that fall into the not category, is that a problem for you?

DR. LINDENFELD: There are really 5 out of the 8 studies that are definitely positive, and one that is positive but that was stopped early but I think it- would still be considered positive, 92201. And then two that showed a trend toward being positive but were not positive. But I think all in all, this is not a problem. It is a very strong set of data.

CHAIRPERSON PACKER: And so that although there are two or three that are not in the category, the answer is that that is not a problem for you?

DR. LINDENFELD: That is not a problem.

CHAIRPERSON PACKER: Okay. Does anyone disagree?

DR. THADANI: I agree with all the statements with the exception of the comparative study. There are only two trials and one is positive

and one is not.

CHAIRPERSON PACKER: That is the next question, Udho.

DR. THADANI: oh, okay. Because she is including just the placebo control. In that case, I think there are only two trials, yes.

CHAIRPERSON PACKER: Okay.

DR. MOYE: Milt?

CHAIRPERSON PACKER: Yes.

DR. MOYE: I guess because I disagree with three, that the trials were not long enough to study this indication, then I am going to have a problem identifying any trials in 5 that do meet the indication. And my concern here is primarily duration.

CHAIRPERSON PACKER: Lem, let me ask you about what you just said, because I actually I think there may actually have been value in having even briefly voted on number 3. Let me ask the question in the following way. The question on number 5 really focuses on efficacy, not on the total concept of approvability. So from a pure efficacy point of

view, would you think that a trial that lasted for 12 to 24 weeks, and all of them did, would be sufficient? I understand safety concerns are different.

DR. MOYE: Right.

CHAIRPERSON PACKER: And potentially separable.

DR. MOYE: Right.

CHAIRPERSON PACKER: So since number 5 is an efficacy focused issue, would your -- are you still concerned about agreeing with JoAnn if that were only an efficacy focused question?

DR. MOYE: Well, I certainly try to agree with JoAnn every chance I get, but I don't think I can agree this time. Because even with the efficacy issue, we are assuming that there is going to be long-term efficacy, efficacy beyond 24 weeks, and we don't have data here that demonstrates that.

CHAIRPERSON PACKER: Let me ask a question, Lem, just if I could. Are you suggesting that in a disease like this -- I understand it is a longstanding disease that goes on for years, et cetera -- that you would like to see efficacy data beyond 24

weeks?

DR. MOYE : If the drug is to be used beyond 24 weeks, yes.

CHAIRPERSON PACKER: Okay. Maybe I can ask the question in a different way. Every disease this committee sees is a long disease that lasts for years, and we never ask for efficacy beyond 24 weeks in any disease that we see. Why should this disease be different.

DR. MOYE: I guess because I disagree with the precedent, I disagree -- excuse me, I disagree with the tradition. I mean I don't know why we don't ask for long-term data for that.

CHAIRPERSON PACKER: Well, the average duration of therapy for an anti-hypertensive drug trial is about 4 weeks. For angina it is about two to four -- well, it is a little longer. Okay.

DR. TEMPLE: That doesn't have to be. You can't do a placebo-controlled trial of hypertension of any duration anymore for ethical reasons. But that actually doesn't stop YOU from evaluating long-term efficacy. You can do a randomized withdrawal trial

after any period you want. Typically, however, even in doing that, we only do it after six months. And to my best knowledge, we have never found a drug whose pharmacologic effect disappears say after six months. That doesn't mean we couldn't, but you don't really expect that.

DR. LIPICKY: But we don't demand that.

DR. TEMPLE: We actually half demand it and probably could be more precise. We ask for evidence of long-term effect in hypertension, but we accept active control trials, which we know are not very informative.

DR. LIPICKY: Right. But they are not of lifetime duration.

DR. TEMPLE: Oh, no. What Milt says is right. You never go for the entire duration of therapy.

DR. LIPICKY: Right.

DR. TEMPLE: How could you ever?

DR. LIPICKY: And the studies we ask for are are sort of is there tolerance or does the effect go away or is there still the drug effect, not is it

still really effective in that sense.

DR. TEMPLE: For what it is worth, there are a few situations, just to recount a couple, in which we have thought longer term information is important. For example, in weight loss drugs where there is a history of effects waning, we have asked for six or sometimes even 12-month data. But again, I have to say not longer than that.

DR. MOYE: Well, is it inadmissible to suggest that after a program of exercise strengthening and reduction of risk factors that there might be reduction of efficacy from the drug? I mean that is just a possibility for a mechanism by which you might have reduced efficacy.

DR. TEMPLE: You mean you permanently make claudication go away? Wow.

DR. MOYE: No, reduced efficacy of the drug.

DR. HIRSCH: Look, there are all kinds of possible permutations of how people might change their walking. They might then develop arthritis and they might have a better arthritis drug. I mean, it is

impossible to think of all the combinations. Let's be practical .

DR. MOYE : Right. But therefore I do think that we as scientists are at our worst when we reason in the absence of data, and we have no data beyond six months suggesting that this drug will be efficacious .

DR. TEMPLE: But, Lem, how far does this go? If you had data that went to a year, then you could say exactly the same thing. And at two years, you could still say the same thing.

DR. MOYE: You are absolutely right.

DR. TEMPLE: And at five years. So where is the right place to draw it. I would say that without. having necessarily thought it through, which would have been better maybe, there is sort of an assumption that when you are dealing with primarily pharmacologic effects, not sort of event things, that you don't expect the pharmacologic effect just to disappear because there is not a lot of history where that has happened. If there were many examples of it or a few even, we probably would change our view.

DR. THADANI: Perhaps a more generic question could be that we know that the drug improved exercise performance. There is no question to that. Now if you give it to the general population with PAD and give them the drug and don't exercise on the treadmill every four weeks, would they show improvement? Are you going to write that in order for the claudication distance to improve, the patient should take the drug and exercise on the treadmill? I am raising just the issue of -- I realize -- because we know that if you just exercise under supervision, and your first slide showed that exercise is as good as anything provided it is done under supervision and not just telling the patient to do it, and I think claudication distance in some studies might have doubled. So say if the drug is on the market, you should tell the person that at least every four weeks, as in the protocol, you should go on the treadmill?

DR. HIATT: I think I can answer that pretty definitively. We have done a lot of exercise training trials and the threshold for benefit is six weeks, three times a week for an hour, for a full

hour. So one treadmill test every four weeks is so far below a training threshold that it is not meaningful.

DR. THADANI: But suppose you did not do any treadmills in-between? Angina patients are the same, so don't take me wrong. Ray remembers **the** nitropatch study, the one on health improvement. Say **if you** took a patient at point zero and give them **the** drug anti don't put them on the treadmill, would you **show** similar benefit?

DR. HIATT: I will try. We are speculating.

DR. THADANI: Say at 24 weeks. You don't **do** any exercise in-between on the treadmill. You give **your** drug and the placebos --

DR. HIATT: Spontaneous sort of activity here?

DR. THADANI: Yes. Just let them do what **they are** doing. Would you show a benefit like this? I am just asking a question.

DR. HIATT: What it takes to make a training response in this disease population **is a**

continual pushing into above-claudication level exercise in a very formal, rigorous fashion. And casual activity or pushing people to do this repeatedly does not produce any clinical benefit. You really have to put them on a device that is moving and get them to do that for period of time up to an hour three times a week. So I think that the sort of casual benefit that you get rrom increased activity or from repeated treadmill testing is way below a training program.

DR. THADANI: Now you are seeing placebo effect to some extent. Placebo with training.

DR. HIATT: Placebo is not a training response. I think it is a familiarization with gait character.

DR. THADANI: Udho, your concern would be understandable if these were open label studies. These are placebo controlled trials.

, DR. THADANI: No, I realize that. I am just saying because the general population may not go on the treadmill. Suppose you were to do a study in which the patient is just given the drug and 24 weeks

later put him on a treadmill, would you see the same effect. That is the issue I was raising.

CHAIRPERSON PACKER: I see. Bob?

DR. TEMPLE: I am not certainly asserting that I think it is necessary because six months seems pretty impressive to me. But if one wanted to pursue this and there were a cohort of patients still on therapy who appeared to have responded, one could do a randomized withdrawal study and gain evidence of persistent effect out to whatever duration they are currently on. We could certainly talk with the company about that. I don't know if there is such a cohort anymore. Well, there must be because we are still seeing new data, so there is.

CHAIRPERSON PACKER: I guess what we need to do for the record is to just get a sense on question 5 of the committee. JoAnn has said that she feels comfortable that there are more trials that show superiority than there are trials that don't, with the ratio being either 5 or 6 to 2 to 3, depending on how one counts. And Lem says he feels uncomfortable for it, primarily because of the issue of only 6 months of

efficacy. So I think what we need to do is just get a sense of the committee. How many of you would vote the way that JoAnn has voted on question 5? Just raise your hands. I guess I don't have everyone's attention, so what we need to do is actually go right down. I didn't want to do this. JoAnn has put forward her sense that the trials do show convincing evidence of superiority of cilostazol over placebo for the claimed indication. Just say if you agree or disagree. Rob?

DR. TEMPLE: Agree.

DR. CALIFF: Agree.

DR. KONSTAM: Agree.

DR. DIMARCO: Agree.

DR. GRINES: Agree.

DR. GRABOYS: Agree.

DR. THADANI: Agree.

DR. HIRSCH: Agree.

DR. MOYE: Disagree.

DR. PINA: Agree.

CHAIRPERSON PACKER: I am sorry, was that unanimous?

DR. MOYE: No, disagree.

CHAIRPERSON PACKER: I agree. Is that unanimous?

DR. MOYE: No.

CHAIRPERSON PACKER: Lem disagrees. Okay, fine. So that vote is 9 to 1. Question number 6, which if any of the trials showed that cilostazol was superior to Trental -- I always have trouble with that -- for the claimed indication? It is exactly analogous to question number 5 except that it now asks for superiority versus an already approved drug for the same indication. Can you review the data for us and reach a conclusion?

DR. LINDENFELD: There is one study that shows a definite benefit of cilostazol over Trental and one that doesn't show any benefit at all. So although I think it is probably better, I think I would be unwilling to say it definitely is better.

CHAIRPERSON PACKER: So your vote is that it is a problem and you think the data are inconclusive?

DR. LINDENFELD: Correct.

CHAIRPERSON PACKER: Okay. How many would disagree with the conclusion that the data are inconclusive? Okay. The committee voted 10 to zero that the data are inconclusive. Number 7, what was demonstrated with respect to the effect of cilostazol on quality of life? JoAnn?

DR. LINDENFELD: I think it shows a benefit on quality of life. We have heard a lot about that and I have been educated today to say that I think this shows that at least physical performance as a measure of quality of life is improved.

CHAIRPERSON PACKER: Okay. Udho?

DR. THADANI: I think if you -- the FDA analysis said that none of the parameters were affected in a positive way. And in quality of life, I think one has to take -- and we argued on that before -- if people drop out with sudden side effects and the event rate is higher, then those should be taken into account. So I am uncomfortable to accept that it showed a definite benefit.

CHAIRPERSON PACKER: Okay. Let's vote on it since there is a disagreement. The question is do

you believe that there is demonstration of a favorable effect of cilostazol on quality of life. Obviously this is being asked because if you agree, it would be incorporated into the labeling and if you disagreed, it wouldn't be. And we will -- I guess -- why don't we start at the other end, Ileana. Alan, if you have any comments, that would be terrific. Alan can't vote, right? The one thing you can't do today is vote.

DR. HIRSCH: But I can comment strongly, right?

CHAIRPERSON PACKER: What was that?

DR. HIRSCH: But I can comment strongly?

CHAIRPERSON PACKER: If you are going to comment strongly, you could probably do that now.

DR. HIRSCH: There is no data set in PAD that is more consistently positive showing a quality of life benefit.

CHAIRPERSON PACKER: Okay. Ileana?

DR. PINA: I would have to agree that the trend is there for quality of life in the functional domain of activity. However, that doesn't embrace the

entire umbrella of quality of life as we have been discussing. But perhaps for this population that may be quite an adequate assessment.

CHAIRPERSON PACKER: So your vote on this is that you do not -- 1 guess you would vote no.

DR. PINA: I am not 100 percent convinced, no.

CHAIRPERSON PACKER: Okay. I mean I understand that one would like to grade their votes, but it really does have to be a yes or a no. So the vote -- 1 guess Ileana, you are voting no?

DR. PINA: No.

CHAIRPERSON PACKER: No? Okay?

DR. PINA: Correct. No.

CHAIRPERSON PACKER: Lem?

DR. MOYE: I would vote no because of these nagging concerns we have for how you handle correctly the patients who had incomplete follow-up in the quality of life assessment. So I would vote no.

CHAIRPERSON PACKER: Udho?

DR. THADANI: No.

CHAIRPERSON PACKER: Tom?

DR. GRABOYS: Yes.

CHAIRPERSON PACKER: Cindy?

DR. GRINES: I think yes with regard to certain components of the quality of life.

CHAIRPERSON PACKER: John?

DR. DIMARCO: I will agree with that. I think it is positive for the physical function scores.

CHAIRPERSON PACKER: Okay. I would vote no. JoAnn? You voted yes, right?

DR. LINDENFELD: Right.

CHAIRPERSON PACKER: Marv?

DR. KONSTAM: I am going to vote yes. And I just have to say I am going I think under a slightly different construct than maybe some of the other panelists are. I view the results of the treadmill exercise time as indicative of improvement of one aspect of health related quality of life. And those were the principle endpoints of most of the trials. And so the answer is, yes, an aspect of health-related quality of life is improved by that measurement. And I would further that by saying that those findings are, to my view, and I think this is what Dr. Ware was

saying, strongly supported by the data in the SF-36, in the physical component of the SF-36. So all the data put together, I think, strongly indicate an improvement in the physical component of health-related quality of life that was expected to be influenced by this drug.

CHAIRPERSON PACKER: Rob?

DR. TEMPLE: I vote yes with a proviso that there should be an analysis where dropouts are considered in a nonparametric analysis of worst case. And if there was still a strong trend, it wouldn't have to be less than .05. I would keep it that way. But with the data we have seen, I vote yes.

CHAIRPERSON PACKER: Let me ask a question. Does that mean that if such an analysis were performed and it *basically* -- it is hard to quantify it because conventionally one would quantify it as being statistically significant. But if the effect were to be substantially reduced, would YOU vote no?

DR. TEMPLE: Substantially reduced is a relative thing. I would say if the P value was

somewhere less than .10, I would still be happy. If it was greater than that, I would say I am uncertain enough and I would like to see more data. Because I think that is an exaggerated worst case kind of scenario. But the key issue here I guess is really would the label be able to say we used Dr. Ware's analysis and the patients feel great when they take this.

DR. LIPICKY: I am sorry, the question wasn't in there for labeling actually. At least that wasn't my purpose.

DR. TEMPLE: Okay.

DR. LIPICKY: It was to get a feeling for whether the" committee would accept quality of life, Dr. Ware's quality of life, as an endpoint without exercise tolerance.

CHAIRPERSON PACKER: No, that is not -- that is a later question.

DR. LIPICKY: Because if you would --

CHAIRPERSON PACKER: That is not the question.

DR. LIPICKY: Well, Milton -- you are

answering question 7, right?

CHAIRPERSON PACKER: Right.

DR. LIPICKY: And you are being asked what did it show for quality of life.

CHAIRPERSON PACKER: Right.

DR. LIPICKY: And if you were overwhelmed by the quality of life data, then somewhere along the line you would get asked the question, and maybe it is in there already, whether you would have done without the exercise tolerance data.

DR. TEMPLE : But that is a completely different question. It is an interesting question, but it is a totally different question.

DR. LIPICKY: I understand. But that is what the question -- 1 am saying that is what the purpose of the question was. So as you are going off on where you are going, I don't care where you are going because that wasn't the purpose of the question.

CHAIRPERSON PACKER: The purpose of the question as I understand it, Ray, had two components. One is do you believe that the measures that were -- the instruments used are reflections of quality of

life, and second whether the drug showed an effect on those measures.

DR. LIPICKY: Correct.

CHAIRPERSON PACKER: They are both incorporated into this question.

DR. LIPICKY: That is correct.

CHAIRPERSON PACKER: And I think what -- 1 get a very strong sense from the committee across the board that they believe that this instrument is reasonable, but I get a very split vote on the committee as to whether the drug showed an effect on this instrument.

DR. LIPICKY: Right. That is exactly the feeling I got and that gives me the answer I need.

CHAIRPERSON PACKER: Right. And in fact everyone who was hesitant was actually almost -- cited the identical reason for hesitancy.

DR. LIPICKY: Yes.

DR. TEMPLE: Milton?

CHAIRPERSON PACKER: Yes.

DR. TEMPLE: I need to ask Rob. In the analysis you are talking about that takes into account

the people who leave, were you referring to the pooled analysis or the individual analyses of studies that you thought ought to have a persistent trend?

DR. CALIFF: The pooled analysis.

DR. TEMPLE: Okay.

CHAIRPERSON PACKER: I guess I would add to that, Bob, that if you are going to do the pooled analysis, I would like to actually -- and I would actually like to see that worst rank analysis as well for assigning worst rank to the people who dropped out because of adverse reactions. I would be a little bit more worried if in the pooled analysis the effect was no longer statistically significant at a nominal .05 level.

DR. TEMPLE: For the pooled analysis.

CHAIRPERSON PACKER: From the pooled analysis.

DR. TEMPLE: Yes. There is no particular way that can happen given the results to date, but it is worth looking at. Can I just ask one question? This is because you believe that -- the people who are not persuaded believe that the quality of life

assessment isn't particularly about whether there is a benefit in claudication terms, but because you believe that the overall quality of life assessment ought to tell something about the totality of your quality of life. Okay. I want to express reservations about that point of view.

CHAIRPERSON PACKER: It is on the record. Number 8, how does the effect of cilostazol vary with regimen? Are the regimens less than 50 mg bid ineffective? Is the 50 mg bid regimen effective? Are regimens greater than 100 mg bid known to be toxic or to be no more effective than 100 mg bid? Actually, JoAnn, I would encourage you to answer this in the most straightforward way possible in terms of describing what you think we know about dose response.

DR. LINDENFELD: We don't know much about regimens less than 50 mg. I believe from this data that certainly 100 mg bid is effective, and I think that makes me also add to the data on 50 mg bid, which I believe is also effective. I don't know that we know that 150 mg bid is more effective or more toxic, but we do know that there are more adverse reactions.

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

trial that shows an effect of the low dose and sometimes the other trials show a trend which is not statistically significant. In the past, the agency has always accepted that kind of data with the low dose as evidence that that could reasonably be a starting dose of the drug because it seems as if it beats placebo at least in one trial. It wouldn't be enough to base the whole indication for it, but it has been enough to at least expand the dosing range.

DR. LIPICKY: Well, that is a very complicated question you are asking, and we will not take credit for the dose ranging trials that were planned here. It would be nicer to have had more than two doses in one trial, which is what we usually would recommend. But indeed if you want me to influence your thinking, each dose studied here beat placebo. So every dose was effective. You basically don't have a very good idea for how the magnitude varies as a function of dose and you really would need to have more doses in the same trial, which would give a better idea. If for some reason or another there was a single low dose study that looked like it beat

placebo, and it was for a drug that was titratable, and in this case this should be a titratable drug because there is an endpoint. Can you walk far enough? No. Well, I will up the dose. Now can you walk far enough? No. Well, I will up the dose. In other things, you don't have titratable endpoints. And it does look as though whatever it is the adverse effects are are dose related. So it would be nicer to give people the walking distance they wanted with the least probability of side effects. So from a thinking process point of view, every dose that isn't placebo would be a reasonable dose to market. And it could be a titrated drug. So that is kind of the thinking process that would go behind it, but it would really be much nicer to see more than two doses versus placebo in a single trial because you get a better feeling and it would also be nicer to see the interval between doses larger. Because then you are more likely to be able to tell whether one dose is different from another.

CHAIRPERSON PACKER: Okay. JoAnn? Bob?

DR. CALIFF: Just a brief comment. I

certainly agree with all of that. There are a couple of things. Just about every time more than one dose was studied, the larger dose was better, often significantly so, which I must say you don't see every day. So there is a fairly strong sense that you have a dose response, even though as Ray says it would have been better if there were three or four doses in each one. But the crucial thing from my point of view would be that we are somewhat worried about potential side effects and that there are fairly conspicuous and dose-related side effects. So you have a better case here than you have for some other situations, like say ACE inhibitors, where you are not really seeing anything dose related, so you say what the heck, give a good dose. Here there is a pretty good case for using a lower dose to start.

CHAIRPERSON PACKER: Okay. Let me just make sure JoAnn has summarized her sense about the doses and she believes the doses of 50 to 150 are effective, but that doses greater than 150 are associated with more side effects. I am sorry, doses greater than 100 have more side effects. Does anyone

disagree with that? Okay. That is what question 8 asks. Question number 9, have cilostazol and its metabolizes been adequately evaluated with regard to enzyme interactions or do you need more data before cilostazol could be approved? And the summary of what is known is presented in the three paragraphs before the question.

DR. LINDENFELD: I think that I would -- before approving this drug, I would like to see levels of either synthestatin or lovestatin with the drug, because I think those are going to be increasingly commonly used and I am not convinced that there is not a problem there. I think there is other data we would like to see, particularly how much enzyme inhibition it has, but I think I am satisfied for the moment with that exception in this patient group.

CHAIRPERSON PACKER: Lovestatin and synthestatin.

DR. LINDENFELD: Synthestatin.

DR. TEMPLE: Milton, can I ask the company if they happen to have any blood sitting around from people who were on those drugs during the course of

trials? It is not that hard to detect an increase in the blood levels because it is very large.

DR. BRAMER: Yes, I believe we do. And prior to this meeting, we were looking into that exact situation of both those statins and any other medications that may be a weak substrate.

DR. LIPICKY: It will only take two days?

DR. BRAMER: They will only give me one.

DR. THADANI: I think given the interactions which we have come across recently in relation to statins, perhaps we ought to look at the antifungal agents just to be sure. Because wouldn't you like to see that it doesn't effect --

DR. TEMPLE : Well, again, one is inhibiting a different drug and now it is being inhibiting by another drug.

DR. THADANI: Sure. I realize that. But for safety reasons.

DR. TEMPLE: Well, Dr. Flockhart explained why they thought they had pinned that down reasonably well. You can agree or disagree.

DR. THADANI: Obviously you had concerns

earlier on because there was diltiazem at 50 percent as opposed to --

DR. TEMPLE: Yes. The question gives what are not mutually exclusive answers. So it is a somewhat defective question. You could conclude that it is not adequately worked up.

DR. THADANI: Sure.

DR. TEMPLE: I certainly would. But that doesn't necessarily imply that you think it has to be done before it is approved. So those are two separate questions.

DR. THADANI: No, no. We need some more data.

DR. TEMPLE: All right.

DR. KONSTAM: Milton?

CHAIRPERSON PACKER: Yes.

DR. KONSTAM: I mean it seems -- I am not sure that we are comfortable that there is sufficient evidence that there is no clinically relevant inhibition of 3A4, right? I would say that is -- would everybody not agree with that?

DR. LINDENFELD: I think we know enough to

say that with the warnings that have been suggested here that 3A4 substrates, one may need to watch the doses. Once we have levels of a couple of these things.

CHAIRPERSON PACKER: Bob, given recent experience with various drugs and the potential for drug interactions, is the agency beginning to think about formalizing what criteria it believes sponsors should follow or must meet? Because this comes up a lot. And in the past, we have tended to simply say that, gee, if you can describe it, that is nice. I think we have been less compulsive about it. Is there a movement that is in place to try to define exactly what needs to be known? Not only in terms of what enzymes may be inhibited or what drugs may be metabolized by enzymes or what the clinically relevant interactions might be?

DR. TEMPLE: Well, those are two very separate questions. We have a guidance already out on what in-vitro tests we expect. In-vitro tests can, at least sometimes, serve as a screen that says you don't have to do anymore. There is no inhibition at good

high doses and that is it. And that is out. We are well along in the in-vivo guidance, which says if YOU can't rule out the need to do things with your in-vitro tests, here is what you need to do. And generally it says use the most sensitive system to pick out the potential. That is, if you are worried about being inhibited by something, test with ketoconozol. If you are worried about inhibiting something, test with synthestatin. We don't want you to test cisipride, because it is too dangerous. Something like that. So that is true.

Now the other question you have raised I don't think has been formally addressed. And that is it how bad is it if a drug blocks a major metabolizing enzyme? How much trouble is it? Well, in the case of mibefridil, that was probably its main trouble. It was a drug that looked very hard to use in the population that you had to use it in. And you could argue that the removal of trifenidine from the market was not really different from that. That was a drug that got in trouble only if you used it with the wrong drugs. YOU could say how to use it properly, but we

knew that it wasn't being used properly. So those are two cases where you could say how to use the drug completely okay, or at least we thought so, and yet the reality was that there would be some bleed-through and it would not be used okay. So we are thinking about that. And part of the thinking is what is the benefit that comes along with this risk.

That said, there is very little evidence that this is an inhibitor of the magnitude of the kinds of drugs we have been worried about so far, but that doesn't mean there is no potential.

CHAIRPERSON PACKER: Abe?

DR. KARKOWSKI: There was one additional concern we had based on the trifenidine experience, which is what is the bioavailability of this drug. This drug will be given potentially on an empty stomach and people might take it with grapefruit juice and what are the consequences of this drug. If this drug had a high bioavailability, one wouldn't care. We don't know the bioavailability. How does that impact on your decisions for post-marketing or whatever studies you would like to see?

DR. TEMPLE : I think there were figures given for its bioavailability, aren't there?

DR. THADANI: No absolute.

DR. KARKOWSKI: Those are estimates based on assumptions that we did not accept and I think the company doesn't feel strongly about them either.

DR. TEMPLE: Okay.

DR. THADANI: There is no IV data.

DR. LIPICKY: There is nothing relative to solution? Are you talking about absolute bio or what are you talking about?

DR. KARKOWSKI: IV to PO studies.

DR. LIPICKY: You are talking -- absolute bio is unknown. That is what you are talking about.

DR. KARKOWSKI: Correct.

DR. LIPICKY: Not that there were not bioavailability studies.

DR. KARKOWSKI: There was a number given in the briefing booklet which was an estimate.

DR. LIPICKY: Yes, fine.

DR. RODIN: Dr. Rodin, FDA. I saw some small sample preclinical data, oral suspension versus

IV, and they looked like the mean. I didn't have a take on the variance, but the mean was quite a low bioavailability there. Something like 16 percent.

CHAIRPERSON PACKER: Does the sponsor have any comments on this issue?

DR. BRAMER: Yes, I do. Several things. We did a C-14 study with an alcoholic solution, and basically you see 74 percent of the radioactivity excreted in the urine. That means 74 percent of the drug was in the body with an alcoholic prep. If yOU look at the performance of suspension versus the alcoholic solution, they were fairly comparable, 80 percent in suspension. And then if you look at the tablet performance versus the suspension, again you have with tablets versus suspension, it is 100 percent. So, therefore, even though we don't have the absolute bioavailability or did not do a particular study, I do believe that this drug is not on the low side of its availability.

DR. TEMPLE: You can't say that. There is substantial metabolism. There could be gut metabolism. You have to know what the absorption of the active

stuff is. What you know is that it gets in, but it could have been mostly in the form of a not very active metabolize. I mean, you don't really know until you look. Right? And this is a candidate for having variable bioavailability because it is a 3A4 drug.

DR. BRAMER: No, I agree that there are limitations to the argument I am making, but I do want people to realize that we have looked at different formulations, tablet, suspension, and solution, andwe haven't really seen marked increases in absolute bioavailability when we go from a tablet to a solution. In solution, we expect to have greater availability.

DR. TEMPLE : But they also haven't seen large differences anyway with variable renal function and variable hepatic function.

DR. LIPICKY: But Abe is worried about double-strength grapefruit juice.

DR. BRAMER: The concentrated stuff.

DR. LIPICKY: Yes.

DR. BRAMER: I think your question about 3A4 inhibition at the tip of the villus with

grapefruit juice is also answered by the Erythromycin study .

DR. TEMPLE : Erythromycin, absolutely. Right. The Erythromycin should give you the approximate answer for grapefruit juice.

DR. LIPICKY: So now what is your worry, Abe?

DR. BRAMER : And there upon inhibition, you did see a doubling, a two-fold increase.

DR. THADANI: Yes. It could go to -- with other drugs, it could go much higher.

DR. TEMPLE: Doubling isn't 20-fold, but it is doubling.

DR. THADANI: You have the IV drug, right? You have the intravenous drug?

DR. BRAMER: I am sorry?

DR. THADANI: You have the drug in IV form?

DR. BRAMER: No, we do not.

DR. THADANI: You don't have it? Okay.

DR. BRAMER: We made attempts to make an IV formulation. The problem with this drug is its

volubility. Japan and the United States took treat efforts to try to make an IV formulation. And the best we could come up with was an IV suspension, which we felt wasn't safe to give to humans.

DR. TEMPLE: I mean, the current recommendation is you are suggesting that people have the dose in various settings, and that is not unreasonable. I think a deficiency still is the lack of information so far about the active metabolize. Because halving the dose might not make any sense. It is not clear that those things are terribly worrisome.

DR. BRAMER: We do have metabolize data. I would like to say that when we look at Erythromycin as an example, we do see impact of 13015 and 13213. And therefore, we do have those pathways well characterized. And those are the only circulating analytes in plasma. So I do want to remind you that we do understand the metabolism of this drug.

DR. TEMPLE: And the active metabolize goes down?

DR. BRAMER: And the active metabolize definitely goes down --

DR. TEMPLE: And the parent goes up. So it would be conservative, I suppose you would argue, to cut the dose down?

DR. BRAMER: Correct.

CHAIRPERSON PACKER: I think the committee -- I will look around -- would encourage the discussions between the sponsor and the division as to what additional information might be required on interactions to satisfy a regulatory need to provide adequate labeling information that would be incorporated into labeling. All right. We will move on to question 10. There has been a slight modification of question 10. Question 10 is really positioned to ask if there are deficiencies in the data base which the committee might consider to be fatal to' approval. With Ray's permission, I will eliminate question 10A, because I don't think any of us know the answer to it. And what I want to do is substitute for 10A the following question. The question is, is the lack of data -- is the present data base on the use of this drug concomitantly with anti-platelet drugs so insufficient that you would be

reluctant to recommend approval? The second is, do you need a better estimate of the effective mortality before you recommend approval? Let me rephrase the first one. Do you need better data on concomitant therapy of this drug and anti-platelet drugs to recommend approval? And the second question is do you need a better estimate of the mortality effect to recommend approval? so question 10A is do you need more data on the interaction with anti-platelet drugs to recommend approval? We will take that question first. And before even -- JoAnn, I will ask you to begin, but these two questions are so important that after you vote on this, I do want to open it up for discussion. Go ahead. First is do you need additional data on the interactions with anti-platelet drugs to recommend approval?

DR. LINDENFELD: I think that there is probably enough data with aspirin to recommend approval and to get some post-marketing data with aspirin. But I think in order to -- and I think I could approve it with the caveat that we do not know what the interactions are with clopidogrel or

ticlopodine. so I think the data is adequate, yes, for aspirin, and I would be willing to approve it. But somewhere it would have to say that we have no idea what the benefits are with ticlopodine or clopidogrel or the adverse events. We would have to make that quite clear.

CHAIRPERSON PACKER: Okay. JoAnn, before taking this around, if you recommended that -- I think what you are saying is that you do not think that the presentation limitation on data base would be an impediment for you in terms of looking favorable on approval. But if you were to actually say that you didn't know if clopidogrel or other anti-platelet drugs were widespread use, that would give or could give any physician that read the package insert some pause. My sense is that that is your intent.

DR. LINDENFELD: That is right. Except no one reads them.

CHAIRPERSON PACKER: Okay. Udho, we are going to go down the line on this. So, Ileana, the question is are you -- do you think the present -- do you need more data on the interaction with anti-

platelet drugs before recommending approval?

DR. PINA: Let me just say that I don't think most physicians read package inserts. So I would have to rely on the marketing people to make that point very clear when the drug is being detailed should it be approved. so the answer is, no, I would not need more data for approval. However, I think that the warning has got to be there. Not because of interactions but because of bleeding, particularly with clopidogrel. Because I think the use is going to skyrocket in the next few months in most patients with vascular disease, even whether indicated or not. I think we are going to see it.

CHAIRPERSON PACKER: Okay. Ileana, just for the record, it really is a labeling issue and not so much whether physicians read labels or not. But if it is not in the labeling, then those who are involved in marketing won't be compelled to convey that information.

DR. PINA: I think it should be in the labeling.

CHAIRPERSON PACKER: Okay. Lem?

DR. MOYE: Well, I think that it is one thing to say that we don't have the information. But then the question becomes what do you do without the information. And I am loathe to recommending approval in the absence of information. Information we must have before we make the recommendations. I am uncomfortable with voting for approval for a drug hoping that I am right. I want to be able to vote for approval knowing I am right, and I can't know it unless I have seen the authoritative data which demonstrates after rigorous scrutiny what the possible relationship is between clopidogrel and the drug at issue here. So I say in the absence of the information, I vote that it is impossible to vote for approval for this drug. And that before we can vote approval -- not vote for approval but vote approval -- we must have the information from the sponsor about the potential interaction here.

CHAIRPERSON PACKER: Alan, you can comment although you can't vote.

DR. HIRSCH: I am comfortable with that. I think that we do need more information regarding the

clopidogrel/cilostazol interrelationship, probably both in-vitro as well as in-vivo, although I concede the current data with aspirin is adequate for me to let labeling do its magic or not magic trick.

CHAIRPERSON PACKER: So for you it would not --

DR. HIRSCH: It doesn't inhibit me from moving to labeling and bringing it to market.

CHAIRPERSON PACKER: Okay. Udho?

DR. THADANI: When we discussed the aspirin use at the last FDA meeting before you were on board, the weakest link was in peripheral vascular disease. But when I see the patients, all of my patients have peripheral vascular disease and coronary artery disease. So they are on aspirin. So given the two studies, one is comfortable. But the question will be patients with peripheral vascular disease are going to be put on clopidogrel because it has just been approved. You are talking about morbidity and mortality data. Somebody might end up on three anti-platelet agents. I would really like to see interactions in terms of safety data before I feel

comfortable to say -- or there should be a black box in the warning labeling that there is no data. But I think I would like to see more data before going ahead and feeling secure that it should be used.

CHAIRPERSON PACKER: Okay. So your vote, if I am reading it --

DR. THADANI: For clopidogrel especially. I would like to see more data.

CHAIRPERSON PACKER: Okay. So yOU would like to see more data before recommending approval?

DR. THADANI: On the safety issues.

CHAIRPERSON PACKER: I understand. I think my understanding, Lem, is that your concerns were safety and efficacy? Because Udho I think is primarily saying safety.

DR. MOYE: My opinion is for both counts, safety and efficacy.

CHAIRPERSON PACKER: Okay. So far, just to summarize, Ileana would not consider it a block to approval, but would like to have it in labeling. Lem says he would like to see data on efficacy and safety before approval. Udho says he would like to see data

on safety before approval. **Tom?**

DR. GRABOYS: I don't think we can depend on the labeling and I think we need to have full information before we let this drug loose.

CHAIRPERSON PACKER: So this is safety and efficacy?

DR. GRABOYS: Yes.

CHAIRPERSON PACKER: I am sorry?

DR. GRABOYS: Safety.

CHAIRPERSON PACKER: Safety. Okay.

DR. TEMPLE: Milton, can I just be sure? There has been a hint that maybe the aspirin data would be informative about platelet interactions in general. What are people saying? They need clopidogrel **data or better aspirin data or better analysis of the aspirin data? We need to be clear on that, I think, as we go along here.**

DR. THADANI: All of the above.

DR. TEMPLE : And also what would -- is this mostly about bleeding episodes? Is there anything else? Is it just bleeding episodes?

DR. THADANI: **In addition to that, I think**

there is a hint of excessive mortality here, 1.3. Whether we buy it or not. That is a different issue.

CHAIRPERSON PACKER: A separate issue.

DR. TEMPLE: Wait a minute. No, I mean the question I am asking about the platelet problem. The platelet problem. You can't get into the mortality problem. That is about bleeding. I just want to be sure we understand what we are being told. It is about bleeding. Aspirin would or would not substitute for specific data on clopidogrel. I think those need to be addressed as we go down the row.

CHAIRPERSON PACKER: Bob, I think the -- what I would like to do is have the committee vote and then get a sense, no matter how they voted, of the specific answers to your question. Because *even* those who would vote one way or another would probably want it to be incorporated into labeling regardless, and then the question is what data do you need. So let's go through the vote. So the question is do you need more data before approval? If yes, is it efficacy and safety or just safety? Cindy?

DR. GRINES: I am not at all concerned

about bleeding. I think that they have done studies with aspirin. I don't see that there has been any bleeding in their serious adverse events. And we routinely give ticlod and aspirin and aspirin and clopidogrel totally off label. So I am not at all concerned about that. What I do think we need more studies on is a combination of this drug with other vasodilators, which I see as a much bigger potential problem.

CHAIRPERSON PACKER: And you would be -- you think that that is necessary before approval?

DR. GRINES: Or a requirement to perform a study after approval for safety issues.

CHAIRPERSON PACKER: Okay. If your feeling is the second, we will address that in question 12. But I think what you are saying is that your answer to this is that you do not need additional data prior to approval on the anti-platelet interaction?

DR. GRINES: Correct.

CHAIRPERSON PACKER: Okay. John?

DR. DIMARCO : I think clopidogrel data

would be interesting, but I don't think it would have to be required for approval.

CHAIRPERSON PACKER: Okay. JoAnn? The question is a little bit different than the one you answered. So maybe you should vote formally.

DR. LINDENFELD: I don't think the lack of data -- 1 think the drug should be approved without additional data, but I would like to see more safety data on clopidogrel. And without that I would like to see clear labeling that we don't know the safety issues.

CHAIRPERSON PACKER: Marv?

DR. KONSTAM : I would not require more data on this subject before approval. But I would like to see a mandate for additional data following approval. Let me say I am uncomfortable about this point because I think that there is going to be widespread use of the agent on top of other anti-platelet agents, and I would raise questions on both sides. I would raise questions about the bleeding, although I am not super concerned about it. But I would like to see some effort done to answer the

question. And I would like to see evidence for efficacy, specifically on top of clopidogrel. I would like to see that done. The reason that I am permissive of approval prior to the acquisition of that data really stems from the very impressive efficacy data set without anything else out there comparable at this point in time. And so for those reasons, I am pushed not to delay approval based on these concerns. But I think the concerns are real, and I would like to see a mandate for more than just labeling, but for acquisition of additional data following approval.

CHAIRPERSON PACKER: Now, Marv -- I am sorry, Ray?

DR. LIPICKY: Well, just one other question and I will just ask Marv. I don't want to go back through everybody. What kind of efficacy are you thinking about? The efficacy of walking distance or the efficacy of saving life that clopidogrel has?

DR. KONSTAM: No, no, no. The efficacy of walking distance. I am not --

DR. LIPICKY: You are not worried about

doing away with clopidogrel's effects?

DR. KONSTAM: I am sorry?

DR. LIPICKY: You are not worried about doing away with clopidogrel's effects?

DR. KONSTAM: I am not sure what you are asking?

DR. LIPICKY: Fine.

DR. KONSTAM: The way I would design it, I would design it as this drug on top of background therapy with clopidogrel.

DR. LIPICKY: Right. But are you worried that clopidogrel has exercise tolerance effects that have never been measured and consequently it would do no good to add this drug?

DR. KONSTAM: Yes. Exactly. You said it. That is the question.

DR. LIPICKY: I see.

CHAIRPERSON PACKER: Okay, we are just going to -- before we talk to -- 1 am just going to ask Rob. Joan just needs to get the vote right. Those -- we just want to make sure we have got the record straight. Those who would withhold -- need

data before approval -- Ileana, you said you need data before approval?

DR. PINA: No.

CHAIRPERSON PACKER: No. I am sorry, those who said they needed data before approval were Lem, Udho, and Tom, is that right? Okay, good. Okay, Rob?

DR. CALIFF: **I** would hope that -- there are a certain number of patients that were on aspirin in one of the studies. And as Cindy has pointed out with regard to bleeding, we are bombarding patients **with so much more platelet inhibition that this stuff does that I** am not really particularly worried, and I would **hOpe** that just going back to that data set would **answer the safety question within a reasonable realm for the aspirin combination. I think whether the drug is looked at on top of** clopidogrel **is** really **a question for the sponsor in a competitive** way. **Because I would think an astute peripheral vascular physician would be loathe to add this to** clopidogrel **until there was some evidence that it really added something and didn't create a problem. But I don't**

think that ought to be a requirement for getting approval. I would think it would be a smart thing to do in terms of improving the competitive position.

CHAIRPERSON PACKER: Okay. My own vote, and I must say that I have waxed -- I have gone back and forth on this one. I take, I think, both Rob and Cindy's point that we have cardiologists commonly throw a lot more combinations of drugs with anti-platelet 'effects on patients without any problems than might exist in this case. But I guess I -- if there were to be a reasonable chance that in the hands of primary care physicians a combination of this drug and clopidogrel would be bad, the last thing I would like to do is to know that a year from now after there are 25 reports of hemorrhage. My sense is that it would be pretty easy to get that experiential data quickly.

DR. CALIFF: One thing I forgot to mention. I also agree with Cindy. Just from the perspective you mentioned, I am much more worried about vasodilators than I am about anti-platelet effect. And it sounds as if in all the trials that people on vasodilators were systematically excluded

from the studies. This drug is a vasodilators. There is experience with blood pressure not necessarily going up and with heart rate going up -- a lot of people with ischemic heart disease. So there are a lot of concerns that I think need to be reflected seriously by the committee.

CHAIRPERSON PACKER: I guess I do need to formally vote, and my formal vote would be that I wouldn't see it as a bar to approval, but I really would like to see the labeling made clear that there is no information on the use concomitantly with clopidogrel. I think we need to let physicians know that.

DR. FORBES: Could I just make a clarification? I have heard this comment twice. Actually, we did not exclude vasodilators and we did not exclude nitrates. We withheld nitrates the morning of exercise. In other words, if patients were having angina -- if they were to that point where they were having angina before they were coming in --

DR. THADANI: We are talking about anti-platelet agents at the moment.

DR. FORBES: Pardon me?

DR. THADANI: We are talking about clopidogrel at the moment.

DR. FORBES: Yes, but the vasodilator comment has come up twice now. And we can't tell you how many patients were on what vasodilators and how many were on them. So I just want to be real clear that we did not exclude those drugs.

DR. THADANI: Milton, if I could make one comment on the anti-platelet agent. I realize, Cindy, I do the same. We are aggressive with them. But those patients are under observation. And I have seen patient's hemoglobin dropping from 14 to 7 on oral agents. So I am not sure that we can be absolutely sure that the two anti-platelet agents are okay. This patient had no bleeding problem. We saw him on routine test and his hemoglobin was 14. This was an oral 2B3A. So I think that those are under protocol and we are watching that. And to give an open blanket statement that three anti-platelet agents can be used in all patients, I think I would be very reluctant on that.

DR. GRINES : I think there is a huge difference between an oral 2B3A, which is under investigation, compared to a drug which has as far as I can tell no bleeding complications at all.

DR. THADANI: But we don't have any data on citocloripine plus this plus aspirin. There are different mechanisms of action, so we really don't know.

DR. GRINES: Right. But we routinely -- there are hundreds of thousands of patients every year in this country just getting stunts and the routine treatment is ticline and aspirin.

DR. THADANI: For four weeks.

DR. GRINES: For four weeks, right.

CHAIRPERSON PACKER: Okay. Bob, before you comment, I think the sense that the committee has is that by a 7 to 3 vote, they would not view the lack of information as an impediment to approval, but they think such information is very important and that the labeling should make clear if the drug is approved that at the present time that information is not available.

DR. TEMPLE: Right. That is what I actually want to ask you about and to the particular comment that Ray stated. The numbers were going by fast, but it sounded like there were something like 500 or 600 patients who had gotten aspirin concomitantly with the drug. That gives you at least some assurance about intracranial hemorrhage. The only intracranial hemorrhage I am aware of is someone who got TPA. So that looks pretty clean so far. Are you saying that even if someone had a fairly substantial aspirin experience that you would still have a very strong statement about clopidogrel? And there are many other drugs coming along or already out there that affect platelets. Is this a matter of establishing for once that the combination with an anti-platelet drug is okay, or do YOU really think that as new drugs come along you have to keep doing it? And I thought what Cindy said matters a little bit. I mean, there doesn't seem to be any real effect here. How far does this go? I also note that people were excluded from NSAIDS, which I would say is more troubling than all the other exclusions since

everybody uses them so much.

DR. THADANI: Bob, on the clopidogrel data, if I remember correctly, there was no combination group. They compared to aspirin, but there was never aspirin plus clopidogrel. So we don't have safety data on a combination of aspirin plus clopidogrel. Remind me if I am wrong. But I do not -- unless my memory is --

DR. TEMPLE: No. But as somebody has said, we have three -- I don't know how many hundred million people have gotten aspirin with ticlopinine.

DR. THADANI: I realize that. But suppose a patient goes on both and then a third drug?

DR. TEMPLE: I am asking a different question. Is this a matter of principle that you need to know how the drug when added to a drug with platelet activity works, or is it particularly clopidogrel that there needs to be data on? What Milton said made me think that it was the latter, and I guess I had thought that it was the former and that people thought that aspirin data would provide the kind of reassurance -- if there were enough of it

would provide the kind of reassurance you are talking about. But maybe I am wrong in thinking that.

DR. THADANI: It is a moving target because clopidogrel is going to be used more. That is why we want the data.

DR. TEMPLE : And there will be an oral 2B3A inhibitor one of these days fairly soon too. So what -- is this a principle or do you have to sort of study each drug?

DR. THADANI: It is a principle. It should be a principle and a safety issue.

DR. TEMPLE: Say again?

DR. THADANI: It should be a principle and a safety issue. If I am going to use a drug, I want to know there is no increased bleeding in clinical practice.

DR. TEMPLE: Okay. Never mind.

DR. KONSTAM: Bob, there is the efficacy question too, though. There is a question of whether or not it is effective on top of clopidogrel.

DR. TEMPLE : Yes, that is a different question.

DR. LIPICKY: Why do you think that that would be a question? Is there any reason for that?

DR. KONSTAM: Sure.

DR. LIPICKY: What?

DR. KONSTAM: Because since we don't know the mechanism of action of this agent --

DR. LIPICKY: Well, you know it was effective on top of that aspirin.

DR. KONSTAM: But clopidogrel is a more potent anti-platelet agent than aspirin.

DR. LIPICKY: And how does --

DR. KONSTAM: And how do we know that?

DR. LIPICKY: Well because patients were on aspirin in these placebo-controlled trials.

DR. KONSTAM: 500.

DR. LIPICKY: Yes, right.

CHAIRPERSON PACKER: We have not seen -- the sponsor will obtain at some subsequent point in time a subgroup analysis of efficacy of aspirin versus non-aspirin patients. We have not seen that. Maybe we will now.

DR. KAZEMPOUR: Yes. We conducted the

aspirin and no aspirin study, and the result is that -- I can read the data for you. For the placebo arm first, the mean walking distance was 13 percent with aspirin. Without aspirin, it was 15 percent. So it was 15 percent versus 13 percent. And then looking at the 100 mg with aspirin is 39 percent and 100 mg without aspirin is 30 percent.

CHAIRPERSON PACKER: 30 percent is the last one?

DR. KAZEMPOUR: 30 percent. So with aspirin, it was more efficacious within the range. But the placebo was no difference between aspirin and no aspirin.

DR. CALIFF: I think that is helpful. The sample size for that was?

DR. KAZEMPOUR: The sample size for the 100 mg with aspirin was 178. Without aspirin, the 100 mg was 720. And the placebo with aspirin was 150 and without aspirin was 754.

DR. KONSTAM: You know maybe the peripheral vascular disease experts in this room can tell me that this is absolutely impossible. But I

would still -- since we don't know the mechanism of action of this drug, I think in my mind it is conceivable that the anti-platelet action of this drug is a major contributor to it. I think clopidogrel is a more potent anti-platelet agent than aspirin. And furthermore, although we have some background information -- we have some information about a small subset of patients that had some -- that had a check box somewhere that they were on aspirin, but that is not the same as really asking the question in a systematic way, does this agent add to clopidogrel. So I would just say that. Now if somebody wants to say there really is no reason to raise that question, I would defer.

DR. THADANI: So your aspirin data is only on 178 patients?

DR. KAZEMPOUR: The one that we have, yes. For the 100 mg, yes.

DR. THADANI: Yes, with the drug. But we were told it is about 700 or 800 patients and that is not true.

DR. KAZEMPOUR: We had study 96202. In

that one, people could take aspirin.

DR. THADANI: But in controlled studies, you only had 178 patients, is that correct?

DR. KAZEMPOUR: 96202 is also a controlled study . But here we looked at all 8 studies that we had.

DR. THADANI: Oh, the one you showed earlier. The 8 studies you showed earlier.

DR. KAZEMPOUR: The 8 studies.

CHAIRPERSON PACKER: Dr. Hiatt?

DR. HIATT: Just briefly. there is very little data on pure anti-platelet effects on treadmill performance and walking distance. There are the three trials on ticlopendine that show very modest effects. Nothing like you have seen today. I have made proposals to other sponsors to look at 2B3A receptors and all that in this particular endpoint. But right now there is no signal with aspirin and there is very marginal signal with ticlopedine. And if you want to explain the benefit this drug purely on its anti-platelet effects, I think it is a weak argument.

DR. KAZEMPOUR: I would like to clarify

one more point. I only mentioned 100 mg. The 178 that I mentioned was only 100 mg. If you add 50 mg to it, you add 125 to that, which the effect was in the same direction. I focused only on 100 mg.

CHAIRPERSON PACKER: And you should probably include the placebo taking aspirin as a comparator.

DR. KAZEMPOUR: If you include that, then it will be about 400.

CHAIRPERSON PACKER: You have to because your treatment effect is going to be placebo corrected.

DR. KAZEMPOUR: Exactly. The treadmill effects are placebo corrected and baseline corrected.

DR. LINDENFELD: I think one reason we would like to see just a little more data on clopidogrel is this question of ticlopedine and cilostazol in Japan causing gastric hemorrhage. We don't have any data, but it is mentioned a couple of times. And it is mentioned so specifically that I have a little concern about it.

CHAIRPERSON PACKER: Okay. I think we

have sent the FDA a clear signal on this. Again, the majority vote of 7 to 3 is to suggest that this is not an impediment to approval. The second component of this question is the present estimate of the mortality effect. Do you need a better estimate before recommending approval? The same concept. Is the lack of mortality data worrisome enough that you would not recommend approval? And, JoAnn, why don't we start with you and then we will open it up for discussion.

DR. LINDENFELD: I think it is worrisome enough not to recommend approval. I think that although these are not heart failure patients and that is where we have mortality data, this is a drug that increases mortality in those patients and several different types of drugs which have contractility and heart rate effects just like this drug. And I think that although the risk of these patients was low, I think as has been mentioned before, Rob mentioned it, I think this will be used in some patients with more risk factors, and I would like to be able to tell the patients that I have some idea of what the mortality effect is.

CHAIRPERSON PACKER: JoAnn, before we open this up for discussion, there used to be a time in the development of drugs for heart failure that if a sponsor came in with trials of 3 to 6 months in duration and that is all, no long-term studies, they could get approval. Now that would be very unlikely. Right now much longer term data is generally required of any new drug for the treatment of heart failure. Throughout the discussion with the FDA, the sponsor was given the impression -- I think this is true -- that the way the drugs were to be developed for the treatment of intermittent claudication resembled the way that drugs would be approved for the treatment of heart failure 10 years ago. By your answer, you are suggesting that the criteria for the approval of drugs for intermittent claudication should now resemble the kind of data base we require for drugs for heart failure. Is that correct?

DR. LINDENFELD: Not exactly. I wouldn't be adverse to that, but I think that at least where we have a drug that we know increases mortality in a certain subset of the population which may overlap

here a little bit, in that setting, yes, I think I would need to have that. When we know that this drug increases mortality several different times in several different studies. Not in the same population.

CHAIRPERSON PACKER: Okay. Actually -- yes, Ray?

DR. LIPICKY: Could I just ask -- I understand that there are a couple of drugs in this class, maybe it is three or four, that have been associated with long-term oral use and in placebo controlled trials in patients with heart failure have been associated with having an adverse clinical outcome. Do you -- those drugs in those diseases were being used at the maximum tolerated doses, were being used in association with Digitalis, were being used in association with diuretics, and were being used in association with other drugs also in the treatment of heart failure. So that what is it that makes you think that that experience is able to be translated and that now that is an expectation when this is at another dose, it is clearly, clearly, clearly, I will say, although I recognize I am exaggerating, at a dose

that is less than will increase contractile force and decrease cyclic AMP in the heart -- yes.

CHAIRPERSON PACKER: No.

DR. LIPICKY: Why do you say that?

CHAIRPERSON PACKER: Based on the rabbit data?

DR. LIPICKY: Yes.

CHAIRPERSON PACKER: So?

DR. LIPICKY: So.

CHAIRPERSON PACKER: We are not rabbits.

DR. LIPICKY: Do you know something different?

CHAIRPERSON PACKER: We are not rabbits.

DR. LIPICKY: No. I am just saying -- I said I was exaggerating. But it looked as though that was at a very low concentration. so what is it -- I just want to know why you are so sure that the other phosphodiesterase experiences in heart failure is translatable to any other patient population in any other setting with any other concomitant medications?

DR. LINDENFELD: Well, I don't think I am sure at all, but I would feel a whole lot more

comfortable here if these similar types of drugs hadn't increased mortality.

DR. LIPICKY: I understand.

DR. LINDENFELD: I am not sure it translates it, but it makes me much more --

DR. LIPICKY: But you are asking for proof that it does not.

DR. CALIFF: But wait a minute. You demand this .00125 for whether somebody can walk a little further on the treadmill. I mean how unsure do you need to be about something like whether somebody lives or dies?

DR. LIPICKY: Well, I would be willing to -- 1 would be willing to say I am willing to approve this drug even if it increases the mortality by 1.3. And therefore, that is just a number and that doesn't matter. So it isn't clear to me exactly why one would argue I must know the number before I can decide about approval. Because then that excludes approval.

CHAIRPERSON PACKER: Ray, before -- this can get very interesting. Just let me make sure. You said you would approve a drug if it increased

mortality -- if YOU knew -- knew -- it would be a big study to know -- that it increased mortality by 30 percent.

DR. LIPICKY: Right.

CHAIRPERSON PACKER: Would you approve a drug if you knew it increased mortality by 200 percent?

DR. LIPICKY: Well, that might be a little harder, but I would still make the same argument and let me make it now. And that is it is not up to you to say to doctors and patients that that is a risk that no one must ever take. It is up to the doctor and the patient to make the decision whether that is a risk that they want to take and not up to you 11 people to say I will not allow you to take a risk like that.

DR. GRABOYS : It is our responsibility, though , to have guidelines for how we are going to then convey this kind of information to the physician, and then the physician and the patient will deal with that.

DR. LIPICKY: Well, fine. That is another

issue. I am just saying I don't think it is -- I don't think I would like to see whether I could make that choice lay in your hands at this instance.

DR. CALIFF: You are doing something -- you turned me off here. Maybe it is on purpose. But consider basically what you are doing is saying we are not going to ever have this information and so we will deprive the patient and doctor of ever being able to make that choice.

DR. LIPICKY: No.

DR. CALIFF: The choice they are making is I am going to take the drug in the absence of any knowledge about whether it may harm me.

DR. LIPICKY: No. I am saying that at this point in time one could say I have a point estimate and it looks bad. I realize it is not informative and that it isn't really a decision, but that is the most adverse thing you could say. So that I don't have to have a highly honed specific point estimate. so I know it is 1.31 plus or minus .05. I can consider approving it on the basis of this. It would have to have very bad labeling and say it has an

adverse effect on mortality. That all drugs known in this class have an adverse effect on mortality and that you don't know if people who are on clopidogrel, whether they will bleed to death, et cetera, et cetera. But that none of those things preclude the consideration of approval. What you are voting on now is you don't know a number and you are saying because I don't know that number, it precludes my even considering approving it. I have to know that number with more precision.

CHAIRPERSON PACKER: Marv?

DR. KONSTAM: I would just like to chime in with Ray for a second and take it another point. Which is let's just take the milrinone signal. Let's take the signal from milrinone in Class III and IV heart failure as an item that is raising this concern. Okay, well that was a 28 percent increased mortality in a group of patients with Class III or IV heart failure with all of the concomitant medications that Ray points out. Now it turns out that that turns out to be very similar to the point estimate of the 1.3 to 1 that we see here. But as Dr. Borer points out, that

is the difference between in the case of milrinone going up I don't know what it was -- from 20 percent to 30 percent one year mortality or more than that -- as opposed to going from 2 percent to 2.6 percent. So I don't think all -- number one, I don't think all potential 28 percent increases immortality are alike. And with this background of 2 percent mortality per year in this population, it is much less concerning than if you had a background mortality of 20 or 30 percent. So that is one point.

The second point is I think we cannot look at this question in a vacuum from the efficacy question. What was the known efficacy of milrinone in heart failure relative to other available therapies? Here we are seeing a debilitating condition for which we have heard from experts in the field that there is nothing else out there for these patients. Now I think that that has to be factored in. There is going to be a risk in this decision, but this is a risk being taken in the background of I might say an efficacy, data set that is better than any that I have seen in my two years on the panel and a drug in

isolation, where there is nothing comparable to it that we know of. So I think for those reasons, I think it is not -- I mean, I get accepting of the signal that we see there and don't necessarily need to be as rigorous as I might be under the other circumstances.

CHAIRPERSON PACKER: And Marv, just to try to elucidate this. The reason for making the distinction here is not because you do not share JoAnn's concerns, because I think from everything you have said you do. It is because of the fact that you are factoring in a risk to benefit relationship which states that there are not -- maybe no other drugs or very little, and there is a benefit as opposed to milrinone where there was no benefit. I guess the analogous situation would be to take a look at examples where there have been drugs which there has been a benefit but also an increased risk like flosequinine.

DR. KONSTAM: Right. That is one point.

DR. TEMPLE: No, that is not correct. Flosequinine had no benefit after three months. That

is an important part of why we won't agree.

CHAIRPERSON PACKER: That is a correct statement.

DR. KONSTAM: So there are two points. One is the clear and unique, at this point, benefit of this drug. And two is the very, very low relatively to the Class III and IV heart failure population -- relatively much less background incidence. So that the theoretical 30 percent, if we picked it, would have a much less overall impact.

CHAIRPERSON PACKER: But let me just have you complete the thought here. I think that everything you are saying -- it goes from 2 to 2.6, what can you say. But the point estimate here is unbelievably coarse and does not preclude an increase of 100, 200, 300 percent, probably even more. Would our equations change if you went from 2 percent to 6 percent?

DR. KONSTAM: Yes, of course it would. But what Ray is asking is, I think, what is the signal that is making us raise this concern in this case with this drug in this population. And the signal that is

making us raise the concern is the milrinone and anoxinone and flosequinine data in heart failure. So I think if that is the signal that is making us raise the concern, then we really have to analyze what the differences are in this circumstance compared to that circumstance. And I think that the differences are so huge that I don't see a specific reason why we would be that concerned in the background of the strong efficacy that is here. I mean that is really the way I would frame it.

DR. THADANI: When you are saying differences are huge, if you take the heart failure population and all the similar classes of drugs, 50 percent of the patients have coronary artery disease. So the increased death is a mixture of whatever reason, but the underlying disease which killed them could be sudden death or not necessarily worsening of heart failure. So that if they have got underlying coronary artery disease and you see some signal that this might be adversely effecting mortality, in the absence of a large trial, one feels very uncomfortable that you could be harming the patient as far as that

is concerned. so I think the fact that you are saying they are Class II, III, or IV failure, the underlying pathophysiology on those patients also is coronary artery disease. And possibly they could die because you are increasing whatever the mechanism is that is there.

DR. KONSTAM: The two differences, Udho, that I am pointing out are one is the background mortality to risk, and two is the strong efficacy signal that we have.

DR. THADANI: But say you've got a 65-year-old male who could walk 400 meters and he could walk another block and you tell him I can give you a drug that you can walk one more block, but there is a chance you might drop dead say 30 percent more. Is the patient going to take it? Or am I going to even give him the drug?

DR. HIRSCH: Can I try that one? Can I try what Marv is trying to say here for one minute? Sort of the last ditch effort here before the PAD expert runs. There have been at least three international meetings where the PAD community has sat

for days on end talking about the drug approval process, and we have hashed this same question of do we learn from these past analogies, for example of PDE inhibitors and heart failure, do we learn anew in a new disease. I just want to recapitulate what Marv said.

Again, whereas there are these class effects that we are all aware of in our community, this is a different disease with a different background. We don't have the same degree of LV dysfunction, so you cannot extrapolate one set of worries. We don't want to have patients die, but you can't make that extrapolation entirely. The second point again, there are no other therapeutic options. To a certain extent, this is an orphan disease where there are not pharmacotherapies that have been effective. Looking for perfection, the life-saving, symptom-ameliorating drug is not going to happen for the first few drugs that come to market. If yOU expect that to be the gold standard, you can just I think personally not expect therapies to come down the road. '

DR. LIPICKY: Just one other small point I would like to make. And that is if you are using the congestive heart failure phosphodiesterase inhibitor stuff as the reason for your suspicion, you have pretty good point estimates of what the excess mortality might be. So there isn't any reason to speculate if that is the bias you are bringing to this about having 500 percent increases. Unless you want to impose other strange things upon something that you don't know anything about.

DR. HIRSCH: But it is imperative that we have better point estimates. I don't want anybody to take from this that we are satisfied with these wide confidence intervals. That can't be the standard for the future."

CHAIRPERSON PACKER: Bob?

DR. TEMPLE: If people are just non specifically worried, that is, because they don't have the answer, that is one thing. If people are focusing on this so-called point estimate, that is really an abomination. There is no point estimate here. This is absolute nothing. If you look at the actual cases,

very few of them are candidates even for having been drug-related. So be worried as a non-specific matter. That makes sense. But not because of that 1.3. That is absurd. But I need to make a point. If yOU look at the number of people who had sudden death, I didn't see anybody -- there might have been one person who might have had progressive heart failure. If you look at the number of people who had sudden death, you need to think about what size study could be done to answer this question, and it will not be small. I am thinking 10,000 or 20,000 or that neighborhood to get the answer to this question.

DR. KONSTAM : Well, I don't think that would be necessary. I mean I would like to see us commit ourselves philosophically at any rate to what -- the question I asked Jeff, which is, well, okay what level of increased mortality would we tolerate given the efficacy magnitude that we have here. And I don't -- and my own answer would be it would be much more than the 1.3.

DR. TEMPLE : Well, the 1.3 is what happened in the susceptible population with the bad

drug. That is our model. That was what milrinone did in that population that has bad heart failure. So why would you think it would be more than that in these people who don't? so you want to rule out a 1.3 percent risk with a population that has virtually -- well as we just saw, there are 1,000 patients here. It is not zero. It has a very low risk of these events. And I think one has to think about what the numbers are going to be. I can't do that in my head, but probably Lloyd can or Lem can. It is a pretty big study we are talking about here.

CHAIRPERSON PACKER: Yes, Bob. I do want to make 'clear that I don't think anybody on this committee is concerned about this issue because of the observed point estimate. That would be absurd.

DR. TEMPLE: I just wanted to make sure.

CHAIRPERSON PACKER: Yes. None of this discussion would be taking place had there not been the prior experience with phosphodiesterase inhibitors and heart failure period. If there had been no previous experience -- well, Rob will modify that slightly perhaps. But if there had been no previous

experience, this 1.3 estimate would have gotten no discussion today.

DR. TEMPLE: Well, it still deserves no discussion, but the general question does.

CHAIRPERSON PACKER: Right.

DR. TEMPLE: But it is worth remembering. The milrinone study, you know the numbers. What did that have, 500 people in it? 400?

CHAIRPERSON PACKER: Milrinone? 1080.

DR. TEMPLE: 1080. But there were three groups, right?

CHAIRPERSON PACKER: No, two.

DR. TEMPLE: Okay. So in a study with 1,000 people, you were able to pull this out in fairly short order.

CHAIRPERSON PACKER: But that had a high event rate.

DR. TEMPLE: But they had a very high event rate. This has a very low event rate. And as I said, I looked at the cases. Very few of them are candidate events. Most of them are noise -- tumors and post-infarction stuff. So that the place that

might be susceptible is a very, very low event rate. So one has to just cogitate with that -- with what the actual number is too.

CHAIRPERSON PACKER: Abe?

DR. KARKOWSKI: Dr. Majuk did a statistical analysis of what the study sizes are. They are in the report. To rule out the size that you see here, you need 20,000 patients. To rule out a doubling, you need about 2,000. To rule out a 50 percent increase, you need about 8,000 patients.

CHAIRPERSON PACKER: Okay, Rob?

DR. CALIFF: This kind of -- I know I am obsessive about this issue. But just to try to give you some idea of why I personally lose sleep over approving drugs for chronic diseases that have associated reasonable mortality rates. If we take the numbers that were given to us, 8 million people in the United States, 4 million symptomatic, and if this treatment is as good as it looks and it really does look good, you would hope all 4 million would get it. But if only 2 million got it and I think the best estimate in the real world of the underlying mortality

is probably about 4 percent. Whenever you do a trial where you require a treadmill test, YOU get a select population and the mortality is lower. The ages are lower. We know we have an aging population. So the people with claudication are not fairly represented by the trials. And that is not a fault of the trials. It is just inevitable. They were good trials. So in those 2 million people, we will have about 80,000 deaths this year. And even if there is a .3 relative increase, and I am not picking that number just because it came out of the studies. It is the previous relative effect of this class of drugs. That is an extra 24,000 deaths. I don't think that is a trivial issue to be concerned about. And also I don't think for me, as everybody knows, it is not specific to this class of drugs. This mortality rate is comparable to many kinds of cancer. And we certainly would accept cancer drugs that improved quality of life even if they didn't effect mortality, but we wouldn't think about not looking at mortality in cancer trials. So 2,000 to 4,000 patients given the drug or not given it, everything else has been taken

care of, I think, in this application. We know the drug works for symptoms. I don't regard that as something that is onerous for a Population of 8 million potential people in the market or whatever you want to call it.

DR. KONSTAM: But Rob, to get that level of effect that you are surmising in your calculation, we need not a study of 2,000. We need a study of 20,000.

DR. CALIFF : Okay. So let's compromise and let's say --

DR. KONSTAM: 10,000.

DR. CALIFF: No. Let's say 4,000 to 5,000, which would exclude the doubling.

DR. KONSTAM : But you don't have any reason to suspect an increase in mortality of that level based on any available data.

DR. CALIFF: I would suspect an increase in mortality in any vase-active drug.

DR. KONSTAM: At what level? A doubling?

DR. CALIFF: I don't know. We are talking about a chronic disease in which people die as a major

manifestation of the disease. We are not talking about pain relief for a few minutes and then someone having a procedure. I just think having an idea of safety with regard to the most important endpoint in the disease is important. Now the sponsor here is caught in a historical glitch, I hope, which I think we ought to deal with in a practical way.

DR. LIPICKY: I am not sure that is true. Because I am not sure I agree with the reasoning that you are laying out.

DR. CALIFF: I am sure you don't.

DR. LIPICKY: Okay. The number of deaths that would occur as a consequence of the incidence of deaths due 'co the disease doesn't influence me any at all. The relative risk to an individual is what ought to be the consideration, not the total number of bodies that come up. If you are interested in the patient, you are interested in that person, not in the nation's problems with burials. So it is the relative risk and it isn't really dependent upon the absolute incidence of death or anything on that order.

Two, from an approvability point of view,

1 don't disagree that it would be important to get a reasonable estimate of what those effects are. But from an approvability point of view, one could approve this drug because of the concerns with the most adverse relative risk that one could think of. And then it could be removed by a post-marketing study. If in fact one wanted to remove it. And this is -- the thing that puzzles me is the aspect of even under worst case scenarios, I think people might elect to do this and it might be better than the worst case scenario.

DR. CALIFF: The problem is unless it is explicitly dealt with, the patients never hear the worst case scenario.

DR. LIPICKY: Well, but that --

DR. CALIFF: And if you had a package insert or a patient insert that said you need to know that our best estimate based on prior knowledge in the absence of any reasonable evidence is that there is a 30 percent higher chance that you will die if you take this drug, and that by the way you --

DR. LIPICKY: Well, that is easy to do.

DR. CALIFF: Yes.

DR. LIPICKY: You can do that.

DR. CALIFF: But it is not very often done.

DR. LIPICKY: Well, but we can. It is not hard to do. If that is the concern. It is sort of where to put these things prioritized and what the real concerns are and the basis of the concerns.

CHAIRPERSON PACKER: Okay. Let's call for a vote. And anyone can say anything they want as they are voting. I think we have had a pretty full discussion of all the issues. The question to the committee is do you think that the -- do YOU think that you would -- well, I am trying to vote yes or no parallel to the time, but I think it is not -- do you need a better estimate of mortality effect before recommending approval. Ileana, we will begin with you again.

DR. PINA: Sharing everyone's concerns, but looking at the numbers that we have, no.

CHAIRPERSON PACKER: Okay. so no, that means that -- just so we make sure because it is a

little bit confusing.

DR. PINA: It means, no, that I don't need any more mortality data right now.

CHAIRPERSON PACKER: Okay. I would ask each one of you to simply say what it is and then say what it means just so that we are not confused. Because no frequently means no approval. Here it means no need for any additional data prior to approval.

DR. PINA: No need for any additional.

CHAIRPERSON PACKER: Okay. Good . Lem?

DR. MOYE : Yes. I think we do need a better estimate of mortality. We have absolutely -- just a paucity of data post-6 months. And with the concerns that have been raised within the 6-month data base, I just am extremely uncomfortable drawing any conclusion about long-term consequences of exposure to this therapy.

CHAIRPERSON PACKER: Udho?

DR. THADANI: My answer is yes, I would like to see more data on the safety issue that the drug is not going to kill patients over the long run.

CHAIRPERSON PACKER: Tom?

DR. GRABOYS: Yes, need more data.

CHAIRPERSON PACKER: Cindy?

DR. GRINES: I would like more data, but not necessarily before approval.

CHAIRPERSON PACKER: John?

DR. DIMARCO: Yes, I would like to see more data. Primarily, I think, because the patients I see have heart failure or arrhythmias and angina and by a way a little claudication. And I think that is a different population than we are looking here where claudication is really their dominant syndrome. But I don't -- 1 can't imagine how labeling can keep it from being used in that other population where we have a lot of concerns.

DR. LIPICKY: But, John, why would anyone give someone a drug to relieve their claudication if they don't claudicate?

DR. DIMARCO: No, they do have claudication, but they also have heart failure and angina and other things and they have been excluded from these trials. But if it is out there, people

will use it in those populations. And I think it would be very hard to label it not to use it in the typical patient with claudication that a cardiologist sees. And that may be different than somebody in a peripheral arterial disease clinic.

DR. THADANI: In real experience, most of the patients I see in cardiology also have claudication. Maybe one is more than the other. So if you have it in the open, you are going to use the drug. Because they also have coronary disease and they might have MI. When you see the patient --

DR. LIPICKY: I understand. But how do you know whether -- how do you even know they have angina if they are regularly processed as claudication?

DR. THADANI: When my patients are in the coronary care unit, they come with unstable angina. You talk to them and they also have coronary disease. And when you talk to them about what happened before that, they said well my leg hurts. And when you do a doppler study, they have both diseases. So I think it is not that clearcut as in this patient defined

population.

DR. LIPICKY: But you wouldn't put them on this drug in the coronary care unit.

DR. THADANI: No, no, but when they go out .

DR. LIPICKY: Six months later. And if they are still exercise limited by claudication, you might use this drug.

DR. THADANI: No, no. They might have a one-year history of stable, intermittent claudication, and then they have unstable angina episodes. Some of them have stable angina episodes. So it is not that clearcut.

DR. LIPICKY: Life is tough, but I am not sure why you would be thinking you are going to give a patient who doesn't have claudication as the limiting symptom this drug.

DR. THADANI: I think it is not as clearcut as the drug trials are making out here in real practice -- at least in my judgment.

DR. TEMPLE: What is the answer to Ray's question? Why would you give someone who has heart

failure and can't exercise this drug?

DR. THADANI: We have more patients with a combination of coronary artery disease and intermittent claudication.

DR. LIPICKY: I understand.

DR. TEMPLE: I am sorry. The people in the trials had coronary artery disease. But if they had so much angina that they had a chest pain endpoint, then they couldn't get in a trial. So they had to have claudication as their endpoint. That is who got in the trial. Why, as Ray says, would You give someone who didn't have claudication in the course of their lives, who couldn't exercise enough to achieve claudication, why would you give them this drug? Sort of non-specific --

DR. THADANI: Sometimes they have both problems.

DR. LIPICKY: How can they?

DR. THADANI: You walk and you've got a little bit of leg pain, but you also have chest pain.

DR. LIPICKY: Do you alternate?

DR. THADANI: Sure you could. I mean, if

you keep them walking, some people do.

DR. TEMPLE: The people you are worried about are the people with ventricular dysfunction, right?

DR. THADANI: Sure.

DR. TEMPLE: Okay. That is the particular group. Now why would they be on this drug if they can't exercise?

DR. THADANI: If you took say 100 patients with coronary artery disease, some have good LV function and some of them have ejection fractions below 40. Unless you measure, you are not going to know.

DR. TEMPLE: Yes, but EF below 40, they are in these trials.

DR. THADANI: We don't know. We have no idea.

DR. TEMPLE: Well, why would they be out?

DR. THADANI: Because they didn't measure it. I don't know. What you are suggesting is information which is not there. They have not provided it to me.

DR. TEMPLE: Yes. Can I make my level of concern clear? I don't believe anybody is going to do a 20,000 patient trial. And therefore people will continue to use Trental, a drug with exactly the same concern that you already have because it is a phosphodiesterase inhibitor too. And there will not be any long-term study of that drug because nobody has to do a long-term study. So that is what you've got.

DR. THADANI: But surely this drug looks so good on profile on its anti-platelet effect --

DR. TEMPLE : Yes. And they will just spend five years doing a 20,000 patient trial. Sure they will.

DR. THADANI: I realize that. But it has got an excellent profile of anti-platelet effect.

DR. TEMPLE: Yes, I know. And it is so good they will spend --

DR. THADANI: So they should be able to do a trial and prove how good the drug is.

DR. TEMPLE: It is not -- you know, they have to answer for themselves. It seems very unlikely, and you haven't asked them, whether they are

going to randomize 20,000 patients into a several year trial. But it doesn't seem too likely and I don't know whether we are supposed to make decisions based on that anyway. But you are setting a standard for symptomatic treatments. Now I -- it certainly is true that the standard is set here because of a concern about a particular class of drugs. I understand that. And that is perfectly legitimate and something to worry about. But you are setting a standard that requires a level of assurance that is very high. I was making a list of all the things you don't know. You don't know whether any drug for arthritis increases the risk for death by 1.3. You don't know that for any antihistamine. You don't know it for any vitamin supplement, and there is plenty of reason to worry about at least one of them. You don't know it for pentoxifyline. You don't know it for any drug now used for angina. I understand that many people are very interested in this and it is good meat for public discussion. But this is very unusual and you should be very conscious of what you are saying here. It says no symptomatic treatments. If there is any

reason for concern, and you can always think of reason for concern, no symptomatic treatments without mortality data, which for low risk individuals means very, very large studies.

DR. CALIFF: Wait a minute. That is not what is being said. I think the concern is in diseases that have a relatively high mortality as a background. Chronic therapies that could affect the underlying disease process should have some evidence. And I think if you look at precedent setting, instead of doing 10 exercise trials, why not do two good exercise trials and do a simple look at what the underlying major morbid events are. I bet the cost of those would be just about the same.

DR. LIPICKY: That is true, but they didn't.

DR. CALIFF: All right. So we have got two things. One is the precedent of what is desirable. And the other is how do you deal with a particular case.

DR. MOYE: And we can certainly express our opinions about the research program with which we

are presented.

DR. LIPICKY: Sure.

DR. MOYE: Now what they have done with reasonable advice was to do 8 trials looking at exercise tolerance.

DR. LIPICKY: Well, I wouldn't say reasonable advice, but all right.

DR. MOYE: Well, advice for looking at exercise tolerance. And unbeknownst to them and unbeknownst to anybody else, this is the data that they have. Now there have been concerns that have been raised in 1998. If these concerns had been raised 10 years ago, I guess our response would have been different. But in 1998, our concerns are sufficiently elevated that we -- some of us feel more comfortable requiring more data at a higher quality level. And I just continue to be uncomfortable with the idea of, well, you know you didn't require this data for a drug that you didn't review actually a few years age. So why shouldn't we have the same low bar in 1998? I mean certainly our standards can evolve as the technology evolves and as the clinical trial

methodology evolves.

DR. TEMPLE : They can, and you need to think about it. But you also, as a committee, need to think about whether the incentives to develop drugs of certain kinds will persist. You don't have to worry about that. We have to worry about that. But it is not a matter of indifference. I am not sure actually you can get 20,000 people into a large simple trial in this condition. I don't know if that is true at all.

DR. CALIFF: You keep saying 20,000, Bob. Your own staff didn't say it would take a 20,000 person trial to do this.

DR. TEMPLE: For 1.3 it does, Rob. That is the hypothesis.

DR. LIPICKY: For 1.3 it does.

DR. TEMPLE: Why would I want to rule out a two-fold increase when in the population that was most at risk it was only 1.25.

DR. CALIFF: Because as a general matter of policy, you ought to show in chronic diseases with high mortality with treatments that effect the underlying disease process that you are not doing a

substantial level of harm.

DR. TEMPLE : That is a very important statement, Bob. So you are saying it actually has nothing to do with the previous experience with phosphodiesterase. It is a general principle, which is what I originally thought it was.

DR. CALIFF : To me it is a general principle.

DR. LIPICKY: But it doesn't contain all of the biases that everyone else is coming from. It is a general principle of developing a new drug, and it isn't because this is a phosphodiesterase inhibitor?

DR. CALIFF: That just adds a little extra level of concern from the usual. I mean I will be the first to admit that these are tough issues. But wouldn't you feel badly if there was an adverse effect, and we have had several examples of that and it makes you worry,

DR. LIPICKY: No, I would not.

DR. CALIFF: You wouldn't?

DR. LIPICKY: Because in fact this has a

very distinct advantage and I would be willing to try to write a label that says -- and include a patient packet insert that says there is up to whatever you want it to name, a 50 percent increase in the probabilities of your dying, and you will get two blocks worth of benefit. Do you want to take this drug? And that is the risk/benefit and the approvability assessment, and it kind of makes me wonder why you think that you have a principle -- not you personally -- that allows you to take that decision making process out of the hands of the doctor and the patient.

DR. CALIFF: So all you need to write the label that you wanted to write is about a 4,000 patient study --

DR. LIPICKY: I have got it already. I don't need any more.

DR. CALIFF: Oh, you've got it?

DR. LIPICKY: Sure I do. I will bring the phosphodiesterase congestive heart failure stuff to bear. That is what everyone else is doing except you, and I have got a real good point estimate from that.

Granted, it is in a different population.

DR. CALIFF : You were just arguing you wouldn't extrapolate from that. Now you are arguing that you would.

DR. LIPICKY: No, I am saying ''

DR. TEMPLE: You would express that as a worst case.

DR. LIPICKY: I am expressing that as a worst case. And I am not -- and I would reject the notion that based on that experience you could expect things like 100 or 200 or 300 or 400 percent increases in mortality in this patient population. So I would accept that as the worst case. I would say I have got my best estimate. That labeling could be gotten rid of by doing a good mortality trial that says, no, it isn't the case in this patient population. Even when we include people with a little bit of rest pain and a little bit of gangrene and so on and so forth.

DR. THADANI: Ray, one other issue I think you have to -- we have been made to believe there are no alternatives. There are alternatives available. All the vascular surgery patients don't like it, but

the recent publication on several hundred patients, if you just give a beta blockade and do the surgery on peripheral vascular disease, the mortality is pretty low .

DR. LIPICKY: How many publications, Udho?

DR. THADANI: There is only one publication.

DR. LIPICKY: Aha, you've got 8 here.

DR. THADANI: I realize that. But the mortality in that number --

DR. LIPICKY: So you are offering one published study as an alternative? Come on. Be real.

DR. THADANI: No, I realize there is no -- there are about 300 patients, but the mortality is less than .5. So I think there are other alternatives available before you are going to increase the mortality double and tell the patient you may die. If I am a physician, I can tell the patient what alternatives are there. The patient can decide which he wants to'take. I will buy that. But you can't say that if you can walk 500 meters and if I am going to tell him that his chance of dying is more, I would

really like to see the data. We are not addressing the issue that it is not effective. I think we are agreeing it is effective. We are just uncomfortable with the safety issues. And I think that has to be taken into perspective.

DR. CALIFF: Milton, actually if Ray could really write a label so that every patient would be informed and make the choice that he described in an informed manner, I would be pretty happy.

DR. TEMPLE: We could have patient labeling. We could have, at your recommendation, labeling to the patient that lays out what is known about drugs of a related class.

DR. LIPICKY: Sure. But I don't know that the other stipulation we made of really an informed consent could be guaranteed any better than you can guarantee an informed consent in the clinical trial.

DR. TEMPLE: Well, I don't know about -- informed consent is problematical. But getting labeling to patients so that they can discuss it and have to discuss it in some sense with their physician is possible. I just wanted to dilate on something

else. What we are hearing here is concern about uncertainty. And nobody likes any degree of uncertainty. And heaven knows we are as sympathetic with that as anybody else. But one still has to ask how much one can rule out uncertainty. For example, there has just been a recent meta-analysis that raises the question of whether beta blockers as antihypertensives are useful. Now you may find that stunning, but the fact is there are not a lot of studies that show that beta blockers are useful, and here we sit and we live with this right now. We have all kinds of recommendations to use that as a first or second therapy, and boom, there is some uncertainty about it. That is fairly stunning. We still don't know for sure whether lowering the blood pressure below 90 is important to -- okay, people are looking, but the data aren't there yet. We could make a list of 100 things that are deserving of attention and that we would like to know the answer to and that are all completely legitimate. And the question here that we are talking about is how much ruling out of uncertainty must one do in each of these settings. I

was giving my list of all the things we don't know because one of the uncertainties are that the many drugs we use chronically we don't have good mortality data for them and it isn't easy to figure out how to get it. Epidemiologic methods I think in my experience are not very good at very low risks -- 1.3 and stuff like that. They give you the wrong answer. So the question is what do you do in that case. And that is what everybody is really grappling with. How far do you go and what price do you pay.

CHAIRPERSON PACKER: Bob, I guess the basis here is not uncertainty as much as it is a history of having been burned a lot with these drugs. But let me ask a question.

DR. TEMPLE: We weren't burned. We got the right answer. They weren't approved.

CHAIRPERSON PACKER: I understand. The question is can you describe a little bit more to us about what a patient handout means?

DR. TEMPLE: Well, sure. We have or are close to having -- we have always had authority to require patient labeling when that was considered

important to the proper use of the drug. The early model was oral contraceptives in which the labeling for patients was a virtual textbook of methods of contraception. It really put the patient into the decision about deciding what method to use. That is easier to conceive of in contraceptives than it is here, but with some effort one could perhaps do it. If there were thought to be a legitimate set of choices to present to patients like here this increases your exercise tolerance but it is closely related to a class of drugs that in a different setting caused this and such and we can't be sure that that risk isn't here, one could try to write those things out doing it as much in lay language as you can without losing meaning, and one could -- the company could agree and we could insist that that labeling be provided to every person who got the package. You can have what is called unit of use packaging, so that every person who gets the drug has to get that labeling with it.

CHAIRPERSON PACKER: And the labeling comes from the pharmacist?

DR. TEMPLE: The labeling is attached to the package. The only sure way to get labeling to patients is to include it as part of the package. That is not common in the United States, but it is the normal way drugs are distributed throughout much of the rest of the world. So that can be done. It is done for most oral contraceptives. It is done for Halcyon. Where you really want people to have it, you attach it to the package. And then they always get it and it is attached to the package, so they can't throw it away.

CHAIRPERSON PACKER: Okay. Bob, can I make the following recommendation? Because I guess the concept of patient -- of a patient handout may or may not assuage the concerns of the committee. Could we do the following? We are just in the middle of a vote. If we could complete the vote with the premise that we will take the vote again with the consideration of a patient label. Would that be satisfactory?

DR. TEMPLE: Your call. Sure.

CHAIRPERSON PACKER: Yes? Okay. We

already heard JoAnn vote. The question is the same question; do you need a better estimate of mortality effect before recommending approval of the drug. And again, this is what might be called under conventional circumstances, I guess, because we are going to take another vote. Marv?

DR. KONSTAM: I will vote, no, I don't seek other information and basically I am very influenced by the balance of the very strong efficacy data set coupled with the fact that I think the concern that is raised stems from the heart failure population. I would, in addition to whatever we come to with regard to patient information, I would hope to see a specific warning with regard to patients with concomitant heart failure. And I guess my comment to Bob with regard to the interchange that he had with Udho before is that I think it is not an ideal world and there are patients with heart failure and peripheral vascular disease, and it is not so clear that patients with limiting heart failure would not be receiving this drug. So I would expect some warning with regard to using the drug in patients with heart

failure.

CHAIRPERSON PACKER: I understand the sponsor has actually proposed on its own to contraindicate the drug in heart failure. That is a pretty strong warning. So that would be consistent with your view on this. I just wanted to complete this vote because we are going to take another one based on the package insert concept. Rob, under what might be called conventional circumstances, do yOU need a better estimate before recommending approval?

DR. CALIFF: If nothing else was going to be done in the future, I would say yes. I need more.

CHAIRPERSON PACKER: Okay. And I would vote yes as well. That would make for 7 versus 3. And now the question is whether the committee would reconsider that vote if the patient was handed together with the drug a piece of paper that would say everything that we are worried about and that wordsmithing could occur between the agency and the sponsor. Something which is not commonly done. The question is would we be reassured if that label -- if that patient label sufficiently highlighted the risks

that we are concerned about with this class of drugs. So the question is would you change your vote -- and this will only apply to those people who voted yes. Would you change your vote if the prerequisite for approval was a patient insert. And let me see, who voted no? We will begin with Lem.

DR. MOYE: I don't think we need a fancy label or a patient insert. I think we need the data. So I am not changing my vote.

CHAIRPERSON PACKER: Udho?

DR. THADANI: I second that. I am not going to change my vote.

DR. GRABOYS: I will third it. I won't change my vote. I think it would create chaos in the physician/patient relationship.

CHAIRPERSON PACKER: John?

DR. DIMARCO : I actually think that appropriate labeling and accepting the contraindication for heart failure patients. Then if we are sure that that is very prominent, then I think that we could relax my prior request for information before approval.

CHAIRPERSON PACKER: I mean, we are talking about a patient handout essentially. Because if it is a package insert, nobody will read it.

DR. DIMARCO : That is exactly right. Something that both the doctor and the patient read.

CHAIRPERSON PACKER: Right. Okay, JoAnn?

DR. LINDENFELD: Yes, I would change my vote. The important thing here, I think, is that it is a drug for people who have a severe illness. And as long as we can be as certain as we can be that the patients understand what the risks are, then I would change and say we ought to go ahead and approve it if we can do that.

CHAIRPERSON PACKER: Bob?

DR. CALIFF: I would change, but I would want two things. One is a patient handout and the second is a commitment to collect one-year mortality data, and I would only require three pieces of information. Did the patient take the drug or placebo. Was the patient dead or alive. And I guess the third is a couple of things. The functional part of the SF-36, which would get the longer term efficacy

data and answer the mortality question.

CHAIRPERSON PACKER: And I guess I would change my vote as well, but it would be conditional pretty much on the same criteria that Rob has outlined, including a patient handout, a formal mortality experience with some long-term efficacy data. That vote is 7 to 3. Marv doesn't have to because he was comfortable with the conventional route. Okay, can I ask -- yes?

DR. TEMPLE: Just one thing about the last couple of points. What relative risk -- what risk increase is this study that they are to be asked to do to rule out?

DR. THADANI: 20,000 patients?

DR. TEMPLE: Well, you can't say the size really. But how big an increase are we looking at here trying to rule out?

DR. CALIFF: This is a compromise between level of uncertainty, which we would all like to be certain, as you said, but we can't be. I would say something like 50 percent increase. Maybe 75 percent. I would have to see the practicality of the sample

size.

DR. TEMPLE: Okay. But we are now talking about a risk larger than the risk that triggered this concern in the first place. This is sort of a general statement now.

DR. CALIFF: That is for you. For me, I am always concerned about chronic diseases.

DR. TEMPLE : That is what I am saying. Your concern is really unrelated to the fact that this is a phosphodiesterase inhibitor. It is what you feel ought to be known about a drug for chronic treatment.

DR. CALIFF: Right.

CHAIRPERSON PACKER: Bob, I think there is actually -- can I fashion a compromise that I think both you and Rob will be happy with? That may be the first time this ever happens.

DR. TEMPLE: WOW , give it a whack.

CHAIRPERSON PACKER: I think what Rob is saying is he wants to rule out a 75 percent or whatever increase in risk of death. Remember in the Promise trial and in many other trials, the point estimate was 1.28, but the right-sided confidence

interval was up to about 1.7 or 1.75. So to rule out a 75 percent increase in mortality, you are not talking about the point estimate. You are talking about the right-sided confidence interval. I think you are. How else would you be able to rule it out. So you are actually talking about exactly the same thing. His right-sided confidence interval at 1.75 is similar to your point estimate, which is approximately the same as the point estimate for the existing data base for PDE inhibitors. Is that logical?

DR. TEMPLE: It is logical. I just want to be sure we know what advice we are getting. I understand Rob quite well, I think, which is that any drug for chronic use ought to have a mortality data base that rules out making things worse. This is just an example of it, but it is not because of anything specific about it. Other people, I think, are concerned mostly because this is related to a class of drugs that was a problem in several other settings. Those are two different theories of why you need more data with different implications. I am not sure we can finish the conversation now. But it is worth

taking note of.

CHAIRPERSON PACKER: They are not mutually exclusive.

DR. TEMPLE: No. But they have a lot to do with how big the study has to be. Because I see what you are saying about the confidence interval and maybe that blends them a little. But we need to think about that.

CHAIRPERSON PACKER: Okay. Can I -- in looking over, I would propose skipping question 11 because 1 don't think there is an answer.

DR. LIPICKY: Fine.

CHAIRPERSON PACKER: And question number 12, the committee has actually answered every single one of these questions already. The committee has said that -- and let me just -- 1 will summarize this quickly and make sure that everyone agrees that they might feel comfortable with a highly conditional approval which would involve both a patient handout as well as a mortality trial. That the regimen that would be recommended, as JoAnn mentioned before, would be 50 to 100 mg bid. That the committee was actually

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?

CHAIRPERSON PACKER : I think everyone on the committee would say at this particular point in time if there were increased -- if we are worried about an increase in mortality at 100 bid, we are really going to be worried about an increase in mortality at 150 bid, especially since that regimen is associated with an increase in the heart rate of 10 beats per minute.

DR. LIPICKY: Fine.

CHAIRPERSON PACKER: Okay. Any other comments? Disagreements? We are adjourned.

(Whereupon, at 6:30 p.m., the meeting was concluded.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

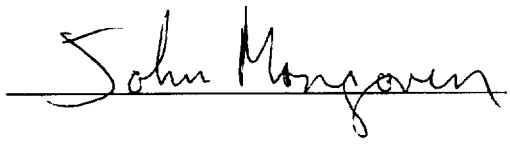
85TH MEETING

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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NOISE WORDS: 385
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