UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DRUG EVALUATION AND RESEARCH

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DIVISION OF CARDIOVASCULAR AND

RENAL DRUG PRODUCTS

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CARDIOVASCULAR AND RENAL DRUGS

ADVISORY COMMITTEE

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Tuesday, January 27, 1997

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The meeting was held in Natcher Auditorium, 45 Center Drive, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland, at 8:30 a.m., Milton Packer, M.D., Chairperson, presiding.

PRESENT:

MILTON PACKER, M.D., Chairman

JOAN C. STANDAERT, Executive Secretary

ROBERT CALIFF, M.D., Member

PRESENT (Continued):

JOHN DiMARCO, M.D., Member

CINDY GRINES, M.D., Member

MARVIN KONSTAM, M.D., Member

JoANN LINDENFELD, M.D., Member

LEMUEL MOYE, M.D., Ph.D., Member

ILEANA PINA, M.D., Member

DAN RODEN, M.D.C.M., Member

UDHO THADANI, M.D., F.R.C.P., Member

BARRY MASSIE, M.D., FDA Temporary Voting Member

CHRISTOPHER O'CONNOR, M.D., FDA Invited Guest

LIONEL RABIN, M.D., FDA Invited Guest

LYNNE STEVENSON, M.D., FDA Invited Guest

RAYMOND LIPICKY, M.D., FDA Representative

JAMES HUNG, Ph.D., FDA Reviewer

WILLIS MADDREY, M.D., Sponsor Representative

JOEL MORGANROTH, M.D., Wyeth-Ayerst

BETTY RIGGS, M.D., Wyeth-Ayerst

DR. MARK SILVER, Public Comment

ALSO PRESENT:

SHAW CHEN, M.D.

ROBERT FENICHEL, M.D.

DR. ABE FRIEDMAN

ALSO PRESENT (Continued):

CHARLES GANLEY, M.D.

URSULA HOPPE, M.D.

RON HORNE

PHIL MAYER

ROBERT MISBIN, M.D.

BRUCE SCHNEIDER

HYMAN ZIMMERMAN, M.D.

C-O-N-T-E-N-T-S

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

(8:35 a.m.)

CHAIRPERSON PACKER: I'd like to call this meeting of the 83rd meeting of the Cardiac and Renal Drugs Advisory Committee to order.

We're in a different place for us. This is the Natcher Auditorium. I think we should petition the division to keep the meetings here. It seems like a nice place.

But what I'd like to do is as we have in the past ask for a just roll call of the Committee, and we have, I think, a full Committee with us today, and in addition, we have a voting expert, Dr. Barry Massie, and I'll ask Barry to begin the roll call or, Ray, do you want to do that? I guess you can begin.

DR. STEVENSON: Oh, yes. I'm present. Is that what you're asking?

CHAIRPERSON PACKER: Just name and institution.

DR. RODEN: That was Barry Massie from UCSF, and I'm Dan Roden from Vanderbilt.

DR. PINA: Ileana Pina , Temple, Philadelphia.

DR. THADANI: Udho Thadani, University of Oklahoma, Oklahoma City.

CHAIRPERSON PACKER: Milton Packer, Columbia University.

DR. KONSTAM: Marv Konstam, Tufts University.

DR. LINDENFELD: JoAnn Lindenfeld, University of Colorado.

DR. MOYE: Lem Moye, University of Texas in Houston.

DR. DiMARCO: John DiMarco, University of Virginia.

DR. GRINES: Cindy Grines, Beaumont Hospital.

CHAIRPERSON PACKER: And I'll ask Joan to read the waivers and disclaimers for this morning's meeting.

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 interested 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 exceptions.

In accordance with 18 USC 208(b)(3), full waivers have been granted to Drs. Milton Packer, JoAnn Lindenfeld, Lemuel Moye, Marvin Konstam, and Barry Massie.

In accordance with 18 USC 208(b)(3), general applicability waivers have been granted to all participants which allow them to participate in today's discussions concerning the broad applicability issues relevant to the general class of inotropic agents.

Copies of these waiver statements may be obtained from the agency's Freedom of Information Office, Room 12A30, Parklawn Building.

We would like to disclose for the record that Dr. Marvin Konstam and his employer, the New England Medical Center, and Dr. Robert Califf and his employer, the Duke Clinical Research Institute, have interests which do not constitute a financial interest within the meaning of 18 USC 208(a), but which could create the appearance of a conflict.

The agency has determined notwithstanding these involvements that the interests of the government in Drs. Konstam's and Califf's

participation outweighs the concerns that the integrity of the agency's programs and operations may be questioned.

Therefore, Drs. Konstam and Califf may participate in today's discussions of Verdia.

With respect to FDA's invited guest expert, Dr. Christopher O'Connor has reported interests which we believe should be made public to allow the participants to objectively evaluate his comments. Dr. O'Connor would like to disclose for the record that he and his employer, the Duke University Medical Center, has received grants from the National Heart, Lung, and Blood Institute, the Veterans' Administration, the National Institutes of Mental Health, the Robert Wood Johnson Foundation, Sanofi-Winthrop, Pfizer, Narvatis, DuPont-Merck, Astra-Merck, Hoechst Marion Roussel, Merck, Wyeth-Ayerst, Boehringer-Ingelheim, Bayer, Bristol Myers Squibb, Parke Davis, Medtronics, Roche, SmithKline Beecham, Searle, Burroughs Wellcome, and Cardiologic Systems.

Dr. O'Connor has also received speaking fees from these firms and consulting fees from all of these entities.

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 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.

And that completes the conflict of interest statement for the 27th of January.

CHAIRPERSON PACKER: Thank you very much.

And we will now ask if there is any public comment.

(No response.)

CHAIRPERSON PACKER: There being no public comment, we'll proceed to the first item on the agenda, which is the evaluation of tasosartan for the treatment of hypertension. The sponsor is Wyeth-Ayerst, and please proceed with your presentation.

DR. RIGGS: Good morning, Dr. Packer, Dr. Lipicky, members of the Advisory Committee, ladies and gentlemen.

My name is Betty Riggs, and I represent Wyeth-Ayerst Research. It's my pleasure today to present the safety and efficacy data for tasosartan.

I was the medical monitor for this program. I also participated in the NDA submission, and as I understand it, the FDA has stipulated that they agree that tasosartan is an efficacious antihypertensive agent when given once daily.

The FDA has asked us to participate in today's meeting because of a concern about an apparent increased dropout rate due to LFT abnormalities compared with other angiotensin II receptor antagonists programs.

As a result of this, we have performed extensive and thorough analyses of our preclinical and clinical data. We've also consulted with two of the world's foremost experts on drug induced liver disease, Dr. Willis Maddrey and Dr. Hyman Zimmerman, who are here with us today. I think you know that both of these experts have consulted for the FDA in the past when questions of drug induced hepatotoxicity have been raised.

As we've reviewed our database and as we've reviewed it in conjunction with our experts, we've come to the conclusion that tasosartan is a safe product. We have a number of reasons why we believe there were some differences, including differences in study design and sampling frequency compared with

other programs, and we will present data to try to clarify some of these issues for you today.

Tasosartan, Verdia, is a new, long acting, angiotensin II receptor blocking agent that has been developed for the treatment of hypertension in a worldwide clinical program that began in 1992. An NDA was filed with the Food and Drug Administration in December of 1996.

Due to time constraints, the FDA has requested that the presentation be focused on the questions before the Commission, which is the effect of tasosartan on liver function tests. Therefore, the agenda for the presentation is as follows.

I will begin with a brief review of the efficacy and non-LFT safety data. Then Dr. Willis Maddrey, a hepatology expert from the University of Texas, will provide an overview of the interpretation of LFT data.

I will then review the tasosartan LFT data, and because of the special nature of most of today's discussions, as I said, we are accompanied by a second consultant on hepatic disease, Dr. Hyman Zimmerman, who can help address any questions.

We are also joined by a cardiology consultant, Dr. Joel Morganroth, who has reviewed our

database. Dr. Morganroth has spent the last few years reviewing data from several drug development programs for sponsors and for the FDA.

After Dr. Morganroth's comments, I will then provide some concluding remarks.

Tasosartan has predictable pharmacokinetics. It is well absorbed orally and has absolute bioavailability of 60 percent. The Pk profile is similar in fed and fasted patients.

The parent compound reaches peak plasma concentrations within one to two hours after an oral dose, and dose proportionality has been demonstrated across a wide dose range, up to 300 milligrams daily.

The long duration of antihypertensive activity is due to two metabolites that have half-lives of 60 and 70 hours.

As previously mentioned, the efficacy of tasosartan has not been questioned by the FDA. The NDA included data from seven placebo controlled studies and one active controlled study.

This single slide is representative of the efficacy of tasosartan replicated in all of our controlled studies. As shown in this graph of the final on therapy, ambulatory blood pressure measurement, the diastolic blood pressure was

controlled throughout the 24 hour dosing interval for patients who were titrated from 25 to 100 milligrams until efficacy was achieved or the highest dose was reached.

The placebo corrected trough-to-peak ratio was .82, indicating that antihypertensive efficacy is achieved with once daily dosing. The circadian pattern of blood pressure is also maintained with tasosartan.

In addition to the studies submitted in the original NDA, we have performed two post NDA studies that have demonstrated the superior efficacy of tasosartan compared to losartan. These studies were designed to determine if tasosartan's long duration of action confers a clinical benefit over an approved angiotensin II antagonist, that is, to determine if there are differences between our drug and others in the same class. These studies are important in defining the risk-to-benefit ratio of tasosartan.

The designs of these studies were discussed with the FDA prior to initiation, and we appreciate the agency's considerable input into the study designs.

We did follow the agency's advice about

using the maximum allowable dose of losartan in order to be fair to the comparative agent.

It should be noted, however, that the FDA has not had an opportunity to review data from these studies in detail.

Protocol 328 was a randomized double blind, placebo controlled study that compared the effects of tasosartan and losartan on sitting and ambulatory blood pressure, as well as on the systolic blood pressure response to exercise. It was designed to address potential differences in antihypertensive efficacy at the end of a once daily dosing interval.

Two hundred and seventy-five patients were randomized to 100 milligrams of tasosartan, placebo, or losartan 100 milligrams daily for four weeks. In this protocol, patients performed an exercise treadmill test at baseline, shown here, and at the end of the double blind period.

This graph shows the results for the primary endpoint, that is, the change from baseline in mean trough sitting diastolic blood pressure at four weeks of double blind, shown here, and placebo is in blue. Losartan is in the gold, and tasosartan is in green.

The results after two weeks of therapy are

shown on the left. Both losartan and tasosartan were statistically better than placebo at both time points. Additionally, tasosartan was superior to losartan at both time points.

As I said earlier, patients performed an exercise stress test at the final week of double blind therapy. This graph shows the results at rest, at Stage 1, 2, and 3 of the Bruce protocol. Tasosartan was superior to placebo at all stages. Losartan was superior to placebo only at rest and at Stage 1.

At Stage 3, tasosartan provided control of the systolic blood pressure that was statistically significant compared with both placebo and losartan.

In summary, this study demonstrated that tasosartan was superior to losartan in controlling the trough sitting diastolic blood pressure, the mean 24 hour diastolic blood pressure, and the systolic blood pressure response to strenuous exercise.

The second post NDA study was Protocol 330. The objective of this study was to determine if the long acting nature of tasosartan confers a potential clinical benefit for patients who occasionally missed doses of antihypertensive medication since noncompliance is a common problem with antihypertensive therapy.

This was a randomized double blind, placebo controlled comparison of the impact of missed doses of tasosartan and losartan in patients with hypertension. At the beginning of the double blind period patients were randomized to one of the three therapies, tasosartan or losartan or placebo. At that time they were also randomized to one of two days of dose interruption, either at Week 4 of double blind or at Week 6.

The interrupted dosing sequences occurred to simulate a period of noncompliance.

Shown in this graph are the ABPM data obtained at the end of the two-day interrupted dosing sequence. Blood pressure is reduced throughout the 24 hour assessment in patients who receive tasosartan.

In contrast, the ABPM data indicate that losartan provides an effect that is no better than placebo during this period of simulated noncompliance.

In summary, tasosartan provided superior antihypertensive effects at all time points tested. During the period of simulated noncompliance, the two days of missed doses, losartan lost its antihypertensive effects, while tasosartan antihypertensive effects remained constant.

In conclusion, tasosartan has a favorable

Pk profile. It is rapidly and well absorbed, and there are no food effects. There's a smooth onset and offset of action. The Pk profile supports the fact that this is truly a once a day drug.

The dosage recommendations are for an initial dose of 50 milligrams once daily in most patients titrated to 100 as needed, and we also recommend a dose reduction for volume depleted patients, renal and hepatic impaired patients.

In several adequate and well controlled studies, tasosartan has shown consistent superiority to placebo. A dose response was demonstrated up to 100 milligrams. When tasosartan is given with diuretics, the antihypertensive effects are additive, and in two controlled trials tasosartan was shown to be superior to losartan for control of diastolic blood pressure at trough and at every time point throughout the 24 hour dosing interval.

Additionally, tasosartan was shown to control the systolic blood pressure response during exercise better than losartan. After two days of simulated noncompliance, tasosartan afforded continued antihypertensive protection, while losartan was no better than placebo.

Thus, all angiotensin II antagonists do

not provide equivalent clinical effectiveness.

Now I would like to review the safety and tolerability of tasosartan. It should be noted that more patients are included in the safety database because of the addition of patients from the European dossier.

A total of 6,149 patients or subjects were included in the safety database. Seven hundred and nine patients are subjects enrolled in the clinical pharmacology-pharmacokinetics studies. Of these, 639 were enrolled in the tasosartan group.

In the controlled and open label Phase 2 and 3 studies, 5,440 hypertensive patients were enrolled. Of these, 4,132 patients received tasosartan alone or in combination with hydrochlorothiazide. The doses studied ranged from ten to 600 milligrams per day.

Over 800 patients received the drug for at least 12 months, and over 100 patients have received the drug for at least 18 months. The doses studied in the long term protocols ranged from 25 to 100 milligrams per day.

The demographic characteristics of patients who participated in the Phase 1 through 3 studies are shown in this table. It is important to

note that more than 1,400 patients were age 65 or older. While the majority of younger patients were white, middle aged males, it should also be noted that a significant percentage of patients were women, especially in the older than 65 age group.

In contrast to other angiotensin II antagonists development programs, non-white patients were not excluded from the tasosartan efficacy and safety studies. Consequently, ten percent of the patients in the younger age group were black.

Treatment emergent study event data were collected in all studies. These data were based on patient's self-report and investigator observation. This table shows the presumably drug related study events that occurred in at least one percent of patients.

The most commonly reported drug related study events were headache, dizziness, and asthenia. The incidence of headache and asthenia was higher in the placebo group. In fact, the incidence of headache was significantly lower in the tasosartan group.

Premature discontinuations for any reason occurred in 12.3 percent of tasosartan treated patients compared with 12.9 percent of placebo treated patients. Discontinuations due to adverse events

occurred in 2.9 percent of both the tasosartan and placebo treated patients. Discontinuations due to other medical events occurred in 1.7 percent of tasosartan treated patients and in 3.6 percent of placebo treated patients. The incidence for other comparators are also shown and were generally similar.

During the entire development program, 13 deaths were reported, four of which occurred two or more weeks after study completion. None of the deaths reported to the company was considered to be related to tasosartan according to the investigator's assessment. Most of the deaths were the result of chronic diseases, for example, MI, stroke, and cancer.

There were no between group differences in ECG or non-LFT laboratory parameters. At FDA's request, creatine kinase data were collected in some protocols. The incidence of CK elevations was similar in patients treated with tasosartan and placebo.

The clinical safety profile observed with tasosartan in our safety database demonstrated that the incidence of drug related study events was similar to placebo.

During a randomized placebo controlled withdrawal segment of one trial, tasosartan was shown to have no rebound effects. There were no apparent

dose related increases in study events with tasosartan at daily doses of up to 600 milligrams, and the discontinuation rate due to clinical adverse events was the same as for placebo.

For the rest of the allotted presentation time, we will focus on data and issues relating to elevations of liver function tests. Before I present the tasosartan LFT data, Dr. Willis Maddrey will present a discussion of the interpretation of LFT data from drug development databases.

CHAIRPERSON PACKER: Before going forward, does anyone on the Committee have any questions about any of the presentation up to this point?

DR. KONSTAM: Can I just ask one question? In the losartan comparative study, was losartan given QD or BID in that study?

DR. RIGGS: It was given QD.

DR. KONSTAM: And just remind us. The differences that you saw are probably explainable on the pharmacokinetic differences between losartan and tasosartan and others. Losartan has a shorter half-life, doesn't it?

DR. RIGGS: The parent has a shorter half-life, as does its active metabolite, yes.

CHAIRPERSON PACKER: Barry.

DR. MASSIE: Yes. Could you just remind us of how the drug is metabolized? Because you said you recommend dose adjustments for people with both renal and hepatic dysfunction. Is that based on known pharmacokinetics of the drug in people with those problems?

DR. RIGGS: Yes. A formal study was performed in hepatic impaired patients, and based on those PK findings, dosage recommendations were made.

DR. MASSIE: is there also renal excretion of the drug?

DR. RIGGS: There is some renal excretion, and there was a formal study in renal impaired patients, and again, the recommendations were based on those PK data.

DR. MASSIE: Thanks.

CHAIRPERSON PACKER: Udho.

DR. THADANI: Regarding the metabolite which has 60 hour half-life, that means really those adjustments should be at least three weeks or four weeks rather than in seven or one week time because a metabolite is more potent probably or at least has a longer duration of action. So in most of the trials -- in some trials I saw that you increased the dose at three weeks rather than one week interval.

How much confidence one has that the doses given is right on combined database?

DR. RIGGS: Based on the PK data that we had early on, our pharmacokineticist felt that our drug would be at steady state after three weeks of therapy, and so we felt that three weeks was a reasonable period after which to titrate.

DR. THADANI: So that would be the recommendation? One should not increase the dose until three weeks have elapsed?

DR. RIGGS: Based on our data, yes.

DR. THADANI: Are you going to discuss something more on the drug interactions now or later on in the discussion?

DR. RIGGS: We weren't planning to make any formal presentation, but if you have specific questions, we are prepared to answer those.

DR. THADANI: I don't know if you want me to do it now or later.

CHAIRPERSON PACKER: Why don't we do it later?

DR. THADANI: Okay. I will have some questions.

CHAIRPERSON PACKER: Rob?

DR. CALIFF: I just wondered. You

presented that there were 14 deaths in the overall experience. I just wanted to make sure we understood the context or the point of that. Do you think that's a low number of deaths, a high number of deaths? How many were in the control group and how may were in the treated group?

DR. RIGGS: The majority of the deaths were actually in open label studies. We did have one patient that I remember in particular from an open label -- sorry -- a controlled study that died of an MI before ever receiving drug. They had been randomized and could have received no more than two doses of drugs.

So the majority of patients were in long term, open label studies.

The majority of the deaths, as I said, were related to chronic illnesses, such as cancer, MI, stroke. We felt after looking at other databases that this was not a high number of deaths. For example, if you compare our 13 deaths to the valsartan experience, they had a very similar number of deaths with a similar exposure to patients.

DR. CALIFF: So there were 13 deaths in the treated group and one in the controlled groups? I'm trying to -- well, I won't belabor it too much,

but it just bothers me to say that people die from chronic diseases since I thought the reason we treated hypertension was to present stroke and heart attack and those things.

It seems like the interaction of the drug with the outcomes for the diseases that we're treating would be important to put into context.

DR. RIGGS: I think --

DR. CALIFF: We'll get back to this later, I'm sure.

CHAIRPERSON PACKER: Yes.

DR. RIGGS: I think if you look at the incidence in our program and you compare it with the age adjusted mortality rates published by the CDC, they're very similar. It was about .6 in our program, and if you look at the age adjusted death rate for a 60 year old man, for example, in this country, you expect about a one percent mortality rate.

CHAIRPERSON PACKER: Ray.

DR. LIPICKY: I can't remember. Do you recall how it turned out that 100 milligrams was the highest dose you studied?

DR. RIGGS: It was not the highest dose we studied.

DR. LIPICKY: Oh. What was the highest

dose?

DR. RIGGS: We studied 600.

DR. LIPICKY: I see. Okay. Do you remember how it was that 100 milligrams was the highest dose of losartan studied?

DR. RIGGS: Yes. As we had discussions with the agency when we were designing the program, it was made clear to us that we needed to use the highest dose in the losartan --

DR. LIPICKY: No, no. I mean when losartan was developed.

DR. RIGGS: That I can't answer.

DR. LIPICKY: So it may not be the maximally effective dose. It's the maximally approved dose, but you don't know what a higher dose would do. I think that's a true statement, is it not?

DR. RIGGS: My recollection from reviewing the SBA from losartan is that they did not have a significant dose response noted, and so higher doses typically did not provide a better antihypertensive effect.

DR. LIPICKY: Was that true for your 600 milligram dose also?

DR. RIGGS: Are you talking about losartan or tasosartan?

DR. LIPICKY: No, yours. I'm switching back and forth, I guess.

DR. RIGGS: Sorry.

DR. LIPICKY: I'm sorry.

DR. RIGGS: I just want to make sure I know what I'm talking about.

In the tasosartan program, we studied 600 milligrams, and basically there was some small increment in the antihypertensive effect when you got to doses higher than 100, but it was not generally statistically significant.

DR. LIPICKY: Okay. Fine.

CHAIRPERSON PACKER: Ray, but just briefly, there is a continuing interest of sponsors to compare their drugs to already approved drugs, and the general way that they do that is they come and talk to the agency, and they present a plan. That plan generally consists of one and now commonly two trials where they attempt to show that their drug is in some way better than the approved drug, and the way they choose the dose of the approved drug is they look at the approved labeling, and they generally choose the highest dose that's approved.

That's probably a very reasonable thing to do if the approved drug -- the dose in that approved

labeling -- that a whole dose range was examined or that the dose that was approved as the maximal dose was the best compromise between efficacy and safety, but if a company didn't do their due diligence on the old drug, there would be no way the new drug would be able to fix the deficits of the old NDA.

Would it still not be appropriate under those circumstances to compare one to the highest approved dose?

DR. LIPICKY: Well, I mean, this is always a half an hour debate, but, in fact, what one is usually doing is comparing two dosing regimens of two different chemical entities, and if a particular dosing regimen of one chemical entity has a better effect at trough than another dosing regimen of some other chemical entity, that may reflect nothing at all about the chemical entity and its ability to lower blood pressure or interact reasonably, but may simply reflect the dosing regimen.

And so it has nothing to do with the intrinsic ability of the chemical perhaps to alter the things. Most often, although we probably recommended that losartan be studied to a gram and we probably recommended that tasosartan be studied to a gram, people rarely will do that and somehow or other decide

100 milligrams is the best dose, often on the basis of another 40 patients not having a statistically significant difference when the dose is changed a little bit, which in my judgment doesn't mean much.

So basically, I think one's stuck comparing two drugs and two different parts of their dose response curve and/or their time effect curve and then trying to draw conclusions about whether or not these two chemicals differ with respect to their -- so there is a dosing regimen difference. That's not unreasonable to define, but it doesn't mean much I don't think.

CHAIRPERSON PACKER: The reason is because, of course, in today's discussion the issue is not just comparative efficacy, but comparative safety, and so it would appear as if at least for today's discussion, the approved dosing regimens of the sartans is one of the comparators that this Committee needs to consider.

In other words, it's not the doses beyond those that the sartans may or may not have. Other companies may have evaluated for the sartans either for efficacy or safety.

DR. LIPICKY: Yeah. Well, to consider in what sense, and I think it's only the sense that you

would consider it that might raise some discussion, but you're right. You can't deal with something you don't have.

CHAIRPERSON PACKER: No, no.

Okay. Dr. Riggs, you can proceed.

DR. RIGGS: I'd like to introduce Dr. Willis Maddrey.

DR. MADDREY: What I would like to accomplish in the next few moments is to provide a bit of a framework for the evaluation of liver abnormalities that are found in the course of drug development and what the significance of these abnormalities might be.

As you're well aware, virtually all drugs cause some type of abnormality of the liver at some time during development and, of course, in the general use of the drug. When looking at this and evaluating the database, as Dr. Zimmerman and I have had an opportunity to do with this drug, we look for the following factors, as do you:

The likelihood that there is or was a liver injury created during the development of the drug that is attributable to the drug.

If such is present, to establish the time of onset, and very importantly, if an injury of any

type is found, to establish its pattern, recognizing there are two large groups of patterns, those which predominantly affect the hepatocites, hepatocellular injury, and others which predominantly affect the ability of the liver to make and transport bile, which is called cholestasis.

We have chemical markers, of course, which allow us to distinguish between these two, the major two markers being the elevation of ALT as the best marker of hepatocellular injury at a test level, and the elevation of the serum alkaline phosphatase, the best marker of cholestasis.

We then want to look at not only the time course, but the course of what happens to the patient following withdrawal. All of these will be relevant to the evaluation of this drug.

I might mention that virtually all antihypertensive drugs have been carefully studied for liver abnormalities since the earlier experiences we had with methyldopa and a quite prominent number of cases of elevations of aminotransferases and some liver disease.

The risk factors that we focus upon are listed here, far too many for a deep discussion, but we're interested in the age of patients who might be

affected. We're interested in the sex of patients who might be affected, recognizing that in general women, particularly women beyond the age of 50, appear to be more susceptible across the board to drug induced liver injury than any other group of patients.

We're interested in dose and duration. Obviously some drugs would cause no trouble at all if used for a ten-day period, but might cause a problem if used for longer than six months.

We're interested in a variety of factors that relate to the patient. The nutritional status is an important factor because of possible interactions in that regards.

We're interested in drug-drug interaction, and this usually leads to a need for knowledge of the cytochrome P450 that is involved in the metabolism of the drug, and of course, we're particularly interested in an interaction with ethanol, which is one of the more commonly used drugs in society.

There's limited value from preclinical animal studies. All of us recognize this. What we learn from our animal studies often is whether or not a drug is a poison, whether or not it affects many tissues. We have, of course, in early development of a variety of compounds thrown some out when a definite

hepatotoxicity often associated with renal toxicity is found.

However, the disconnect between animal data and human data is disconcerting and disheartening, and enormous numbers of studies have amounted to naught in predicting whether or not a drug will cause hepatic injury once used in man.

What we're focusing on is the importance of events that are observed in clinical trials. The factors to look at this include the frequency and the pattern of the biochemical abnormalities, the number of patients affected, as well as the sex and age.

The maximum height of the abnormalities is important because that determines the strength of the signal that some problem may be present.

Of most importance on this slide is the next to the last line: the association of any biochemical elevations with any manifestations clinically that the patient has a liver disorder, and then the course of resolution following a withdrawal gives us some comfort that any change that occurs will be transient and will resolve over time.

I want to comment on one drug that we've studied extensively as an example, and that is isoniazid. Isoniazid, which is, of course, one of the

more widely used and useful drugs in the world, causes elevations in the ALT in ten to 20 percent of patients who receive the drug. Most of these begin within two months of starting treatment, and most resolve without the necessity of stopping isoniazid. We do not know the exact explanation for this, but we think these are adjustments of metabolism and the ability to use alternative pathways. But it is important that ten to 20 percent of patients on isoniazid have some elevation.

Severe injury with jaundice occurs in one percent of patients who receive isoniazid, and there is a marked increase in individuals beyond the age of 50 years. Patients beyond the age of 50 years who receive isoniazid have upwards to a two percent chance of developing a clinically significant liver disease, and across the board women are at greater risk than men.

Now, fulminant hepatic failure develops in ten percent of patients who develop jaundice. I want to point this out because this is the strongest signal that we look for in determining whether or not a drug is going to have major problems. As opposed to the situation in viral hepatitis, a condition in which jaundice is relatively common and deaths fortunately

relatively few, if a patient becomes visibly jaundiced, and for that means a bilirubin of greater than three milligrams per 100, you will have roughly a ten percent chance of mortality. This was proven in studies that Dr. Zimmerman and I participated in with the drug selacryn. It has certainly been true in a variety of other situations.

So the strong signal that we look for is the development of hyperbilirubinemia or jaundice.

Other factors in the isoniazid story were the continued treatment after the appearance of symptoms. If a patient developed symptoms, and often they're nonspecific with anorexia, nausea, malaise, and fatigue, but those patients who persisted in taking the drug after the onset of this change in health were those most likely to develop injury.

There was usually complete resolution in nonfatal cases, and isoniazid did not lead to a chronic hepatitis that continued beyond the time the drug was used. This is the focus of what I think you'll see in Dr. Riggs' presentation about tasosartan, and I think where our attention should be focused.

The major signals, the signals that will mean that a drug should not be released or will be

likely if released to cause a definite amount of trouble include the development of acute liver failure, known to some of you as fulminant hepatocellular necrosis. This is obviously a serious thing. Even one or two in a database is often enough to prevent the development of a drug.

The development of other symptoms, particularly anorexia, a bit of nausea, malaise, and fatigue, more difficult to assess, but these are also important in evaluating whether or not the drug is doing real damage to the patient or has the potential of damage to the patient.

I have focused on clinically apparent jaundice, and obviously the other serious manifestations follow on the syndrome of acute liver failure.

The intermediate signals are the ones that we can most easily measure, and these are the ALT elevations. We focus on ALT well beyond that of the AST. The ALT is the single most important test to us in evaluating.

Starting from the bottom, an ALT of normal to up to three times normal in an asymptomatic patient usually is of no particular significance. From three to five, greater than three to five times the upper

limit of normal, it does mean the possibility is there that there is some inflammation in the liver, but in an asymptomatic patient this should only heighten awareness.

Around five times the upper limit of normal, the awareness should be heightened even further and follow-up measures taken with rechecking in short order. Greater than eight times the upper limit of normal Dr. Zimmerman and I conclude is a significant signal and one that should lead to some action on the part of the clinician.

It's a quite minor signal to find any elevation. In fact, upwards to five percent of some drugs commonly on the market right now will have elevations that are slight within the first several weeks.

Please understand that these are inexact points that we're discussing here. We have to focus on symptoms. We have to focus on the ALTs. I put up what I do in the next three lines.

If I find a patient on a new drug with a greater than three times, I know that this patient has a minimal to moderate amount of inflammation. This doesn't mean liver disease in an asymptomatic patient, and I usually follow that patient up within a week or

two.

If I find greater than five times, it increases my awareness. I usually get a blood test within a day or two to see if a trend is being established with the line going up rapidly, and I think the prudent situation would suggest that a patient with greater than eight times the upper limit of normal, unless there is an absolutely compelling need for the drug, the agent should be withdrawn.

It's very important in trials, and you'll see with this drug a compilation of what happens to patients who are found to have elevated ALT levels and who continue to take the drug. I already mentioned in isoniazid there's a self-correction in a vast majority of these, and Dr. Riggs will show you a self-correction in a large number of patients taking the agent under discussion.

What you would like to focus on are the percent who resolve while remaining asymptomatic throughout while continuing the drug, suggesting alternative disposal. You'd like to know if there are any patients who progressed, and if so, progressed to what, and you'd like to know if there are a group of patients and how many who roughly stayed the same with a rather stationary but elevated level of biochemical

tests.

I wish to make a comment about a small group of patients in this database who started into the trial with an elevation of aminotransferases beyond the upper limit of normal, a real life situation. Fortunately there are relatively few in the database, but enough to allow you to look at those patients who began with a normal ALT versus those who began with a slightly elevated ALT.

There is no credible evidence that drug induced liver injury is more likely to occur in asymptomatic patients with no other risk factors, who have slight elevations of ALT. This is useful in the real life practice of medicine, particularly in complicated patients who are on multiple drugs, any one of which could have caused a slight elevation of the aminotransferase.

I will close with comments about monitoring. The monitoring of a drug is a very serious consideration whenever we find any abnormalities, and as I mentioned, we find abnormalities in almost every agent. We've had to face this in venues similar to the one we're in today regarding the drug tacrine for Alzheimer's disease, which has a quite high percentage of elevations of

aminotransferases. We've had to face it across a broad number of other agents.

We're interested in monitoring when there is a definite risk established. We're interested in monitoring particularly if we know the time course of the risk. We wouldn't want to focus on monitoring after three to six months if all of the risk occurred in one week or vice versa.

We're interested also in considering monitoring if there's a likelihood that the information gathered would lead to an action that would benefit the patient. In isoniazid, I would submit that it would not benefit the patient greatly if you stopped every patient who showed an elevated aminotransferase because the ten to 20 percent would have been stopped for a drug that is most useful.

However, if you had a monitoring and stopped only for a strong signal, there might be benefit, although it's not yet proven.

And finally, about monitoring. Monitoring is very difficult to carry out in a practice situation. Patients do not like to come in regularly to be monitored. Doctors do not like to recommend monitoring. I think I could point only to the statins to show you how few people follow the monitoring

recommendations for any of these large number of statins, which fortunately cause abnormalities of liver tests in several percent of patients, but never, almost never, cause any significant liver disease.

Monitoring is not generally very predictive. It gives more comfort to writing the recommendations than in the following of the recommendations, and the timing of monitoring, if such is chosen, must be based on observed abnormalities.

Dr. Riggs will show you the data related to tests of tasosartan. One of the reasons I was asked to present at this point in the discussion is to provide this framework. I think that you will see from this database that there have been no strong signals, not any of the major signals relative to drug induced injury from this drug.

You will see that there have been elevations of aminotransferases in a number of patients, and this is all in the background material and will be further presented.

A decision about how to follow this up we can discuss further if you so wish. I would think that most of the time, even an expansive database like this, we only learn enough to be prepared for what we see in the first year or two after a drug is on the

market, and possibly additional information that could be gleaned from follow-up outcome studies in association with what will appear spontaneously through the reportage mechanism in place will allow us to determine the ultimate safety of tasosartan.

Thank you.

CHAIRPERSON PACKER: Questions? John.

DR. DiMARCO: I enjoyed that presentation.

Could you just enlighten me a little bit about what's the mechanism of the injury that leads to the enzyme elevations?

DR. MADDREY: In most cases, we believe that drug induced hepatocellular injury is the response of a metabolite of the drug in a possibly susceptible individual. You noticed on the earlier slide I mentioned genetics. There are certain instances now in which rather clearly we can show abnormalities in one or more of the cytochrome P450s. We just don't have good tests yet.

We think it's not very much allergic. Allergic was a theory of the past and may be important in some drugs as a secondary phenomenon, but most drugs cause their injury by the effects on the cell of a primary metabolite.

CHAIRPERSON PACKER: Udho.

DR. THADANI: A couple of questions. One of the issues always is that you see these blips in a sense as, you know, your ALT will go up or AST goes up, but then it comes down without any concurrent other drug therapy. Obviously that complicates it.

What's the mechanism of blips? Is it the ultra regulation, liver hepatocellular injury occurs, then normalizes? Is there any biopsies on that or radionucline studies to look at that?

DR. MADDREY: The question about what about the transient blips is a very important one and one for which we do not have a complete answer.

I had the opportunity early in the statin experience to biopsy some patients who had developed statin increased aminotransferases, and from that we came to the conclusion that the statin elevations were actually a build-up of the HMG CO A, and that with time follow-up in those patients reveal very little liver disease, suggesting either a feedback that stopped the production of so much of it or alternative pathways to get rid of it.

Other suggestions that we have, but not strong proof, is that a number of hepatoprotectants, such as the augmentation of glutathione or the augmentation of sulfation or glucoronidation,

processes that might help, or the opening of an accessory pathway for management of an intermediate.

The important point is that we don't know. The second important point is for every ten that go up, most will come down with continued drug, and so we want to pick the signal for stoppage at such a level that we do the most good for the patient if the drug is beneficial and the least possible harm.

DR. THADANI: To take it further, sir, if you were to -- the drug is causing some hepatic injury. If you increase the dose, you would think the injury would get worse if the drug is directly responsible for some injury?

DR. MADDREY: If a drug is directly responsible for the injury and it's from a metabolite, increase in the dose would make it worse, and conversely, possibly decreasing the dose would make it better, although it's most of the time better if you're worried about a drug in a patient to stop it completely. Let everything get back to a baseline. Start again possibly with a lower dose.

DR. MADDREY: The other question, I think you showed different levels of threshold of stopping or continuing the medication especially when you're doing open label studies. I can see that, but a lot

of times we stop the medications two times or three times, ALT abnormality.

How much confidence one has that if you say the abnormality is three times and you continue the drug it won't be eight times or patient will not go into hepatic failure eventually?

I realize there's no case of jaundice or anything. What confidence of the studies out there to address this issue in any other double blind study, not particularly this drug?

DR. MADDREY: Well, the best evidence in this study, as I recall the information you're going to see, is two-thirds of the time when a blip occurred, continuing the drug was done safely and with a return to the baseline of the drug despite continued dose.

DR. THADANI: No, I realized. Say if it goes to three times and you stop the -- you do not stop the drug. You feel confident this patient will never develop hepatocellular injuries in the long run, not only for this drug; for any drug in particular?

DR. MADDREY: Well, let's go to another drug. I do not stop anyone below five times the upper limit of normal with isoniazid. I do not stop anyone with several other drugs. I don't want to mention

too --

DR. THADANI: Well, you know, isoniazid is a different example. You're treating tuberculosis. The patients are, you know, maybe -- I'm just -- other drugs than statins.

DR. MADDREY: The statins, there's no reason to stop a statin in an asymptomatic patient for an aminotransferase elevation less than five times the upper limit of normal, and in an important situation I would go to eight clinically because of the experience we have with the statins, with remarkably few liver diseases ever developing in those drugs despite quite marked elevations in some patients.

DR. THADANI: And how often, say, if it was five times? You'd do it every week, every four weeks or what's the threshold in practice?

DR. MADDREY: Dr. Lipicky would have to help me because he's written most of these. I was involved in the earlier statin labelings in which we went very heavy on monitoring and having backed off it based on experience over the years. Right now I think the recommendations are only once or twice within a year.

CHAIRPERSON PACKER: Rob?

DR. CALIFF: This is really an

interesting, difficult issue obviously, and maybe from your experience -- I doubt if you have empirical data on this -- but I'm interested in knowing. When there has been a drug which has been found to really have hepatotoxicity, what I want to try to understand is how much are you limited in seeing that if the studies are done with patients who are otherwise completely healthy versus patients who might have co-morbidities or be on multiple other medications.

Is it usually just an idiosyncratic thing where it shows up equally in otherwise totally healthy people, as in the more sort of complicated mix that one sees when a drug is out?

DR. MADDREY: We obviously have real trouble with that issue. We evaluate lots of cancer drugs. When that happens, it's hard to know. We evaluate AIDS drugs. Very difficult to know what to attribute in AIDS.

This is a relatively clean background situation. You're talking about patients with hypertension. Now, obviously in the real world this will be used in a number of co-morbid situations, including heart failure and lung disease and things like that. There will be background noise here.

I think this will be easier for us to

evaluate than a drug for oncology or AIDS. You just look at what the signals are. You count the number of problems and the seriousness of the problems, and you make a judgment.

We've been involved with the need to withdraw several agents. We are much more likely to favor withdrawal of an agent that is, say, a diuretic than we would be an agent that is useful in AIDS, and this is where the judgment of the agency and its consultants and the company come to play.

DR. CALIFF: Well, I'm trying to ask a slightly more complicated question than that. I mean, I understand that at face value this is a fairly straightforward problem because the studies have been done in clean patients, so to speak, but what I'm asking is how often is it that the problem actually shows up later because there is some sort of an interaction with commonly used therapies in a population or exacerbation of the underlying problem because of a portion of the population may have co-morbidities or other problems which were never looked at in the initial studies because the populations were clean and not representative of what we see in practice?

DR. MADDREY: I can --

DR. CALIFF: An example might be a drug like mobefrodil which has recently had some difficulties that were not picked up in the clean populations, not with regard to the liver, but --

DR. MADDREY: Yes. I can't -- of course, you're talking about something we could spend a lot of time and we do spend a lot of time thinking about it. I look at the release of a drug as just a point on the curve of the safety analysis. You've got a base here of upwards to 4,000 patients. These were, quote, unquote, relatively clean, even though some died. So that suggests some real sick people were in there.

Not a patient here died of liver disease or any manifestation of liver disease. I'd be interested in assessing a drug's true potential more after a year or so on the market looking at serious events.

What you're getting here is you've had comfort zone number one. It didn't do anything to animals. Comfort zone number two, this drug did not give you any of the major negative signals in your prerelease trials. You will then get comfort zone number three from a combination of what happens in a carefully done outcomes trial, plus what happens in the market.

We only picked up the co-interaction, the interaction of alcohol and acetaminophen after acetaminophen had been out a long time in the marketplace, and then we realized that that is an important interaction secondary to the use by alcohol and acetaminophen of a common P450, and that would not have been picked up because you would have excluded heavy drinkers had acetaminophen been evaluated the same way you're doing here or you would have made every effort to do that.

CHAIRPERSON PACKER: Rob?

DR. CALIFF: I mean, I guess that's actually my point. For later discussion I'm wondering if the studies included before release the real populations that we treat, whether we might pick up some of these things before they're unleashed.

I don't have the answer to it, but the acetaminophen example may be one. Maybe we shouldn't exclude alcoholics because we sure treat a lot of them in practice.

CHAIRPERSON PACKER: Lem.

DR. MOYE: Yeah. Dr. Maddrey, you helped me to gain some appreciation of the apparent lack of harm from some mild, isolated elevations in liver function tests, and though I can't quite say that an

isolated elevation in LFT is not such a bad thing, I really can't say it's a good thing.

But whether we believe in the risk associated with elevated LFTs, isn't an elevation in somebody's liver enzyme something the doctor should know about? I mean just because we think that -- I'm not saying that you meant to imply this -- but just because we believe that perhaps an isolated elevation in liver function test may be benign, still the doctor is better off having that information to integrate into his fund of knowledge and make some determination as to the suitability of continuing the patient on the medication. Do you agree with that?

DR. MADDREY: To an extent. I must tell you though that -- now, I'm a hepatologist, not a cardiologist, and I appreciate the difference --

(Laughter.)

DR. MADDREY: -- I must tell you that I would hate to stop ten to 20 percent of patients in isoniazid. I'd also hate to stop five to seven percent of patients who are receiving some nonsteroidals. Now, I'm not sure nonsteroidals are particularly useful drugs, but I can tell you that if you measured every few weeks after starting patients on nonsteroidals, you're going to find some elevation

certainly in the three range with many of the nonsteroidals available on the market today, and these are not leading to much in the way of liver injury.

I think you've got to decide what are you going to do with the information and is the signal strong enough and the risk great enough to warrant getting the information, and that's what your Committee will need to deal with.

DR. MOYE: Right. The doctor may decide that, in fact, he wants to adjust dose. She may decide that maybe the patient needs to be warned about alcohol ingestion for a given period of time. There's several options a physician has when confronted with an elevated LFT.

However, if what you said was true, and that is monitoring is very difficult to execute in practice, doesn't that -- shouldn't that make us concerned about drugs that require monitoring, if in fact the monitoring -- our comfort level is increased if monitoring is ordered, but if it's not executed, then perhaps the patients are even morbid?

DR. MADDREY: I'm not sure how far to go here. I would suggest the following thing. The minute a monitoring schedule is in the book, woe be to the doctor who does not follow it or recommend it. As

far as possible other consequences, one of which is financial and the other is legal, there are all kinds of implications here. I wouldn't pretend to know the answer to that question.

CHAIRPERSON PACKER: Okay. There are a number of the members of the committee who want to speak.

JoAnn.

DR. LINDENFELD: Dr. Maddrey, I'm interested in your ideas about the use of two drugs that have similar modest elevations in these liver function tests. What would be your prediction, and thus your recommendation, with two drugs that have these elevations?

DR. MADDREY: We run into this all the time, and I'm sure you do, too, since you use multi-drug therapy. You play the odds. You look at the one known to have the most frequent abnormalities.

For example, I don't worry much if I see a random something early in the course of a statin, but I might worry a great deal if I saw someone who had started on valium, an extraordinarily safe drug, if that person had an elevation. If the person were taking valium and a statin, then I would blame it on the statin, and I would make my mind up as to what I

was going to do just on clinical judgment.

DR. LINDENFELD: Just slightly more complex than that, what would your recommendations be for follow-up when you're using a drug that has this level of liver function elevations with another drug that we know commonly does, for instance, a statin? Would you recommend more frequent monitoring when both drugs have this problem?

DR. MADDREY: Yes, I would.

DR. LINDENFELD: And sort of could you give us a rough idea what that would be when you have two drugs in this one to two to three percent range?

DR. MADDREY: No, I can't. I'd have to go drug by drug. If a person had a fungal infection and was receiving a conazole and was also receiving this one, two drugs, the conazole is a well known cause of liver abnormalities. It would almost have to be drug specific, depending on what I know about the metabolism of the various drugs.

I become particularly interested in drug-drug interaction when it's known there is a common P450 subspecies involved in metabolism.

DR. LINDENFELD: So, for instance, with the statins and this drug you would be a bit more concerned?

DR. MADDREY: No, I don't think so. I wouldn't be particularly concerned about statins and this drug based on what I know, but I don't know at all about this.

CHAIRPERSON PACKER: I'm totally confused. Since almost every drug that we know of can cause liver function abnormalities, increase in transaminase, and if one assumes that if you use two drugs together your risks are greater than one drug alone -- and I'm not certain that's true, but I think you sort of implied that it might be true --

DR. MADDREY: Could be additive, and it could be interactive.

CHAIRPERSON PACKER: And one would imagine that given the extremely large number of drugs that most people we see take, for better or for worse, that patients might -- we might end up recommending that patients come back to physicians every week or two forever.

DR. MADDREY: Yes.

CHAIRPERSON PACKER: But what you've also emphasized, it doesn't matter what we recommend because they won't do it anyway.

(Laughter.)

DR. MADDREY: That is the truth.

(Laughter.)

CHAIRPERSON PACKER: Well, it's glad to know that we're useful.

Ray.

DR. LIPICKY: I'd like to do three things, I think, maybe only two. One is that there is someone as guest of the Committee that was not here at the time that introductions were being made, who is Dr. Lionel Rabin from the Armed Forces Institute of Pathology, who's sitting in the front center row next to Dr. Stevenson, and he might be called upon. He knows a lot about the liver and what's good for people who have liver troubles.

And then the second aspect is that I think I want to address something Rob brought up, and although our experience is really relatively small, and this is an experiential statement I want to make and it's limited to labetalol, dilevilol, cellocrin, each of which is a well recognized hepatotoxin that causes significant clinical disease.

The underlying status of the patient, that is, whether they were sick or non-sick or complicated or not complicated or anything else, in those three circumstances had absolutely nothing to do with whether they got serum enzyme elevations and/or

developed clinical illness.

So I don't think that the degree of sickness of people is likely to be important based on those three anecdotal experiences.

And I guess the last thing that I want to ask you a question is the kind of guidance that you were laying out seems to make a great deal of clinical sense. How many times have you sat down with the data available within one NDA, applied those rules, and figured out whether you were right or wrong post marketing? Once, twice, zero?

DR. MADDREY: I think we try to apply these rules generally back to each NDA. Dr. Zimmerman could comment. We applied this back to the cellocrin NDA data. We applied this back in another way to the benoxiprofen NDA data. So we have done this, and --

DR. LIPICKY: So that's two.

DR. MADDREY: That's two. I think that --

DR. LIPICKY: But you did that after you knew that these were hepatotoxins, right?

DR. MADDREY: The reasons that we were concerned though were not ever the aminotransferases alone. It was --

DR. LIPICKY: I understand.

DR. MADDREY: So we never --

DR. LIPICKY: Okay. So --

DR. MADDREY: -- put these rules back.

DR. LIPICKY: So from a prognostic point of view, you've never tested whether these notions really work?

DR. MADDREY: No.

DR. LIPICKY: Retrospectively they seem okay.

DR. MADDREY: Retrospectively, seem okay.

DR. LIPICKY: Okay. Then just one other question, I guess. Well, never mind. I'm done.

CHAIRPERSON PACKER: Before we proceed further, could we ask Dr. Rabin to come to the microphone? Do you have any insights for us on any of the issues?

I think that we are -- as you're coming to the microphone, let me say that we, I guess, do labor under the advantage or disadvantage of largely being cardiologists, and hepatologists and cardiologists are different, and I guess what we're hearing is that where some elevations of transaminases, perhaps the majority of elevations of transaminases affect hepatologists like first degree heart block affects cardiologists.

A hepatologist faced with a concept of

first degree heart block would go crazy because of the word "heart block," but a cardiologist faced with a first degree heart block might not. We might say, "Well, we see this, and we see this a lot, and it usually doesn't mean very much unless it gets more severe or it becomes symptomatic."

So the analogy here isn't totally crazy, and we get sensitized because transaminases aren't something we are comfortable with, just like heart block isn't something that a hepatologist is comfortable with.

So we're in an educational process right now, and we should try to make the most of it.

Dr. Rabin.

DR. RABIN: The difficulty in resolving some of the issues which are being raised. Very often minor or mild elevations in liver function test abnormalities or liver enzyme abnormalities sometimes do indicate a certain level of liver injury, and there are many times when there is no significant damage as far as the liver is concerned.

If the liver biopsy is the gold standard for assessing how much damage might be present or whether any change is significant, then the question arises: at what point do you recommend getting a

liver biopsy on a patient where the transaminase abnormality is two times greater than normal or five times greater than normal and so on?

At this point it is very difficult to make any assessment just based on laboratory findings and some of the nonspecific, general -- nonspecific symptoms which a patient might experience whether he's on one drug or several drugs.

At this point I cannot make any assessment as to the safety or to the predictive changes which might follow, but at least where there is a significant abnormality in the liver enzyme and related tests, I believe that there comes a point where the problem has to be resolved by a morphological examination of liver tissue obtained, which would be obtained by performing a biopsy.

I don't know whether that answers any of your questions or concerns with regard to what has been presented already.

CHAIRPERSON PACKER: Barry.

DR. MASSIE: Dr. Maddrey, you mentioned that the bilirubin or rises in bilirubin to three do provide some prognostic significance. Is there a lower signal in bilirubin that either would prompt a biopsy or be concern? Should we be looking rather at

maybe the ALT is the signal to think about other things, but for instance, if somebody's bilirubin starts off at .4 and rises to 1.3, is that a more reliable predictor of subsequent events than ALT going up? Is that something else that can help us?

DR. MADDREY: My colleague.

DR. ZIMMERMAN: My name is Zimmerman.

As Dr. Maddrey pointed out, a bilirubin elevation in the patient who has hyperenzymemia, hypertransaminasemia becomes important.

As he also pointed out, there are two types of liver injury. In cholestatic injury, you may have bilirubin elevations with minor elevations of the transaminase that are meaningful with regard to liver injury.

On the other hand, in patients with hypertransaminasemia, that's a first clue, and bilirubin elevations at that point, in the patient with elevated transaminase, becomes significant with regard to real liver injury.

So three or four milligrams are clearly less threatening than 20 milligrams, and certainly the higher the bilirubin, the more threatening, but once the elevated transaminase is in the range of eight, ten, 12 times the normal and bilirubin elevation, it

becomes meaningful, and lack of it is reassuring in that regard.

Does that answer your question?

DR. MASSIE: Well, actually I'm looking for something more sensitive, and it may not be available to us. Three, above three there's a ten percent change of going on to liver necrosis. To me that's --

DR. ZIMMERMAN: Sensitivity is provided by transaminase elevations to such a degree that they reflect minor liver tickling rather than liver injury, and it's only when the levels get high enough that they --

DR. MASSIE: Well, what about a bilirubin that's less than three where the risk is already substantial, but having gone up from normal? In other words, if the ALT goes up threefold --

DR. ZIMMERMAN: Probably any bilirubin elevation associated with a significant transaminase increase has some significance, but then the higher the value, the more meaningful.

DR. MASSIE: I understand the higher. So if it goes up to 1.5, but it was normal beforehand in the presence of an ALT, that might be a better reason to be concerned than the ALT going up fivefold or even

eightfold without a bilirubin rise.

DR. ZIMMERMAN: Yes. It's like comparing a BR interval of one-tenth of a second prolonged.

CHAIRPERSON PACKER: Let's see. We've got Ileana.

DR. PINA: This has actually been very instructive in how to look at these liver abnormalities, and if you're a clinicians and you're going to start a drug into one of these higher risk groups, you mentioned gender, female, said particularly over the page of 50, the two percent versus a one percent.

After you've started somebody, the drug is working. Whatever your achieved endpoints have been are there. When do you get the first lab test? And if that lab test is normal and there are no ALT elevations, do you stop right there? Do you do it again in a month on a practical sense?

DR. MADDREY: Well, that is a practical question, and I think that depends on the drug in question. For example, with nitrofurantoin and related drugs, I think you should check the patient even out to a year. On many other drugs, all of the injury we might expect to see would occur in the first three months. So that's where I think the guidance

that the agency gives through the approval process tells you what to do.

Some drugs you should never check. I would see no reason to ever check anybody on a benzodiazepine at all ever. There's just been too little background noise at all.

Ray?

DR. LIPICKY: I have two questions I'd like to ask. One is sort of correct my clinical impressions, I guess. I have in my head that liver problems that could be characterized as cholestatic, bilirubin elevations, alkaline phosphatase elevations in the absence of transaminase stuff, is basically not much to worry about.

On the other hand, if you have enzyme elevations and you don't have bilirubin and alkaline phosphatase, then you are really polishing off cells, and you should worry.

Now, where has my clinical education gone wrong?

(Laughter.)

DR. MADDREY: No, it's not gone wrong, but just as all hepatocellular injury is not the same, all cholestatic is not the same. Benoxiprofen was pulled, and it was a cholestatic drug, because it had severe

injury potential, whereas most chlorpromazine jaundice, which is cholestatic, will go away. It might take months and months to go away. Hepatocellular, the same thing.

I think the worst of everything here is a strong clinical signal associated with a markedly high aminotransferase. You usually find the aminotransferase after you recognize the strong clinical signal.

DR. LIPICKY: Right. Okay. Fine. And then the second thing that I wanted to ask is I want to make an assertion and see if you agree or disagree.

In our experience with labetalol, dilevilol, and whatever that other one was, the thing that was convincing was, indeed, a fairly large number of people who got clinically ill

DR. MADDREY: Yes.

DR. LIPICKY: And the number of people that had indications that might lead you to think they might get ill were fairly numerous, but not very much. I mean they had little enzyme changes.

So if one figures that the incidence of clinical disease will be, say, ten percent of those people who, in fact, develop enzyme abnormalities, then basically to get this database of a lot of people

who have clinical disease, one basically would need to be in the 10,000, 20,000 range to be able to look at that.

So is it your suggestion -- well, I guess there are two questions I'd like to ask. One, whether you agree with what I've just said, and if you do, then I want to follow it up.

DR. MADDREY: I agree with most of it.

DR. LIPICKY: Okay. Then let me follow it up.

So is it your suggestion then that the American public paying for a drug to treat their hypertension should, in fact, provide the database by finding this large number of people that have clinical illness, or is that something that should occur before the American public pays the price?

DR. MADDREY: I think that decision is what is up to this panel based on what you think about the strength of the signals.

DR. LIPICKY: Okay.

DR. MADDREY: I saw nothing in this database to make me think there's a strong enough signal to warrant mandatory monitoring.

DR. LIPICKY: Okay.

DR. MADDREY: However, as I pointed out,

I view the approval of a drug as just a point on the curve and would be very interested and would easily change my opinion in the first year or two after release as we've had to do with other drugs recently, depending on whether new signals appeared because of the size of the database.

CHAIRPERSON PACKER: Ray, the question is a very critical one. Obviously that's what this committee meeting is all about, but given the enormously high frequency of LFT abnormalities, it is sort of a general drug phenomenon?

If one concluded one needed more before approval, it would not only affect the review of this drug, but would greatly increase the requirements for a safety database for everything that agency sees because so many drugs have this predilection.

DR. LIPICKY: Where is the data that supports that statement, that so many drugs have that predilection? It seems to me that within the NDA databases that we've shown you in the stuff that we sent out that, in fact, this seems to come out of that database as having more of a signal than usual, and that is, in fact, what brought it here.

The usual signal is something that's easily manageable, and it sort of gets at what Rob is

going to get at probably later in the game, but that is we really do look at drugs of this nature that are approved on the basis of a surrogate without looking at the real efficacy because we've not agreed tasosartan is effective. We just say it's an antihypertensive.

And we certainly do not want to have things go out that have one in 1,000 incidence of serious stuff, but if we're only requiring a 2,000 or 3,000 patient database, we obviously can't make a statement about things that are one per 1,000.

So we look for signals very carefully, and when it appears that a signal might be there, we, like you are now, are always in Never Never Land.

CHAIRPERSON PACKER: Okay. Marv.

DR. KONSTAM: I just wonder if we could ask Dr. Rabin to come to the microphone again and would comment specifically on the scheme proposed by Dr. Maddrey and whether he agrees with it with regard to the level of ALT that's causing concern.

I interpret his presentation as indicating that until you get to eight times or at least five times the upper limit of normal of ALT you really would not be terribly concerned at least to the point of discontinuing a drug, if I interpret it correctly.

I wonder if you could say if you agree with that or whether I've misinterpreted it.

DR. RABIN: I don't know whether I can be in agreement with that because very often it's very difficult to make a correlation between the actual numbers of the abnormal laboratory findings and what we see when we examine a liver biopsy to identify liver damage. It is not uncommon that there is poor correlation between the laboratory abnormalities and what we find morphologically when examining a liver biopsy.

DR. KONSTAM: Well, but to deal with this data set, I guess one of the signals that we have here is that there is a certain number of discontinuations, and those discontinuations are based on ALT elevations in part, and I guess one of the questions that we're going to have is whether those decisions were made rationally by the investigators

And so I think it's worth, you know, just honing in on whether or not, you know, we agree with Dr. Maddrey's scheme, that it really doesn't make much sense based on what we know to necessarily discontinue a drug based on a three times upper limit of normal increase in ALT.

DR. RABIN: Well, I'm just wondering

whether it should be a matter of clinical judgment as to whether a clinician in care of a patient, finding abnormal liver enzyme tests, liver enzyme and related tests, at what point should there be confirmation or an attempt at confirmation by obtaining a biopsy and assessing any morphologic changes, and whether this can be correlated with the finding.

The name of the game really is clinical pathologic correlation, and in many instances or I might say it is not uncommon that clinical pathological correlation can be quite difficult.

CHAIRPERSON PACKER: Dan.

DR. RODEN: Thanks, Milt.

I had a couple of questions perhaps for Dr. Maddrey. I am still confused about the mechanism of elevation of transaminases. Is that a sign of hepatocellular injury?

Can I just get a yes or a no?

DR. MADDREY: Yes, I think so.

DR. RODEN: Okay.

DR. MADDREY: I think that if you have elevated aminotransferases at the 3X range, you rather definitely will have at least minimal inflammation. I believe below that you might find not anything at all.

DR. RODEN: But it means cells are releasing their enzymatic contents?

DR. MADDREY: It means that aminotransferases, which are inside the cell and supposed to stay there, are now for some reason outside the cell. The cell has either leaked or one or two have exploded. That's what it means.

DR. RODEN: So it seems to me there are two causes for elevated transaminases. I mean, one is that they're being released. The other is that they're not being eliminated at the same rate.

So how are transaminases eliminated?

DR. MADDREY: As all proteins. I forget the half-life of them, but it's pretty quick. So they stay in the liver cell normally. There's a little bit of transaminase in everyone.

DR. RODEN: Right.

DR. MADDREY: Just the normal turnover. This just suggests there's been an accelerated release. There's no evidence there's a block in elimination.

DR. RODEN: Okay, and then just for my own interest, can you tell me which system has genetic defects that cause liver disease?

DR. MADDREY: Debrycoquin, a drug that

many of you --

DR. RODEN: No, that doesn't cause liver disease though.

DR. MADDREY: A debrycoquin?

DR. RODEN: No.

DR. MADDREY: Yeah. Yeah.

DR. RODEN: Having spent the last 20 years of my life studying it --

DR. MADDREY: I thought the P --

DR. RODEN: I don't think debrycoquin -- the debrycoquin polymorphism is associated with liver damage.

DR. MADDREY: I'm going to turn to my colleague here.

DR. ZIMMERMAN: You're right. Debrycoquin doesn't cause liver disease, but it's a useful marker for P450 2D6.

DR. RODEN: Right.

DR. ZIMMERMAN: Now, P450 2D6 fails to inactivate peraxoline maleate, and peraxoline maleate leads to liver injury. So people who are defective in P450 2D6, an item that you identify with debrycoquin now develop the liver injury.

May I also comment on Dr. Rabin's appropriate comment? He's quite right that in a

smoldering disease like Hepatitis C correlation between the biochemical markers and injury are poor.

That's quite different from drug injury that occurs during the evolution of use of the drug. There the correlation is really quite good, as has been pointed out by Dr. Maddrey. You know what is true when there is twofold elevation, by and large, and when there's tenfold elevation. So the correlation is much better there.

So the truism you heard is right, but it doesn't apply to the setting of drug induced injury.

DR. RODEN: It seems to me the problem is that we don't really -- I mean we're using -- the evaluation of this drug is going to involve the evaluation of what Rob Califf almost certainly will call a surrogate endpoint for efficacy, and we're being asked to evaluate the other end of the risk balance equation using a surrogate endpoint for toxicity.

And people around this table have spent a lot of time thinking about surrogates in one way or another, and it seems to me this is not a very well understood surrogate, and that it might be a marker, and it might not be. That's not a comment that needs an answer.

CHAIRPERSON PACKER: John.

DR. DiMARCO: We've heard a lot about single point in time estimates of enzyme elevations. This is a drug that might be used continuously for years and years and years. What's the effect of, you know, what you said is a continuous liver injury, even if it's very low level? Do we have any idea what a continuous elevation at three times normal for 15 years would product?

DR. MADDREY: Well, I tried to pass that one off to Dr. Zimmerman, and he wouldn't receive it because we just don't know. We just don't know.

CHAIRPERSON PACKER: Let me try to, John, follow up on that.

If someone had an increase of three times normal and because recommendations for monitoring are not frequently followed, the possibility of a drug induced or drug associated increase in LFTs that would go on for months is not a crazy idea. It could happen.

And I guess what you're saying is because of the way the drug trials are constructed and carried out, there isn't a whole lot of experience knowing what happens under those circumstances. Is that fair?

DR. DiMARCO: Because when you're really

talking about it is that these enzyme elevations cause -- are a marker of continuous or of liver injury. If it's continuous, the liver eventually might not be able to compensate. Is that correct or can the liver always compensate?

DR. ZIMMERMAN: There are a number of phenomena that interplay in this. First of all, acute liver injury, hepatocellular damage of importance, will either occur during the first few months of taking the drug or not occur at all.

On the other hand, chronic injury does occur with some drugs, probably involving more than just some minor injury being prolonged, but probably an immune response to it because a form of chronic hepatitis does occur with some drugs, and there are characteristics that are those resembling autoimmune disease.

So the answer to your question is chronic injury can occur in some settings, but probably reflects more than just a little bit of elevation going on for a long time, but the factors that affect that are not at all clear.

CHAIRPERSON PACKER: Ray.

DR. LIPICKY: Can you give me a feeling for what the enzyme elevation means? That is, let's

say one percent of the liver cells suddenly drop dead. How high would that make the enzymes go?

Let's say ten percent of the liver cells suddenly drop dead. How high would that make the enzymes go?

DR. MADDREY: No, we can't do that with any specificity. Some of the highest we absolutely see is in a cardiovascular situation or a patient with chronic congestive failure who develops an arrhythmia and will show amino transferases in the may thousands that will go down rather rapidly.

I think in that situation it shows the cells are stressed and have released a lot of enzyme. It doesn't necessarily mean, of course, they've all died because we get levels in that situation not dissimilar to what we get in fulminant hepatitis.

I don't think there's a very good correlation between the number of cells damaged and the height of the enzyme in any clinical setting that I can much think of.

DR. LIPICKY: So this isn't sort of like for myocardial enzymes where, you know, nothing comes out of the cell unless the cell is dead?

DR. MADDREY: No, this is just a market. A cell can leak --

DR. LIPICKY: And we're, in fact, mass --

DR. MADDREY: A cell can leak enzymes, we think, and remain viable. Does it shorten its life? Who knows? I mean we don't follow individual cells.

This is just a clinical surrogate trying to pick up what I would consider a relatively weak signal, but a signal not to be denied after a certain level, and we have picked this 8X just based on clinical experience.

CHAIRPERSON PACKER: Udho.

DR. THADANI: I think Milton made a comment about a parenteral. As a cardiologist when I'm attending on the intensive care unit, I see these enzyme blips all the time, patients with unstable angina, heart failure. It's very rare that we ask a hepatologist to come unless the levels are very high or a patient is jaundiced.

Now, the difficult sometimes one has is when in these trials you stop it because you're watching the patient three times normal. The question came up, and as you alluded, bilirubin probably is an important marker.

So if you're saying you're not going to watch the patient and once the bilirubin goes up it could be risky, and in the database looking at a lot

of A II blockers, one doesn't find hepatitis evidence as with other drugs. Does that give you confidence that it may not occur, but the fact that drug has been stopped it could occur maybe in patients who are sensitive to some hepatocellular injury, that eventually they may get a glubin (phonetic) increase or can you be sure they will never get it?

DR. MADDREY: I just can't give you a solid answer to that. I'd have to evaluate it situation by situation in a clinical setting.

DR. THADANI: See, the question becomes relevant even in the post, you know, after the drug approval. Some of the briefs (phonetic) have been given. Maybe one in 700 will get some hepatitis based on elevated bilirubin and the liver injury, not cholestatic type, which is a different issue.

And the question then comes that you need thousands of patients to even address that, and we have no way of doing that.

And the other problem is when the open label studies, when I look at it, a lot of patients are on other drugs, too. So how one can be sure in the open label studies the drug in question is causing it or other drugs' addition might be making it, that becomes very difficult at least when I review it.

DR. MADDREY: Yeah.

DR. THADANI: I just want your comments because you suggested in post marketing you should follow it, but post marketing we don't control other drugs at all. Half the times patients don't even tell you what they are taking over the counter. They might have had a flu-like illness or something which could bump your enzymes. How do you know it's a drug, not the other thing going on?

DR. MADDREY: You don't, and you use a weight of evidence approach. In a situation such as this, you probably will have patients only on two or three of the drugs, not ten or 12. You rank those drugs by what you know. You look at individual situations. You look at the strength of those clinical signals that appear, and then you just come up with a judgment, and you hope you've made the right one.

CHAIRPERSON PACKER: Dr. Maddrey, before you sit down, you mentioned that symptoms are an important determining of your level of worry. Just to clarify, you mentioned anorexia and nausea and malaise, fatigue. Obviously jaundice would be in that category. How about fever?

DR. MADDREY: Fever is not very important

in most drug induced liver injuries. Right upper quadrant abdominal discomfort, not as often pain as a dragging sensation that just something's not right occurs, too, but actually fever is not important with most drugs.

There are a few, halothane being an example in which fever has been a major thing. Some of the methyldopa cases had some fever early on, too. There have been a few other fevers, but most drugs we see do not produce fever at the time of the liver injury.

CHAIRPERSON PACKER: Is fever a symptom? In other words, when you talk about --

DR. MADDREY: If you get hot and that leads to a measurement of it, it crosses over there.

CHAIRPERSON PACKER: No, no, I'm sorry. In determining the degree that the drug has passed a clinical threshold --

DR. MADDREY: No.

CHAIRPERSON PACKER: -- of the symptoms, is fever one of them?

DR. MADDREY: No, it is not. No, fever to me would suggest some kind of a complication, but not necessarily a liver complication.

CHAIRPERSON PACKER: Okay. Thank you very

much.

We've had an important general discussion about the issue of drug induced liver function abnormalities. The Committee has been provided with a summary by Dr. Fenichel of the agency's experience with selected agents as it relates to their predilection to cause liver function abnormalities or hepatotoxicity, and the summary is very instructive in the sense that it appears as if much of what we learned during drug development may or may not predict what happens in the course of long term therapy.

There have been many examples which are listed here, including, I think, perhaps one of the more striking examples which is tacrine, which caused no liver function abnormalities or hepatotoxicity in animal studies, caused a lot of liver function abnormalities in the clinical trial development, but apparently has not caused much of a problem at all in terms of hepatotoxicity post marketing.

On the other hand, there are the reverse patterns as well, and Dr. Fenichel, as well as many other members of the agency, are here as resources to the Committee to talk about any of these other experiences as the committee requires as the discussion unfolds.

Now to the specific example of tasosartan. Dr. Riggs.

DR. RIGGS: Detailed analyses of all data concerning liver function test abnormalities in the tasosartan development program have been performed, including preclinical and clinical data. There were no laboratory or histopathological findings in our preclinical toxicology studies, and this is also the conclusion of the FDA reviewers.

Consequently, I will not be presenting preclinical data. However, Dr. Gerald Fisher, head of our Drug Metabolism and Toxicology Group, is available to answer questions from the panel.

Highlights of the important analyses of the clinical data will be presented in detail, including a comparison of the findings with losartan as published in the literature.

Definitions used during the analyses of the LFT data are summarized in this slide. The data were analyzed separately depending on whether the patient's baseline was normal or abnormal. The level of potential clinical significance for transaminase values was three times upper normal limits for normal patients and three times baseline for patients who had abnormal baseline values.

This was based on the 1979 publication form the Fogarty conference and the recommendations of our consultants.

In this presentation, patients' abnormal transaminase values are defined as resolved if these parameters return to less than two times upper normal limits or baseline.

Discontinuation due to LFTs was counted only if this was the primary reason for discontinuation specified by the investigator on the case report form.

For simplicity of presentation, I will combine data for the Phase 2 and 3 controlled and open label studies, in contrast to the detailed breakdown of data shown in the executive summaries provided to members of the panel.

In the Phase 2 and 3 studies, 4,409 patients treated with tasosartan monotherapy or combination therapy had at least one on therapy laboratory evaluation. Of these, 1.8 percent had a potentially clinically significant transaminase elevation.

Of the 3,776 tasosartan treated patients who had normal LFTs at baseline, 1.9 percent had potentially clinically significant transaminase

elevations.

This combined analysis of all Phase 2 and 3 studies represents the worst case scenario since it includes patients from both double blind and open label studies, plus patients treated with monotherapy or tasosartan plus hydrochlorothiazide. Thus, it more closely reflects a real world experience.

Before I discuss the incidence of discontinuations that received the focus of the FDA review, I would like to discuss those patients who did not discontinue despite LFT elevations. These patients are an important group to examine because in contrast to patients who discontinue study drug, their fate is known and is not open to speculation.

In fact, the majority of patients with transaminase elevations in our clinical program did not discontinue the study. Forty-nine patients in controlled and open label studies with potentially significant elevations who remained in the study, the laboratory values returned to normally in fully two-thirds of the patients, while those patients continued treatment with tasosartan.

This occurred even with maximum elevations as high as nine and a half times upper normal limits in the controlled studies and over ten times upper

normal limits in the open label studies.

In the remaining one-third of patients with elevations who remained in the study, the patients were entirely asymptomatic and their LFTs returned to normal at the end of the study when tasosartan was discontinued.

An example of one such patient who had resolution on therapy is shown in this graph. This patient was treated with 300 milligrams of tasosartan for four weeks in Protocol 201. At three weeks of therapy, the patient's ALT increased to nine and a half times upper normal limits. The patient was asymptomatic and remained on treatment.

Both the ALT and AST had resolved to normal limits prior to the end of the double blind treatment period as shown by this line.

Considering the total group of 83 patients with potentially clinically significant LFT elevations, no patients had clinical sequelae, such as significant hyperbilirubinemia or jaundice, hospitalization or drug related deaths due to liver failure.

As I've previously mentioned, one of the reasons that we were asked to present tasosartan to the Advisory Committee was because of the FDA's

concern about the discontinuation rate due to LFTs in the tasosartan program. This was felt to represent a risk with tasosartan not seen with other angiotensin II antagonists. The next few slides will address this issue.

In the control trials, ten of 2,550 patients, .39 percent, who had at least one on therapy laboratory evaluation, discontinued because of LFT abnormalities. In all ten cases, LFTs returned to normal.

In the open label studies, 45 of 1,859 patients discontinued because of LFT elevations. In 43 patients the laboratory values resolved. In two cases the last laboratory value was less than three times upper normal limits, and no further follow-up is available since both of these patients were placed on alternative antihypertensive medications that can cause LFT abnormalities.

During the review of our NDA and in the background material provided for this meeting, the FDA has compared discontinuation rates seen in our program with those of other antihypertensive dossiers. We believe that this across-dossier comparison is probably not valid for the following reasons.

There is a marked difference in the

frequency of laboratory sampling in our program compared with others. The duration of studies was longer in the tasosartan program for the controlled trials.

Also, we did not prespecify the rules for discontinuing patients due to transaminase abnormalities.

The next few slides will illustrate the impact of each of these factors. Since we did not prespecify the rules for discontinuing patients due to laboratory abnormalities, the discontinuation rate in our program was a reflection of the investigator's judgment, experience and training.

For example, one European site was responsible for 30 percent, or three of ten patients, discontinued for transaminase abnormalities in the controlled trials. One of the three patients was discontinued for values that were only two times upper normal limits.

It should be noted that despite accounting for approximately one-third of the dropouts, this site enrolled only two percent, or 51, of the 2,550 patients in question.

In trying to put the LFT data into perspective, we also examined the FDA medical reviews

for losartan and valsartan to determine the designs of their studies. In the tasosartan program, laboratory samples were collected much more frequently than in either the losartan or valsartan programs. The impact of the difference in sampling frequency is significant and is shown in the next two slides.

This patient graph was shown to you previously. The patient had a nine and a half times upper normal limit elevation in ALT during tasosartan treatment in Study 201. This transient rise and fall in the transaminase values was detected by the frequent sampling schedule shown at the bottom of the graph.

This is a simulation of data for the same patient in the previous slide using a different sampling schedule, the one used in valsartan Study 10 shown at the bottom of the graph. With this regimen, the patient's transient rise in transaminase values would have been completed missed. In fact, because of the transient nature of LFT elevations in the majority of our patients, approximately 30 percent of the elevations would have been completely missed by a less frequent sampling schedule.

The impact of the frequency of laboratory sampling on the incidence of transaminase elevations

is shown in this slide. In the controlled trials with tasosartan, 32 patients out of 2,550 on monotherapy or combination therapy had elevations that were of potential clinical significance or an incidence of 1.3 percent. Since 12 of these patients had resolution of the abnormal labs on therapy and prior to the end of double blind treatment, they would have been missed by a less frequent lab sampling regimen, such as the one used with valsartan. Thus, the incidence would have decreased to .8 percent.

In addition to the sampling frequency, the length of some of our studies was longer than in the losartan development program. As shown here, no losartan controlled studies had a duration of treatment longer than 12 weeks. This is in contrast to two of our controlled trials that lasted longer than 12 weeks.

The discontinuation rate in our program was affected by study duration. Half of the discontinuations in the controlled trials occurred after 12 weeks of therapy. Had our clinical program included only shorter studies, as did losartan and valsartan, the tasosartan discontinuation rate would have been lower. Therefore, had our studies resembled those of the valsartan program, 50 percent of the

discontinuations due to LFTs in the controlled trials would not have occurred, and this would have left us with an overall discontinuation rate of five of 2,550, or an overall incidence of .2.

This figure might not have raised a reviewer's concern since the valsartan discontinuation rate of .16 percent.

If one completed Table 2 from the FDA background package using data from the tasosartan controlled trials which was similar to other programs, that is, excluding dropouts after 12 weeks as shown in the highlighted row at the bottom here, the incidence of discontinuations due to LFTs is similar to other programs, especially that of ysartan.

Study duration also has an impact on the overall incidence of abnormalities. For example, in the tasosartan controlled trials, 11 of 20 cases of transaminase elevations occurred in patients who were treated with tasosartan monotherapy for more than 12 weeks. If the program had included only controlled trials of shorter duration, these would have been missed, and the incidence rate would have been even lower.

Remember that we have performed all of these post hoc analyses to establish the well known

fact that comparisons across different databases are subject to methodologic bias.

After a review of the NDA database, we felt comfortable with performing post NDA studies using the laboratory sampling frequency that was used in the valsartan program. These post NDA studies, Protocols 328 and 330, are the studies demonstrating superior efficacy of tasosartan over losartan that I showed you previously.

While tasosartan was shown in these two studies to have superior efficacy, we believe that tasosartan is similar to losartan with regard to safety. This is based on a review of the literature, as well as on our own post NDA studies.

When tasosartan and losartan were studied under the same conditions, the incidence of potentially significant ALT elevations was similarly low in both groups. In fact, only one patient who was treated with losartan, 100 milligrams, had an ALT elevation that was greater than three times upper normal limits. There were no tasosartan patients with greater than three times upper normal limits elevations in these two studies.

Furthermore, no patients discontinued because of ALT elevations because they did not have

the opportunity.

Recent reports from the literature have expanded the knowledge of losartan's impact on LFTs. A recent review of 16 double blind and four open label studies by Dr. Weber reported that elevated ALT was the most common laboratory adverse event reported in these studies. It occurred in 1.9 percent of losartan treated patients, an incidence that is similar to that seen with tasosartan.

In response to a case report that appeared in JAMA in 1997, Merck responded with a letter that described the following statistics on post marketing experience with losartan. Approximately two million patients have received losartan treatment during the past three years. Only 80 post marketing reports of liver function abnormalities have been received to date by Merck. Thus, while LFT abnormalities have been associated with Losartan in the marketplace, the incidence is low, as has been the severity.

This supports the fact that as a class the angiotensin II receptor blockers have an excellent safety profile, although occasional laboratory abnormalities may be reported. Based on our data, we believe that tasosartan performs like other members of this class.

In summary, there is no evidence of drug related hepatotoxicity in the tasosartan preclinical studies. In the clinical database, 59 percent of patients with elevations did not discontinue, and in two-thirds of these patients the laboratory findings resolved on therapy. No patients with elevated LFTs experienced clinical sequelae associated with these laboratory findings.

When losartan and tasosartan are studied under the same conditions, the incidence of transaminase elevations associated with both drugs is similar.

In conclusion, we believe that tasosartan is safe and manifests no greater evidence of hepatotoxicity than other marketed agents. Wyeth-Ayerst is confident of the safety of tasosartan. We are planning to perform a large outcome study once the drug is approved. This study will answer important questions about the morbidity and mortality associated with hypertension, but it will also provide a large enough data set to answer additional safety questions.

CHAIRPERSON PACKER: Well, we'll take some questions at this particular time from the Committee, and let me ask the Committee to restrict their questions to the specific data or specific example of

tasosartan as opposed to the general discussion that came earlier.

Marv.

DR. KONSTAM: Maybe you touched on this, and I may have missed it, but with regard to the ten patients or the 13 patients, whichever number you want to take, do we know anything more about those patients, about what might have entered into the clinical judgment to discontinue those patients?

In other words, what degree of investigation has been carried out to see whether there were associated clinical features that might have prompted the clinician to interpret the elevated ALT as indicating a need to stop?

DR. RIGGS: We've looked at these cases very carefully, and as I said, in our program we did not provide any guidance in our protocols for the investigators to decide when to discontinue a patient. It was strictly up to their judgment.

We did ask them to provide us with all of the study events that occurred for every patient, including the ones who discontinued, and for the discontinued patients we wrote an extensive narrative summary that was provided to the FDA so that if we needed additional data we could obtain that from the

sites as well.

In reviewing those ten cases, we did not find anything that would indicate there was an additional problem with the patients that would cause them to discontinue. There were no patients that were jaundiced of those ten. There were no patients who had any kind of major symptoms of liver disease.

DR. KONSTAM: So none were fatigued. None had general malaise. None had anything, and maybe I'd like it expanded to the 13 patients because I guess the additional three patients were patients who were stopped for some other primary reason, but the FDA identified elevated ALTs or some LFTs abnormalities in them; is that correct?

DR. RIGGS: That is correct. Remember when we were looking for -- trying to do an analysis of the discontinuation rate for LFTs, if this is a signal of anything -- and we're not confident that it is -- but if it's a signal for anything, I think you have to restrict your analysis to what the investigators tell you, and if they tell you that they're not discontinuing the patient for a transaminase elevation, we didn't take that.

But whether it's ten or 13, let me make a couple of additional comments. There was one patient

who was treated with 300 milligrams in the 201 study who discontinued because of transaminase elevations who reported a feeling of nausea typically associated two hours after taking the dose of medication. Sometimes the patient had another episode of nausea in the evening. So that patient did have some symptoms associated with the transaminase elevations, but did not have hyperbilirubinemia and did not have any symptoms of apparent liver disease.

DR. KONSTAM: Okay. So that was one of the ten.

DR. RIGGS: One of the ten that had what I think were fairly minor symptoms.

DR. KONSTAM: What were the reasons that the three other patients were stopped, the ones in whom the elevated LFTs were identified after the fact?

DR. RIGGS: We actually have a back-up slide that talks about that. If I could have Carousel B, Slide 37.

I think while we're waiting for the slide to come up, one of the very first patients that you're going to see in the control trial is listed as having been discontinued for bilirubin, which would probably catch your attention.

However, it's important to note a couple

of things about this patient. The patient entered the study with an abnormal bilirubin. The upper normal limits were 1.3. This patient entered with 1.4, and gradually crept up during the course of the study to approximately two. However, no transaminase elevations occurred, and during continued therapy with tasosartan that patient's bilirubin actually returned to his baseline of 1.4 on therapy.

So it's not clear to me that that was something that was completely related to tasosartan, and in fact, the patient was again asymptomatic.

DR. KONSTAM: But that was one of the discontinuations?

DR. RIGGS: One of the discontinuations that the FDA was -- we listed discontinuations for transaminase elevations.

DR. KONSTAM: Right. So why was that patient discontinued? That patient was discontinued because of or reportedly because of an elevated bilirubin?

DR. RIGGS: Right, which had returned back to his baseline before the patient was discontinued. So it's not --

DR. KONSTAM: So at the time of discontinuation the bilirubin had returned back to

that patient's own baseline?

DR. RIGGS: Yes.

DR. KONSTAM: Okay, and the other two patients?

DR. RIGGS: One patient -- could we have Carousel B, Slide 37? Thank you.

One patient had right lower quadrant pain. This was a woman who had watery diarrhea in association with this pain.

The third patient reported asthenia, which was one of the most commonly reported study events that we had in our entire database.

The open label patients discontinued for a variety of reasons, and I think it's important note that the second patient on the list there for the open label studies actually didn't discontinue, but completed the study according to the investigator.

CHAIRPERSON PACKER: Udho.

DR. THADANI: Yeah. There's also -- I think the FDA review suggested that there were a total of 68 discontinuations as opposed to your -- I realize you gave us three. So there must have been some more on the open label discrepancies. You said 58, right?

DR. RIGGS: Yes. I'm sorry. What was the request of your question?

DR. THADANI: The total discontinuations according to FDA were 68.

DR. RIGGS: Yes, and that includes these listed on this chart.

DR. THADANI: These?

DR. RIGGS: Yes.

DR. THADANI: So all of them are listed here?

DR. RIGGS: Yes, yes.

DR. THADANI: The other issue is that looking at the database, it seems like when you combine the drug with hydrochlorothiazide, the incidence of LFT abnormalities goes up a bit more.

DR. RIGGS: Right.

DR. THADANI: So is there an interaction of the two drugs? Because those are commonly used two drugs because some patients have no control on blood pressure, one, and you're going to add a very cheap drug, hydrochlorothiazide. So what's the significance of that interaction on the LFT abnormalities?

DR. RIGGS: We actually did a formal PK study, and as far as I know, there was no drug interaction, but I'll ask Dr. Phil Mayer of our Pharmacokinetics Group to comment on that.

DR. MAYER: Phil Mayer, Clinical Pharmacokinetics.

There was no clinical PK interaction between tasosartan and hydrochlorothiazide in a straightforward drug interaction study.

DR. THADANI: So why does the LFT abnormalities goes to several fold?

DR. RIGGS: I think that's a difficult --

DR. THADANI: Is there an explanation?

DR. RIGGS: I think that's a difficult question to answer. Hydrochlorothiazide in and of itself can cause transaminase elevations, and maybe Dr. Maddrey or Dr. Zimmerman would like to comment further.

DR. ZIMMERMAN: Liver injury with chlorothiazide is very rare. There are one or two cases in the old literature, but with all of the widespread use it's very rare you can incriminate it.

I can't speak about enzyme elevation per se, but overt injury has been very rare.

DR. THADANI: But the enzymes do go up quite a bit more, and if you believe enzyme release is some hepatic injury, whatever it may be, so the combination is doing something more. Is it just unique to this, or is it unique to all the other

similar AT1 receptor blockers?

There must be data on other drugs as well, right?

CHAIRPERSON PACKER: Udho, I guess before -- what are you referring to when you say there is --

DR. THADANI: I think it was provided by the FDA tables in which the level goes up more percentage-wise to about four rather than 1.2 percent.

CHAIRPERSON PACKER: In the general --

DR. THADANI: In the combination.

CHAIRPERSON PACKER: In the studies or in the individual patients?

DR. THADANI: In the studies.

DR. RIGGS: This is in the open label studies.

DR. THADANI: Open label.

DR. RIGGS: Which is further confounded --

DR. THADANI: Sure.

DR. RIGGS: -- by longer duration of therapy and other issues as well.

DR. THADANI: No, I'm not saying that this drug in open label studies has a problem.

DR. RIGGS: Sure.

DR. THADANI: But is it unique to just this particular combination with the AT1 receptor plus

hydrocholorthiazide or other agents, too? And I just couldn't help noticing. Although nobody can -- necessarily from liver failure per se, but incidence goes up.

DR. RIGGS: Right. I think it depends on the individual compounds.

CHAIRPERSON PACKER: Rob.

DR. CALIFF: I have a couple of questions both for you and for Ray. Let me just say I think you've done a great job of clearly presenting the data, but I'm maybe confused about a couple of what the rules are when you go in and talk with Ray about how to do these studies.

But first, just one data derived question that I want to make sure we have straight. What you presented implied that if you correct for the number of times you looked at LFTs that there really is no difference among the sartans, and I'm interested in whether the FDA has independently done that type of analysis.

Is that a valid conclusion for us on the panel to take home in these deliberations?

DR. LIPICKY: Well, we've not done that analysis, and I believe that as you look through the memo that Dr. Fenichel presented, there was a table

there that lists the frequency of LFT determinations in a variety of trials. That's pretty accurate, but it probably is not 100 percent right. Maybe 99.9 percent, but it's pretty right.

And what you see is that there were some programs that were not as infrequent as others, but in fact, tasosartan was more frequent than them all. I'm not sure that you can conclude that the incidence of liver enzyme abnormalities was due to the frequency with which blood samples were obtained, and Dr. Chen is standing at the microphone back there who has one other comment that would address that very point.

CHAIRPERSON PACKER: Dr. Chen.

DR. CHEN: Shaw Chen, FDA reviewer.

About the impact of frequency of the monitoring on the dropout rate, I think there's disagreement within the agency about how we should look at the open label study, but in the open label study the frequency of monitoring is every three month, not every week, and the dropout rate there is two to three percent, and they're very consistent across three open label studies, and you can argue that's because of investigator's preference or bias or any single site concentration.

Thank you.

DR. RIGGS: Could I make one clarification?

While what he said is true for the maintenance part of the open label studies, we actually did have frequent monitoring during the titration period so that patients were monitored every week until they got to a stable dose. So they still had the opportunity to be dropped from the study or to have an elevation noted because of the frequent sampling early on.

DR. CALIFF: So right now then the sponsor's assertion is that it really is the frequency of sampling that accounts for the apparent difference in incidence of elevation, and we don't really have independent confirmation by the FDA. Is that -- have I got that correct on both parts?

DR. LIPICKY: I think you have that correct, but I think that the general feeling within our community is that it could be a factor, that is, frequency of sampling could be a factor, but doesn't seem to be exclusively the factor.

DR. CALIFF: Well, that gets into my next two questions, which I'll try not to drone on about, but I think it might be useful to understand for this particular program and in general. How is it that one

decides to do blood tests every month or every, you know? It almost seems like a self-defeating practice because you end up looking at things so often that you never find out what would have really happened had the drug been used in practice because you see all of these things, and people behave differently in the course of the study than they would in practice.

Wouldn't it be better to measure less frequently, let some people get jaundiced, and really find out what the drug does before it gets on the market?

Ray, I'm interested. Are you telling people to measure blood samples once a month as a good way of doing clinical trials?

DR. LIPICKY: I don't think -- well, to the best of my knowledge, we don't tell people how frequently to measure laboratory stuff. It's up to them to do the frequency that they wish. We would not object to once a week, and we don't object to once every three months. I mean you basically have seen the table laid out in Dr. Fenichel's review.

So I don't think we recommend. If it were up to me, I guess I don't see any reason to not collect frequently because if you believe the sponsor, we wouldn't be having this sponsor today had they not,

and I think that this is a useful meeting.

(Laughter.)

DR. CALIFF: So let's follow the logic of that one.

DR. LIPICKY: So, yeah, yeah. I'd rather not actually.

So if one were going to do very large scale morbid/mortal trials, I believe -- and be really looking at things like death and irreversible harm and so on and so forth, then I think that the other kind of searches for things become relatively immaterial because those are the things that are of real import.

In these kinds of programs, in fact, this kind of search is not crazy to do because it may be what we're looking for are signals. So I'm perfectly comfortable with things being monitored more frequently and where, in fact, one has the opportunity to do what we're doing today and figure out whether there is a signal there as a consequence of that monitoring.

I guess I don't have any real evidence that I can present that what I have just said works any more than I have evidence to present that doing the alternative would work better.

DR. CALIFF: Okay. My last question is

related, and I would like to hear from the sponsor what their thought process is about both these issues. I mean is it really the case that for chronic diseases with morbid and fatal endpoints that you advise people to do 12 week studies as a way to find out whether the treatment is beneficial to the patients that we're trying to treat? Is that the advice that you're currently giving people when you go to meetings with them before they design the studies?

DR. LIPICKY: No.

DR. CALIFF: It's not the advice?

(Laughter.)

DR. CALIFF: Well, they seem to all be doing. So I'd at least be interested in hearing the sponsor's perspective on why the frequent sampling and why such short studies for such an important disease.

CHAIRPERSON PACKER: Well, there's two separate questions, and they have two totally different implications.

DR. RIGGS: I'll take the last one first. As we try to do drug development programs in any particular indication, we pay a lot of attention to the general guidelines provided by regulatory agencies worldwide, and the length of the studies really are designed to meet those guidelines, and so that's how

we decide generally how long the core program studies will be.

I think if you want to answer morbidity and mortality questions, those are usually not required in the context of a drug development program for hypertension. So those are typically done later and would obviously be much longer and much larger.

CHAIRPERSON PACKER: There are guidelines that specify the duration of antihypertensive trials?

DR. RIGGS: There are actually guidelines recently issued in Europe that do specify the length of the trials, and they do require now some longer term studies. You have to do some that are up to six months in controlled situations.

CHAIRPERSON PACKER: And in the U.S., the status of the antihypertensive guidelines is?

DR. LIPICKY: Draft.

(Laughter.)

CHAIRPERSON PACKER: Okay.

DR. CALIFF: Can we at least hear the thought process on why so frequent, the monitoring?

DR. RIGGS: The question is why did we do such frequent monitoring, and I actually wish that I could blame Dr. Lipicky for this, but I can't.

(Laughter.)

DR. RIGGS: I can only blame myself as the medical monitor. Early in the program when we started this drug development, there were no approved angiotensin II antagonists, and there really was not a lot in the literature to tell me the safety profile. Merck was clearly the leader in the class, and they were being very close-mouthed about publications. So it was very difficult to glean information.

Our preclinical profile was clean. I've told you that. In our Phase 1 studies, we found one patient who had been treated with 200 milligrams for ten days who three days after the last dose of tasosartan had an elevation in transaminases that was about four times the upper normal limits.

That was the first report we had, and honestly didn't know whether that was something that I needed to pay a lot of attention to, whether it was going to ultimately turn out to be something like the ACE inhibitors that occasionally cause cholestatic jaundice and death or whether this was something that I didn't need to pay attention to.

Being a very conservative medical monitor and someone who actually did not want to do harm to patients while developing an antihypertensive agent, I chose to be very careful with monitoring.

One may say that that was a mistake, and maybe I shouldn't have done it, but I did it anyway.

CHAIRPERSON PACKER: As a follow-up, having now had this experience, what would you do if you had to do it all over again?

(Laughter.)

DR. RIGGS: It would depend on what I saw and how concerned I was, and if I was concerned, I probably would do the same thing all over again, and I would probably live to regret it.

CHAIRPERSON PACKER: Udho.

DR. THADANI: I think, you know, I can compliment you that you did it, weekly monitoring, and you picked up something which we are not aware with the other medications might happen, too.

It's very similar even in the hard endpoints like acute myocardial infarction based on CK release. It's a moving target twice normal, three times post angioplasty, five times surgery, and if you were to do it every day, I'm sure one would pick up more numbers even in those studies.

That's not the issue. One other issue I want to address now is the interactions. I asked earlier, and I don't think you're going to show anymore so I'm going to ask you about one other

important interactions with this drug to CYP3A enzyme system.

And a lot of patients now are going to get therapy not only for lowering the blood pressure, which reduces the stroke rate, but also for abnormality in lipids, and I think we recently approved a drug and that is coming into light, and I saw there was one case of regular myeliasis on similar staten, which could be due to the staten.

But given the factor with the interaction for a subset for CYP3A, which includes simvastaten, probably the other drugs, is there anymore database than what is available now? And because looking at the Possicor (phonetic) story, the levels went up six to eight times in the post marketing database.

So I'd like some data on that or if you have any data.

DR. RIGGS: Yes, I would like to ask Dr. Phil Mayer again to comment on drug interactions.

DR. MAYER: Actually I need Carousel Y, Slide No. 34.

Since you had a question earlier about drug interactions to these, this is our nearly complete drug interaction program with nine drug interaction studies that were performed here listed on

the top of the slide.

In these cases, the results are that there were no major pharmacokinetic interactions, and in the case for additive therapy with other antihypertensive agents, there was actually an additive lowering with blood pressure.

DR. THADANI: But is the database enough?

DR. MAYER: Hold on one second. This is much fancier than what I'm used to dealing with.

These are actually the areas under the curve to show you the specific data for each of those drug interaction studies. For tasosartan on the left-hand side and enoltasosartan, the major active metabolite, on the right-hand side, these are AUC measures for each of the drugs. On the left would be the drug alone or -- I'm sorry -- tasosartan alone, and on the right-hand side of each of these columns would be the drug with concomitant therapy.

The simvastatin that you're referring to is the last drug interaction study here, Number 139, but if you do actually look across the table here, you can see that there's actually no difference for either the tasosartan with or without the concomitant therapy, for tasosartan on the left and enoltasosartan on the right.

There's only one place that there's the statistically significant difference, which was in the nicardipine drug interaction study, and in that case even though there's a lower level of enoltasosartan, there's actually additional lowering of blood pressure with the two.

DR. THADANI: What you are showing here are the drug levels of the compound under discussion, but what about the drug levels of simvastatin because that's the relevant issue because they went up? These are drug levels?

DR. MAYER: That's correct. These are drug levels of tasosartan and its metabolite.

In each of these studies except for the simvastatin and the ibuprofen, we measured the other concomitant drug, but in the simvastatin study, we did not measure that because we were more interested in the effect of simvastatin on tasosartan and enoltasosartan, that 3A4 conversion that we have here, and we did not measure simvastatin concentrations from a pharmacokinetic perspective for that study.

DR. THADANI: I think that would be probably a relevant story, you know, what we have heard from the previous story because if it goes up high you could make the drug cheaper by reducing the

rows one-fourth or stopping that issue.

Another important interaction is the P450. I know you picked up atenolol. What about metropolol, which is more metabolized?

DR. MAYER: No.

DR. THADANI: Because that's a commonly used drug, too.

DR. MAYER: For actually the 3A4 drug interaction study that we chose to perform was simvastatin because of a more higher rate of concomitant therapy.

We also looked at ibuprofen for looking at a 2C9 interaction, but the simvastatin drug interaction study that was chosen specifically for 3A4 isozyme.

CHAIRPERSON PACKER: Dan.

DR. RODEN: Let me just ask this in a different way. What enzymes are required for the biotransformation of this drug and its metabolites, and does this drug or its metabolites inhibit the function or enhance the function of any of the known metabolic pathways of other drugs?

DR. MAYER: Okay. Actually if you want to move the carousel back to Slide No. 1, that same carousel, is the metabolic scheme.

Okay. What you'll need to focus on is the middle of or central part of the slide here with tasosartan as it's metabolized by 3A4 and 2C9 to hydroytasosartan, which is a short-lived metabolite; then enoltasosartan again by 3A4 and by 2C9 to hydroxyenoltasosartan.

These are the isozymes that are involved in studying this. We've looked at effects of drugs on these steps, that is, 3A4 and 2C9, looking at various inhibitors, such as simvastatin, ibuprofen, erythromycin, but we have not looked specifically at the reverse, if that was what your question is also, whether tasosartan would inhibit these isozymes.

DR. RODEN: So is tasosartan a 3A4 inhibitor?

DR. MAYER: No, we don't believe so. There's no evidence that I've seen clinically or in any of our drug interaction studies, but we don't have specific in vitro data for examining the IC50 of tasosartan on various other substrates.

DR. RODEN: And you said you did clinical studies with erythromycin and simvastatin?

DR. MAYER: It hasn't been with -- the simvastatin was a clinical study, but the erythromycin was an in vitro study to look at the interaction of

erythromycin on tasosartan.

DR. RODEN: Right. So the simvastatin, is that an inhibitor of 3A4?

DR. MAYER: Yes, yes.

Let me go to the next slide here actually. I can show you just --

DR. RODEN: Is that a very potent inhibitor of 3A4? I mean, I thought that the best probe if you want to ask the question clinically is to use ketoconozole or perhaps mobefrodil, but the statens are not famous for being potent inhibitors of that enzyme.

DR. MAYER: Yes.

DR. RODEN: They may be competitive.

DR. MAYER: Exactly. The in vitro drug interaction studies that we've performed --

(Laughter.)

DR. MAYER: Thank you very much for your concurrence with our in vitro program.

We looked at several --

DR. RODEN: I wanted to see it in vivo.

(Laughter.)

DR. MAYER: We ran several 3A4 inhibitors in an in vitro study. Ketoconozole was without question the most potent inhibitor. Erythromycin was

a little less potent. Simvastatin still had marked inhibition of the first step. If you recall from the tasosartan to hydroxytasosartan, that's a 3A4 step. So there was some inhibition there. It was a poor inhibitor, however, the second step, but if it inhibited even the first you wouldn't get formation of the enoltasosartan, the active metabolite.

And really just a judgment call based on more frequent concomitant therapy, and the sivastatin drug interaction study was the one performed from this group.

CHAIRPERSON PACKER: Dr. Chen, did you have a comment that you wanted to make as the medical reviewer?

DR. CHEN: I'm sorry. This is not related to the metabolic, but I just want to point out that not all of the studies were frequently monitored. For weekly monitoring of liver functions, about seven of the 15 studies, and out of 68 dropouts, seven are from those frequently monitored study. The rest are not.

CHAIRPERSON PACKER: Okay. Can we have a -- is there any comment from Dr. Hung, the biostatistical reviewer regarding any adjustments that he or his colleagues may have made with respect to the frequency of monitoring or the duration of the trials?

DR. HUNG: This is Jim Hung, FDA statistical review.

The analysis has not been adjusted for the frequency or duration. We do have a table for individual studies. That was in appendix somewhere.

CHAIRPERSON PACKER: Okay. Can we proceed with Dr. Morganroth's presentation?

DR. MORGANROTH: Thank you very much, Dr. Packer, ladies and gentlemen.

I only have two slides and actually a very brief comment because I am a cardiologist and, like Dr. Maddrey, know the difference between trying to address cardiac versus hepatic issues. So my comments will be very brief and relate really to the issue of how does one review a laboratory safety database.

One does what was done in this program, to look for those laboratory parameters that appear to be different on the active agent being studied compared to the placebo or to controls, and when you identify laboratory abnormalities, the question, of course, raised is: what's their clinical significance? Should those levels of abnormalities in any particular parameters impact on approvability because it changes the risk-benefit ratio, or should it impact on labeling as how one describes the drug in terms of

warnings or frequency of physician related actions?

In this particular case, when you have laboratory abnormalities and want to make those decisions, wouldn't it be nice if we had prospective trials that told us what these markers really meant in the clinic after a drug is approved? And unfortunately we rarely do have such information prospectively.

So the next step is to do what? To ask an expert. So we call on the liver experts and ask them, you know, "You have a lot of experience in this, but if you think about it a while, if you study the disease entities and you have experience in other drug databases, what do you make of all of this data? Is it something we should be concerned about or not?"

And that's where by definition it almost has to be left, except in this particular case, though we've heard from Dr. Maddrey and others that the tasosartan database, at least in his opinion, from what I understood from his presentation, does not appear to have a strong enough signal to make it of concern, wouldn't it be nice if we had some actual data to look at?

And, in fact, thanks to Dr. Fenichel and his colleagues at the FDA, they've put together the

background piece you've all received. I took the opportunity to look at that data and add a little bit to it from a few SBAs and produce one slide that I'll show you, if we could have that slide, which is to take just the data you have in front of you, plus, again, a little supplemental information.

I don't attest to the validity of any of these specific numbers because they're just taken out of those papers. I'm frankly uncertain in the selacryn line. I'm particularly not certain of some of these numbers because that SBA was pretty thin when I looked at it.

But what I tried to do was to say what's the issue here. The issue is do we put a drug out on the market and be surprised. No. So we want to figure out a way not to release a drug and be surprised after marketing with something that's going to either cause that drug to be withdrawn from the market or, secondarily, to cause a major change in labeling that gets a lot of energy in a lot of people.

And there are four drugs in that group in your handout, and I have added one, selacryn, and there's others, oraflex and others, that could be added that turned out after they were released by the FDA to have some post marketing event. A couple of

them, dilevilol and selacryn, were bad enough that the drug had to be withdrawn from the market. Voltaren and rezulin have had, let's say, labeling changes of concern.

There were three drugs that I've listed here, or actually two drugs plus a class of drugs called the sartins that are in green: tacrine, mevacor and sartan, that so far seem to be okay since they've been on the market. It doesn't appear to be a regulatory issue that's been raised. That is, there's not a lot of deaths.

And I've added all of the sartans together though. As you know, almost all of that is losartan. The majority of it is the losartan database.

Now, all the rest of these four columns is really the issues that are in the questions to this panel, and what the really boil down to is: are there any surrogates that you can look at in a clinical database to predict what's going to happen to a drug after it goes on the market relative to this liver function problem?

And the first surrogate is what did the preclinical data show, and I think we've had adequate information from the experts, and it's clear that the preclinical histology doesn't appear to be very useful

in terms of predicting what's going to happen. Being negative doesn't appear to be any different than being positive according to this retrospective meta analysis-like approach.

How about the frequency of transaminitis using the 3X level? Here you can see that there once again appears to be no striking differences between the yellow and the green drugs. Tacrine was already pointed out to be a pretty interesting one that has this huge 25 percent incidence of transaminitis that resulted in the post market situation to no important adverse events.

This, of course, is not always the case because a drug like selacryn, I think, the 23 percent may just be abnormal. I couldn't tell by looking at the SBA, but it seemed to have a fair enough high frequency, but even the 25 in the green group doesn't seem to be very important. So I don't think this surrogate is very strong, if you will.

How about discontinuation rates? We've heard that that's very subject to investigator bias and what they've been told or how frequently they were monitoring in various areas. We've heard in the tasosartan base that a third of the discontinuations occurred in one European center that only produced two

percent of the data. So I'm not sure how important theoretically even this discontinuation rate issue is.

But as you can see, there again doesn't appear to be any relationship between the numbers and the events that have occurred post marketing.

I think that the simple conclusion that I've reached is that if you have liver deaths in a preapproval NDA, the likelihood is you'll probably get liver deaths after you put the drug on the market when you expose to even more people, and I guess that isn't too profound a statement, but unfortunately the way I look at this data is that's the only thing we're left with.

If you want to know who's going to get liver deaths after you get on the market, you only can be pretty certain if you had liver deaths before you put it on the market, and there isn't appearing to be a signal. Even these asterisks have to do with what's called serious, and I'm not sure what that means, but I think it means jaundice at least in most of these cases, and I'm not even sure that that signal, which is what I would have hoped would have been the best surrogate listening to Dr. Maddrey; someone who gets icterus and what have you should be enough to predict, but so far that doesn't appear to be the case, at

least for tacrine and the one valsartan case that you know about that's in that handout.

So in summary, if you don't know how to deal with this adjusted tasosartan issue, because if you believe the sponsor and you assume that everything goes away when your frequency of sampling adjusts, then there's no issue at all. I mean there is no issue.

But I want to make the assumption that it doesn't because, you know, otherwise it's not an interesting question. So let's assume that tasosartan does, in fact, increase the frequency in discontinuation rates because no one can absolutely prove today that the sponsor is right. What does that mean?

Well, I think the predictability of that is relatively low. So if we apply this kind of concept to this database, the fact that tasosartan had a negative preclinical work-up to me doesn't have much predictability of what's going to happen if it's placed on the market.

The fact that it has a higher than other sartans, if you assume that, which we're going to assume for the sake of this discussion, is higher discontinuation rate and percent LFT elevation. To me

those surrogates, according to the experts and according to what we've seen in this kind of analysis, does not appear to be highly predictive.

The fact that they haven't in 4,000 patients had any liver deaths would make me fairly comfortable to predict with a fairly high likelihood of being correct that there isn't going to be a lot of liver deaths or presumably any liver deaths if the data on the previous slide were correct.

But, frankly, I don't know the answer to that question, and it seems to me that though I don't think tasosartan is that different than the other sartans, and I think there's a low chance of really important liver deaths post market, that the only way to find out is to measure it, that is, to put the drug on the market and to have an important post marketing surveillance study as the sponsors plan and look carefully at that issue, and I think that's probably, and I think that's probably true for every drug that has these issues of surrogate changes without liver deaths in the preclinical area.

Thank you very much.

CHAIRPERSON PACKER: Udho.

DR. THADANI: On the previous slide you showed, you said probably the only way to predict is

deaths, and there was no death in rezulin.

DR. MORGANROTH: If we can flip that slide up, please.

DR. THADANI: It's on your slide with the summary.

DR. MORGANROTH: Yes, I remember, right.

DR. THADANI: I don't know if that comment even holds because I know in the other groups there were, and yet in the post marketing database there were some deaths. So I really don't know myself.

DR. MORGANROTH: Well, my --

DR. THADANI: -- zero out of 4,000 or 2,700.

DR. MORGANROTH: Right. My only comment is just the one you're making. You asked why did rezulin have no deaths out of 2,500 patients and then have deaths that occurred post marketing.

Well, I believe we should ask the liver experts who are more familiar with this issue, but I believe those cases so far of death have been sporadic, if you will. There's only a handful of them, but an important concern to change labeling, not enough to take it off the market.

So when you have sporadic deaths and you don't know if they're going to be persistent and real

and really change risk-benefit, then you change labeling. You don't take it off, and I think that zero out of 2,500 wouldn't have given me as much comfort as zero out of 4,000 or 5,000, you know, for this issue, assuming that these deaths are related to rezulin in the post market area.

All I made was a very simple minded statement that probably isn't objectionable that says if you have liver deaths premarketing, you know, in X number of patients, then chance when you put it into a large number, you know, huge times X, that you're likely to also have liver deaths, and if you don't have liver deaths, it doesn't mean you won't, but the only way I think you can tell is to measure.

DR. THADANI: I think that's the problem because you probably need 50,000 patients where the incidence is going to be so low of hepatic failure. So one can never be certain until you have gotten that database.

DR. MORGANROTH: Totally agree.

CHAIRPERSON PACKER: Marv.

DR. KONSTAM: You know, Joel, I agree with a lot of what you're saying, but I draw a slightly different conclusion. I mean, I conclude that, you know, you just can't conclude anything from the NDA

data sets as they're presently being constructed because even if you look at those drugs that have appeared to cause problems post marketing, it's for the most part a pure play of chance whether or not there were a couple of deaths in that data set, in those data sets, given the number of patients studied.

You know, the difference between zero out of 2,500 versus one out of 3,200 versus four out of 2,290 is pure play of chance.

DR. MORGANROTH: My comment would be I hope I didn't say anything different than you just said because --

DR. KONSTAM: Right.

DR. MORGANROTH: -- I didn't mean to. If I did, all I'm saying is that if you don't have deaths like in the tasosartan database, that doesn't mean you won't when you go on the market. All I'm saying is if you do have deaths, then it seems to me that's the only thing unfortunately surrogate-wise, if you will -- it's not even a surrogate -- that you're going to have them afterwards.

So it gives me no comfort that taso is clean, except that as like other sartans, you know, there hasn't been any problem like in other sartans, depending on if you believe the adjustment is not

going to be a great change. The only way to tell is to measure it.

DR. KONSTAM: That's right, but I guess the challenge is then to ask ourselves: are there circumstances in which we do an adequate trial preapproval to document to satisfy ourselves whether or not there is a real mortality associated safety issue here or not, and that's really, I think, the question as far as I can tell.

And then the question then becomes, you know, when do you decide to do that, and are there signals that you can look at in terms of laboratory findings or something else that triggers you to say, "Well, this is a case where we should go and look and do a real trial of 10,000 patients or what have you in order to answer that question."

And I think that's really the challenge. I'm not sure I see the answer to it. I don't see the answer to it in the data that you've presented because what you're saying is that just forget the LFTs because they're not going to help in terms of making that decision.

I mean, is that the point that you're making?

DR. MORGANROTH: Yeah, I think so, and let

me give you an analogy to something we all know better, and that is QT interval in Torsades. It's not that different an issue, is it? Because let's say you see a very small, three millisecond increase in the QTC and there's no Torsades in a 4,000, 5,000, 6,000 database, and I'm picking a QT, you know, that occurs in some drugs, but not the ones that are obvious, that are, you know, much longer, 20 millisecond mean changes with five, six percent over 500. So there's a signal.

I'm saying there is a signal, but the signal is very weak, and you raise the same question. How do you tell whether, you know, that is going to be a problem when you put the drug on the market, when there is just a weak signal but nothing else, and I'm making the analogy that this is a weak signal using the experts to guide me in that, frankly, because I don't know if it's weak or strong. It seems weak, and they agree it's weak.

And my answer would be, like you said, you'd have to decide to do a study. Now, you do a study premarketing. Well, I think for an incidence of zero out of 4,000 and you're looking for -- take rezulin. I don't know what the number of deaths are, maybe three or six or whatever, something, a handful

like that in hundreds of thousands, you know, of patients worldwide that have been taking that drug, if not millions for all I know. Maybe Dr. Maddrey could comment.

The size of that study would have to be what? You know, 100,000 or more to have any point estimate reliance and probably closer may be to a million patients, impractical, impossible.

And the same issue for QT. I mean, that's why no one tries to do that. So as Dr. Maddrey has suggested, the only way to -- and now I'm suggesting -- the only way to really tell is you've got to put the drug out on the market with the feeling that the signal is weak enough that you're not concerned and that it doesn't appear to be different from other drugs in a class that also haven't been a problem, and you do it post surveillance. Otherwise how would you ever find that information, whether it causes liver failure or not, you know, real incidence of liver failure?

CHAIRPERSON PACKER: Dr. Fenichel.

DR. FENICHEL: Yeah. I'm not speaking to disagree really with Dr. Morganroth's general conclusions because I really don't know what to think, which is why we, of course, brought this topic to this

meeting, but I do want to update his slide of the green and the yellow drugs.

The other sartans now have approximately 13 serious liver injury cases with two deaths reported in the United States out of something like a million or two million patient-years of experience. So on the first hand, because there are deaths post marketing, that makes the class a yellow class instead of a green class, I suppose.

On the other hand, it says -- it speaks very much to what Dr. Morganroth has said and what other speakers have said, that in order to detect events of that incidence, if deaths in trials are the only way to detect deaths in marketing of that incidence, then the trials, indeed, have to be on the order of tens of thousands of patients, and if that's not acceptable, then we must find another signal or we must look to after marketing studies of some relatively unprecedented size.

CHAIRPERSON PACKER: So just for the record, thus far, Bob, we have 13 cases approximately?

DR. FENICHEL: Yes, I think that's right. I should say, you know, my memo of background information for the Committee has been alluded to several times. It was prepared in a way which does

not allow it to be publicly distributed yet, although it could be with some fairly simple redaction, and I apologize to the audience that that was not contemplated before the meeting.

So I can't say that I know the detailed data very well for each of these things. If Dr. Roger Goetsch is here from Epidemiology at FDA or Susan Lu also from Epidemiology, it was they who prepared some of this post marketing surveillance data and may be able to speak to the specific cases.

But that's correct. It's mainly losartan data just because it's the market leader, and there's some contribution from valsartan. Irbesartan is approved, as is known, has been approved so recently that it does not contribute.

CHAIRPERSON PACKER: Now, obviously I would imagine that it's very difficult to assess actual risk since there may be -- one is fairly confident about the denominator, two million people exposed, but one is not necessarily confident about the numerator because not all cases are necessarily reported.

DR. FENICHEL: I think most people would say that in the case of major liver failure, liver failure requiring transplantation as shows up in the

triglitazone database, rezulin, liver failure leading to death which there are two cases here, I think the reporting rate on that is probably pretty good.

Liver disease, simply meaning jaundice, which may be looked for with some reliability in clinical trials, I have no idea what the reporting rate on that is, and I'm sure it's quite low.

CHAIRPERSON PACKER: Okay. Barry.

DR. MASSIE: The way it's phrased, it sounds like there's at least some contribution from both valsartan and losartan to that 13 cases.

DR. FENICHEL: I think that's correct. Yes, that is correct.

DR. MASSIE: Okay. So we have two sartans that cause serious liver toxicity?

DR. FENICHEL: Probably. I mean there is always a question of whether they are really causal, but in some of these cases, they are, as I recall, positive rechallenges with fairly convincing sequences, and so forth. So I think that, yes, it's pretty convincing.

CHAIRPERSON PACKER: Bob, before you leave the microphone, at what rate of reporting does the FDA begin to say that something similar to actions taken for rezulin should be considered? In other words,

what is the threshold?

It is obviously not one case, and it's obviously more than one. What's the threshold? When does a database become sufficiently disconcerting that you say that the public should know more than they know or that labeling should be changed to reflect this knowledge?

DR. FENICHEL: Well, the answer is there is no fixed rule, but certainly in the case of bizarre occurrences, angiosarcoma of the liver, vaginal adenocarcinoma, it doesn't take very many cases to associate something with a drug, and no matter how low the frequency, those things get into labeling.

Other situations like an increase in liver failure, which of course occurs in the population, what we believe with troglitazone, as I recall, the relative risk of serious liver injury compared to the background rate in the population of noninfectious liver injury; the relative risk was something like doubled or sextupled or something like that. It's some small, but non-zero, you know, nonunitary multiple.

Dr. Hal Davis is here, I know, from Epidemiology and may want to remind me of what the correct figures are, but those are sufficient to get

something into labeling for sure. Sometimes they are sufficient to take relatively drastic action in terms of "Dear Doctor" letters, and so on.

Sometimes things just ooze into labeling with the next printing. It's really very hard to make a general statement.

CHAIRPERSON PACKER: Because since you're asking the Committee as to its advice about labeling, the Committee is being asked about how to respond to a database which at the present time has no serious liver function abnormalities. So it's valid for us to ask you how you respond to a database which has serious liver function abnormalities, a post marketing surveillance database.

So what I guess I'm confused about is how many events do you think that it would take, 13 and two, for you to say there's something more to it. I know it's a really hard question. There's no threshold, but at some point in time the frequency of reporting may also, by the way, be heightened if there's an awareness that there's interest in the question.

This Committee meeting might, in fact, foster that. So one might actually see some of the reporting of these events go up after this meeting.

DR. FENICHEL: Well, you're asking for a threshold for action as if there were one action. There are multiple possible actions, and the several questions deal with them really.

One could, on the basis of the available data, decline to approve tasosartan pending some additional study. One could approve it just flat out with no different labeling from those of the other sartans. One could approve it with a requirement, with an understanding that some post marketing study will be done. One could, on the basis of what is of concern about tasosartan and what is known about the other sartans, do something about the labeling of all of the sartans.

So, yes, saying that tasosartan is like the other sartans does not necessarily mean that it or they get the current sartan labeling. There are many possible outcomes recommended by the Committee, and I'm not prepared to estimate a threshold for any of them, let alone all of them.

DR. LINDENFELD: Bob, just before you finish, do you have a rough idea from the cases you reviewed of what the average duration of drug exposure has been in the cases of liver failure? How long has it taken, on the average?

DR. FENICHEL: It varies from drug to drug. With dilevilol, which is the case I remember best, the average was about two months. In the cases of -- in the open label trials of tasosartan, the liver enzyme abnormalities leading to dropout, that dropout occurred as I recall after an average of about 140 days. I think that's a correct recollection.

Juan Carlos, is that right?

Yeah, that's right.

CHAIRPERSON PACKER: It's particularly interesting because this is going back to what Rob said earlier. If the vast majority of antihypertensive placebo controlled trials are two to four weeks in duration, occasionally six to eight, but one is seeing LFT abnormalities as a safety issue at two months, and even if one trial in an NDA, if one does one trial for six months, this is according to the European recommendations.

One has an amazingly small experience in most antihypertensive drugs in the window of vulnerability for this side effect.

DR. FENICHEL: Yeah, well, this is, of course, true, and it is very much a Califf theme that we are looking at drugs which in prospect are used in very many people over a long period of time, and we

are making decisions on the basis of what sounds like a lot of people, but are really few.

If you go back to the previous meeting of the Committee where we talked about clopidagril and talked about the CAPRI trial, one of the largest trials, not necessarily the very largest, but one of the largest trials ever to be considered by this Committee. It was a trial which allowed us to acquire approximately 16,000 patient-years of experience with the drug, a very unusual size database.

Well, that compares to what we now know about the approved sartans, which is, as I say again, between one and two million patient-years. You can't get that information any other way.

CHAIRPERSON PACKER: Ray.

DR. LIPICKY: It might be worth throwing a couple of numbers around, and these are order of magnitude numbers, but, you know, the clinical benefit of an antihypertensive is something in the order of one per thousand. So if there are really adverse problems that have a frequency more than that, you're very close to where you would not like to see things be.

And I can't remember if it's one per thousand patient-years. It's something on that order.

So clearly, that's a threshold and a cause for concern. I would guess that in the experience that we've had with things like agranulocytosis and liver problems that the number of cases of clinical cases where you can never make cause-effect associations -- I mean you never know whether these cases are due to drug -- you start believing things sort of when you start -- at least I start believing things sort of when there are 20 or 30 of them because then they're sort of believable, and up until that threshold you never know as far as I'm concerned.

So the number of cases and the incidence of cases are two almost disparate things, okay, and they're not connectable, I don't think, and in the case of tasosartan, since the total duration of exposure is on the short side compared to the amount of time that it usually takes for known hepatotoxins like labetalol and dilevilol to produce clinical illness, the issue is not was there clinical disease, but was there a signal here that says tasosartan affects the liver.

And indeed, there were rechallenges that one can look at from that point of view, and so the issue is really looking in the crystal ball and saying, well, if it goes out there as one in a

thousand cases, a possibility, and if that is a possibility, should it be ruled out?

CHAIRPERSON PACKER: Okay. Udho.

DR. THADANI: Of all the patients, you mentioned two deaths and 13 hepatic failure. What was the exposure in those patients? I know you showed the database. Was the exposure very short or they didn't have associated hepatitis or something else happening?

DR. FENICHEL: Well, these are fairly confidently attributed to drug, and that it might turn out on much closer examination that all 13 are drug related or even can be determined. You know, I can't say that.

Is Dr. Goetsch here, by any chance? Because I have some documents with me that I can review and provide the answer to that question a little bit more about how long people were on therapy before they --

DR. THADANI: Yeah. Is the duration like these trials, where they have to go for several years? I'm just curious.

DR. FENICHEL: Well, it can't be for several years because we're talking about the sartans, the oldest of which has not been around for several years. I don't know how long the exposure was in

those cases. I can tell you in a few minutes.

DR. THADANI: Okay.

CHAIRPERSON PACKER: Okay. Ileana.

DR. PINA: I think it's an important question when we talk about drafting guidelines for future studies, and, Ray, you've seen the European guidelines that you say are out there for hypertension studies, and the FDA's are in draft form. Is that what you were saying?

DR. LIPICKY: That's right.

DR. PINA: Because we're talking about long term drug exposure. Then we're going to be drafting guidelines for drugs studied much longer than the usual eight, 12 week, short term trials. Do you have any idea what the European guidelines right now are asking for time-wise?

DR. LIPICKY: No, I don't.

Dr. Hoppe, do you know off the top of your hat what the European guidelines call for? I just don't remember.

Dr. Hoppe is from what used to be or still is the German VGA.

DR. HOPPE: Right.

DR. LIPICKY: Is it still or it was?

DR. HOPPE: Well, it's not the VGA. It

changed its name to BFARM, but actually it's the same institution, not better, not worse, I think.

So the European guideline call for two comparative trials, preferably performed for six months or more, and these trials should be active controlled.

DR. LIPICKY: And the only thing I'll point out, although that's very informative, is that this is a few hundred patients.

CHAIRPERSON PACKER: We know.

DR. LIPICKY: All right.

CHAIRPERSON PACKER: Dan.

DR. RODEN: I want to express sort of a sense of scientific frustration here because it seems to me that the data that Joel presented puts the issue of liver toxicity into some perspective. Tacrine is an outlier because there is such a high incidence of abnormal transaminases, and yet clinically apparent liver disease is not a problem.

So it seems to me that what we're dealing with is a phenomenon that must have multiple mechanisms, and I haven't heard anybody say anything about the mechanism at the molecular level for liver injury by this drug or by any other drug, if it exists.

The other sense of frustration that I want to express is -- and I think this actually is relevant to our discussion as opposed to my first comment, which may or may not be, and that is this term that I've just heard this morning for the first time spoken, and that is "the sartans."

I don't understand why we are making the assumption that this is a class action. I grant you that there appears to be an issue with liver toxicity with two other drugs that appear to block this particular receptor, but unless there is something that somebody can tell me either about a common chemical structure that causes liver disease or a common molecular mechanism, is block of AT I receptors in and of itself likely to produce liver damage in some subset of patients, then I think we ought to just take those other drugs as experimental.

It's conceivable there's a class effect, but I think we're leaping to an assumption that may not necessarily be justified.

I'd love to hear from one of the liver guys if there's anything to say about mechanisms, particularly with respect to the tacrine story, just because it helps focus what we're supposed to talk about here.

DR. ZIMMERMAN: By and large you can't talk about a class action. I mean a class of drugs and the kind of liver injury it produces. Take the NSAIDs. They're a drug like diclofanac. Don't take them yourself. Just talk about them.

(Laughter.)

DR. ZIMMERMAN: They're a drug like diclofanac with a large number of cases reported. there are other drugs like ibuprofen, very rarely involved, and some even less frequently involved.

The class does not determine it. The molecularly structure, the active metabolite to which it's converted play the role, and so except where there are very close structural similarities and similar metabolites, the class of the drug and the pharmaceutical role of the pharmacologic effect do not predict whether injury will occur.

Is that your question?

DR. RODEN: Well, I guess may question is, I mean, does anybody have any clue about the mechanism of liver damage by losartan, by tacrine, I mean, at the molecular level? So can we say that this is or is not a class effect? I mean that would be a helpful thing to know.

DR. ZIMMERMAN: I don't think you can

predict a class effect.

CHAIRPERSON PACKER: Bob.

DR. FENICHEL: Yeah, I just returned to answer Udho's question of a few minutes ago. Looking at some of the serious liver disease cases that have been reported post marketing with the approved sartans, going down the list, the latency of time on drug, I see one month, three months, unknown, one and a half months, 11 days, one and a half months, four to six weeks, several months, whatever that means, less than a month, and ten days. That's not a complete sample. That's all I can lay my hands on right away.

CHAIRPERSON PACKER: Okay. Dr. Riggs, could we ask you to summarize and we'll go on to the questions?

DR. RIGGS: I have very brief concluding remarks.

In summary, we believe that tasosartan should be approved for the treatment of essential hypertension. It is safe and effective. LFT abnormalities associated with tasosartan are transient, asymptomatic, and do not represent a significant safety concern.

Monitoring, in particular, is not warranted, and we propose to conduct a large post

marketing study after approval, following consultation with the division on its design.

Thank you.

CHAIRPERSON PACKER: Okay. Thank you very much.

I think the Committee doesn't have any additional specific questions for the sponsor, and we will go on to the formal questions from the agency.

The Committee has had, I think, a considerable educational experience this morning, and now we are being asked to take that education and apply it to formal recommendations to the agency.

I will not read the introduction, except to say that hepatotoxicity is a recognized occasional adverse effect of some approved antihypertensive agents, including methyldopa, all of the ACE inhibitors, and many others. In some cases, physicians are asked to perform periodic screening. In others it's been the source of nonapproval.

Let me also before going on to the questions read one interesting conclusion from Dr. Fenichel's analysis of drug induced hepatotoxicity. He reminds the Committee there are two possibilities here. If tasosartan is outstandingly hepatotoxic and it were approved on the grounds that it was effective

and the data do not distinguish it from drugs with unremarkable safety records, then the public health will suffer.

On the other hand, if tasosartan is as safe as other commonly used antihypertensives, but it were nonapproved on the grounds that (a) it is under a cloud and (b) the world has no great need for another sartan, then this sponsor will have been penalized for its collection of better than average data, and future sponsors will be given perverse incentives.

(Applause.)

CHAIRPERSON PACKER: With that charge, question number one: what do the animal data suggest regarding the hepatotoxicity of tasosartan and the other sartans?

We'll turn to our primary reviewer first, Dr. Thadani.

DR. THADANI: I think one of the issues obviously comes up. We cannot predict much, and there was so much species differences that one can't say much, and there has been no major concern.

CHAIRPERSON PACKER: Does anyone on the Committee disagree?

(No response.)

CHAIRPERSON PACKER: Question number two. There were no cases of clinically apparent liver disease in the clinical trials of tasosartan, only one case in the trials of other sartans, perhaps now two cases. How much reassurance -- well, I should say 13 cases, two deaths --

PARTICIPANT: No, no, no, no. This is in the trials.

CHAIRPERSON PACKER: No, in the trials. Sorry. One. that's right.

How much reassurance does this provide?

Udho.

DR. THADANI: I think that given the database, a few thousand patients, it gives you some reassurance, but when the incidence is going to be low, obviously you need thousands of patients. So it gives me some reassurance.

Now, if you're lumping all of the sartans together here and obviously you need exposure for thousands of patients to address the issue. So I think I have some reassurance, but in order to be totally convinced, I think you need a lot of post marketing database to address that issue, unless you are willing to do trials of 50,000, 60,000 patients, and some of the trials are ongoing on this.

CHAIRPERSON PACKER: Ray.

DR. LIPICKY: Udho, just to clarify your comments a little bit, what does "some" mean? So there were zero deaths seen.

DR. THADANI: Yeah.

DR. LIPICKY: So that means it doesn't kill everybody?

DR. THADANI: Well, I think the problem is if you take all hypertensives in general population. We know some people have strokes, and some are going to die of myocardial infarction, and some are going to die. Again, that's also age dependent, and we know obviously that if you look at it, we had discussion on antihypertensives not long ago, that lowering the blood pressure, that was a conclusion, although the question is which drug you use. Drugs have been different. Diuretics that have been okayed reduce the stroke rate by, say, 50 or 52 percent.

And I think using that as a target, lowering of blood pressure, is probably good in preventing the stroke, and to some extent that thread.

Now, the reason I was hedging on my remarks since there are no deaths, at least there's some reassurance. That's why there's some reassurance, because if there were a few deaths, then

you'd really worry about especially with the hepatic injury, and the deaths are more common, I think it would raise a red flag.

The fact there are no deaths and then I hear Bob saying that he has got 13 cases now, but with the exposure which is not different than the trials now, because what you said just now, there were two deaths and 13 hepatotoxicity with other sartans in which exposure has been one month, two month, three months, which is within the trial period, and obviously there are several million exposures.

So to address the issue of absolute safety, I think you'll need thousands and thousands of patients, and really -- but that was my remark. I hope I answered your question you're addressing.

CHAIRPERSON PACKER: Yeah, Udho, I think the question doesn't ask whether you are persuaded that the drug is entirely safe. I think the question that is asked here is whether the absence of clinically apparent liver disease is reassuring, and to what degree it's reassuring.

Because I think a little bit further on we're getting into the issue of how persuaded you are about safety, but I think that this is really a question that I think focuses on our response to the

presentations of the hepatologists who instructed us that if we don't see clinically apparent liver disease, that that should be reassuring.

And the question is: do you agree with that? Is the presence of no such cases in the existing database reassuring?

DR. THADANI: I think, again, obviously it's reassuring that nobody had a clinical liver disease, but with one caveat. Because the trials, the way they were conducted, a lot of patients who had LFT -- ALT levels going beyond three were stopped, I really don't know what would have happened to those patients if you continued the drug, and I think you have to put that caveat in, that you can't give a blank statement, "Don't do it," because I don't think the hepatologists know the patient level.

I know 67 percent that are blips and came back normal, but there were 33 percent that may not be blips. So if you continue the drug, say, with LFTs three times or 2.5 and four months he goes to ten times, I think that that data is not there yet.

CHAIRPERSON PACKER: Rob.

DR. CALIFF: I think Lem was.

CHAIRPERSON PACKER: Oh, Lem. I'm so sorry.

DR. MOYE: I feel somewhat less reassured than Udho does, I think, because I think we're all handcuffed by the low incidence rate of the event in which we have such great interest, and with this low incidence rate, this sample, even though it is a large sample by many standards, is still not large enough for us to have any reassurance, and we need to be assured that the population from which the sample is derived is not going to see liver disease.

That's the important issue for us, and to what degree does the sample reassure us? The incidence rate is so small; the sample is so small that, in fact, we can get no reassurance from this.

CHAIRPERSON PACKER: Rob?

DR. CALIFF: Yeah, I guess my response to the question is that I am moderately reassured by the clinical trials that have been done. It's a modest experience. Nothing terrible happened, but the two points that -- and I'm also somewhat reassured by the fact that Ray said that in his experience he hasn't seen a lot of this. Hepatotoxicity seems to be idiosyncratic and not related to the underlying population.

But, you know, I wouldn't really call what's been done here clinical trials. I would call

them well done physiologic experiments because the trials really don't represent the patients we've seen in practice or the situation in which the treatment is going to be used in the real world.

So in the setting of a clean physiologic experiment, things look pretty good.

CHAIRPERSON PACKER: Marv.

DR. KONSTAM: I'm not reassured. I guess the most I think you could say is that there's obviously no death signal in the data set or severe liver dysfunction signal in the data set, but, you know, for example, if you assume that the incidence of LFT abnormalities was in the one or two percent range, and if you assumed that -- and that that was real -- and that ten percent of those patients were to go on to have severe liver failure, then, you know, you're in the range of one in a thousand.

And in the range of one in a thousand we might not see any clinical cases, and then one in a thousand over what period of time? And so at that level, we may well not see any case, and I guess this is just what Lem was saying, but just in more specific terms.

We might well not see that in the data set that we have. So I can't see how -- and yet I don't

think that we would approve the drug. If we knew that there was a one in a thousand incidence of death from another antihypertensive agent, I don't think we'd approve the drug.

So I don't see any reassurance. I think we're going to be left with saying, you know, is there enough of a signal in this LFT abnormality to make us say, "Identify a trial that will give us that reassurance," and then I'm not sure how big that trial is going to have to be.

So I guess we'll get to that, but I can't see how you can say you're reassured that there is no clinically relevant hepatotoxicity from the data set.

CHAIRPERSON PACKER: Marv, let me just pause for a second. You must be a little reassured. I mean, to the extent that there is a database, it's better to have no cases than to have some.

DR. KONSTAM: No, let me be clear. By saying I'm not reassured, it's not an indictment of the drug and is not necessarily commenting on the level of concern that I have about the LFT abnormalities. It's a broader lack of reassurance. I mean it's a lack of reassurance about -- and this relates to what Rob is saying -- it's a lack of reassurance with the type of data that we accumulate

in antihypertensive trials.

And so if you ask the question, are you reassured, you know, the answer just is no because we don't have a database in any of these trials big enough to detect, say, with certainty a one in a thousand rate of severe hepatotoxicity.

CHAIRPERSON PACKER: Maybe the way of phrasing this, and then I'm going to ask Lem to comment, is that what I think I hear Marv saying, Rob saying, and Udho saying is that there is some reassurance, but it's not the kind of reassurance that you're looking for. Is that fair?

DR. MOYE: What kind of reassurance is that?

CHAIRPERSON PACKER: No, the kind of reassurance you're looking for to be able to feel secure about a regulatory decision. I want to try to reach a consensus here, and is that accurate, Marv? Not really.

DR. KONSTAM: I think if you're using the term "reassurance," I don't think we're going to wind up with a sentence that I'm going to agree with.

CHAIRPERSON PACKER: Lem.

DR. MOYE: I think I might disagree with you a little bit, Milt. I think no deaths in this

small sample is no reassurance, absolutely no reassurance. If we had adequate power, of course it would be. In fact, with adequate power, you could have a few deaths and still be somewhat reassured, but in the absence of adequate power, no deaths for me means no reassurance here.

CHAIRPERSON PACKER: Barry?

DR. MASSIE: The statement really doesn't say no deaths though. It says no clinically apparent liver disease, and I think that the absence -- well, I don't think it's the same thing -- the absence of even a bilirubin elevation of three or a symptom has to be somewhat reassuring in a database of 4,000 people.

Now, is it reassuring enough to have no concern? Of course not. So I think it's the modifier, somewhat, moderately, whatever it is, but it's not like there's no data. There's no data on mortality. I think that's fair to say, given the numbers, but on liver disease, I think there is some data.

CHAIRPERSON PACKER: Ray.

DR. LIPICKY: I think that was the gist of the question. That is, in fact, this is for liver disease, clinically apparently liver disease. That's

what was being asked about. None of that was observed.

And the reason that one discusses enzyme elevations and/or bilirubin and/or alkaline phosphatase is from the vantage point of trying to get a feeling for whether or not this is likely to be -- whether this drug could cause liver disease.

So the enzymes don't enter into this. The thing is there were no clinically apparent liver problems noted, and that fact alone, does that give you any reassurance?

And from the vantage point of what reassurance means here, Lem's interpretation is sort of what we were thinking about with that word, was the confidence limits here are very wide, and so not seeing and not observing anything doesn't tell you very much.

CHAIRPERSON PACKER: Let me ask a question before going back to Lem.

Ray, has there been an example of a drug which produced no abnormality of liver function during the clinical trials, but produced clinically apparent liver disease after its approval?

DR. LIPICKY: Well, if you accept the 13 cases of sartans post marketing, the answer is yes.

CHAIRPERSON PACKER: There were no abnormalities of liver function --

DR. LIPICKY: That were detected.

CHAIRPERSON PACKER: -- that were detected during clinical trials.

DR. LIPICKY: That anyone thought would represent a signal.

CHAIRPERSON PACKER: Okay.

DR. LIPICKY: Now, whether you should take that as evidence of anything, I'm not sure. If you take those things that cause liver abnormalities frequently, labetalol, levilol, dicrinothin, the answer to the question you asked is no. There was always something in the database, and in fact, labetalol was approved with full knowledge that there was actually 25 cases of liver disease, all reversible, and therefore, it was approved with labeling that said, "Draw enzymes frequently." And I can't remember what, but I believe once a month, and the real issues with all of these things were that people, when they become sick, really get pretty sick, and that all that's happening is they're getting sick, is their enzymes are going up a little bit each month.

CHAIRPERSON PACKER: Maybe just to clarify, Dr. Zimmerman, Dr. Maddrey, any knowledge

that you have of a drug totally clean in terms of transaminases during clinical trials that produced clinically apparent liver disease post marketing?

DR. ZIMMERMAN: I'm not sure, but looking, from what I know of the rezulin data, it seems to me the severe cases that appeared after marketing were a total surprise.

Now, I don't know what the enzyme data were beforehand. I know there were no important cases beforehand. Rezulin, troglitazone.

CHAIRPERSON PACKER: We may have someone who's --

PARTICIPANT: I think of the 2,510 cases, the earlier slide was correct. There were two cases of jaundice in patients who were clearly symptomatic.

DR. ZIMMERMAN: I didn't know that.

PARTICIPANT: No, there's no doubt about that. There were three cases with transaminases of greater than 1,000 in patients who were totally asymptomatic, but those two others with jaundice were symptomatic, and when the drug was discontinued and, of course, it was reversible fortunately.

DR. ZIMMERMAN: On the other extreme, you have the example of tacrine where almost 50 percent of the patients developed enzyme abnormality and hardly

any liver injury occurs. There's something greatly missing between the frequency of enzyme abnormality and its predictability for overt disease.

CHAIRPERSON PACKER: Marv.

DR. KONSTAM: You know, just to stay in the abstract for a moment, I mean, I think that we have to ask the question at what level of certainty would we like to be in terms of ruling out serious adverse events in antihypertensive agents. That to me is the question.

And so I think you can look at this data set quantitatively, and you, I think, probably would wind up concluding, for example, that you can rule out major toxicity at the level of one per hundred patient-years, but perhaps not at the level -- I don't think at the level -- of one per thousand patient-years. You won't see that here.

And so that's really the question before us. I mean, I think the question is in general terms at what level do we want to rule out serious adverse events, and if we do decide that we want to be certain at the level of one per thousand patient-years, then we should be designing clinical trial programs to rule that out. We don't have one here.

CHAIRPERSON PACKER: But I just want to

make sure that we remain focused here. Let's assume that there were another NDA for the treatment of hypertension this afternoon, and that NDA had 4,000 patients, and in the entire NDA database there were five cases of increased LFTs, more than three times normal, and giving an overall incidence of LFT abnormalities of .02 percent. I didn't calculate it out, but something low.

And because it was beneath the FDA reviewer's radar screen, it didn't come to the Committee, but I think everyone on this Committee the next time it gets a drug for the treatment of hypertension is going to pick up the books that we receive and look directly at the LFT section, and it's going to find a couple of cases of LFT abnormalities. I guarantee you you're going to find this.

DR. KONSTAM: Can I? I think you're hitting -- this is exactly what the quandary is going to be that we face here because if, in fact, we're concerned about the LFT signal, then we're going to have to say what do we recommend be done about it, and I'm not sure that we're going to have the gumption to advise designing a trial that will with certainty really get at the question that we want, which is: is there a one in a thousand or what have you likelihood

of severe hepatotoxicity?

That would be what we would have to do if we wanted to pick up on this signal that we're seeing, and that's the dichotomous choice that we have.

DR. MOYE: Speak for yourself on the gumption issue.

PARTICIPANT: Right. Why not have that gumption?

DR. KONSTAM: I'm not saying we won't, but that's the decision that we're going to have to make.

CHAIRPERSON PACKER: Let me just emphasize. The point that Lem is raising is a point which is a generic issue as to how much safety you need to feel comfortable or reassured about a drug that is given long, long term based on approval of a surrogate endpoint with a difficult to calculate risk to benefit relation because one actually isn't measuring benefit. It's what was said earlier. There's a surrogate for efficacy, and there's a surrogate for safety, and you put two surrogates together, and you've got real problems.

And there is a real issue here. So if you just keep that in mind because any recommendations we make here should, if we're true to ourselves, be generalizable, and we need to just keep that in mind.

Please.

MR. SCHNEIDER: Yeah, I'd just like --

CHAIRPERSON PACKER: Could you identify yourself? I'm sorry.

MR. SCHNEIDER: My name is Bruce Schneider from the sponsor. My background is statistics.

And I just want to make a point about this issue of power and what you can see with these sample sizes, and if you accept the notion that all patients exposed in this entire clinical trial program, and they had some possibility of developing a clinical event, you can work out --

CHAIRPERSON PACKER: Could you pick up the microphone? We're having -- that's great. Thanks.

MR. SCHNEIDER: If you accept the possibility that all clinical patients exposed had the possibility of having a clinical event, then you can do some calculations here, and for a one in a thousand underlying rate, which is what some people have been talking about, a 90 percent power would require a sample size of 2,300 patients.

Looking at this in a different way, with the 4,000 people exposed to tasosartan in this trial, again, assuming that you had a one in 1,000 rate of occurrence, then the probability of seeing no events

is .018 or 1.8 percent.

So you do have reasonable chance of having seen at least one event if that were to have occurred.

DR. KONSTAM: Yeah, if we assume that the underlying rate was one in a thousand.

MR. SCHNEIDER: If you assume the rate were one in a thousand.

DR. KONSTAM: If it were one in 5,000 --

MR. SCHNEIDER: If it were one in 5,000 or one in 10,000, of course, the numbers become much higher.

DR. KONSTAM: Yes. There's a time element also that we've got to deal with because are we talking about one in a thousand or one in thousand years of exposure, patient years of exposure, or what are we talking about? Because if we're talking about one in a thousand over one week of exposure, you know, that's not going to be sufficient. So you --

MR. SCHNEIDER: I'm just talking about patients exposed. I'm not --

DR. LIPICKY: You drop everybody who was likely to develop a problem. So that's just not a fair calculation.

MR. SCHNEIDER: Well, you have to talk about exposure, actions taken during --

DR. LIPICKY: No, no, no. Look. It is not just exposure. These are idiosyncratic things. It isn't just the number of patients, and every patient that might have developed something was eliminated because they weren't allowed to continue, on the whole.

So those numbers just aren't fair numbers to cite I don't think.

MR. SCHNEIDER: Yeah, I think you need to understand what all the assumptions are here, but I just want to try to clarify something in terms of pure number calculations.

CHAIRPERSON PACKER: I don't -- Ray?

DR. LIPICKY: Well, Milton, can I just say one thing? I don't know if it'll be useful, but you know, we're not trying to establish here the sort of absolute incidence that would make anybody worry. You know, I did cite some numbers as guidelines, nor try to come to grips with having hard data for approval for antihypertensives. I don't think we need to try to go through that decision making process.

But as I see this problem and the reason we're here is that for every antihypertensive, if there is no signal by QTC prolongation or enzyme elevation or something like that, generally we, maybe

not after you guys are done with us, but we are generally willing to not ask the hard question of do we really know whether this is useful, okay, and go along with the surrogate.

Just like for treatment of headache, you know, you see pain relief and you don't want to see a mortality trial to be able to be sure that people don't die more frequently when they are headache free. So we take that, but indeed, the problem is exactly what we're talking about. When is there a signal in the data that would make those precepts wrong; that that's one of the things we're talking about.

And I guess the alternative would be that you could come to the conclusion it is irrational to think you can try to look for these signals, and therefore, you should always insist on the morbidity/mortality trials.

CHAIRPERSON PACKER: Would you like the Committee to consider that?

DR. LIPICKY: After you're done with these questions.

(Laughter.)

CHAIRPERSON PACKER: Okay. We will try.

I think it would be fair since number two is such a pivotal question to go down the Committee

and simply ask individuals whether or not they are reassured, and if they are, to what degree they are reassured, and you can state why.

And, Cindy, why don't we begin with you?

DR. GRINES: I'm moderately reassured by not having any clinically apparent liver disease, and it was my understanding that some of the cases that had elevated LFTs were maintained on therapy and abnormalities went away on their own.

So, in fact, those patients were not all withdrawn from the drug, and despite that, appeared to not have any serious problems.

CHAIRPERSON PACKER: John.

DR. DiMARCO: I'm not sure what reassured means. I don't think this reassures me that there will be no incidences of liver disease or death due to liver disease if this drug were to come out worldwide. However, I don't think that the incidence will be particularly high.

I think we have some reassurance that it's not going to be a high incidence, and exactly where the line between too high or when is a low incidence too high to accept I think is a very difficult one to say.

I don't think we know how low it is or how

high it is. We know it's not above some final number.

CHAIRPERSON PACKER: Lem.

DR. MOYE: Yeah, I'm not reassured for the reasons I gave earlier, and also for the fact that we really don't know the -- we don't have the link between the chronic mild occurrence of elevated liver enzymes and long term clinical sequelae. I mean that's an important link not to have.

In the absence of that and because of the low incidence rate, I am not reassured.

CHAIRPERSON PACKER: Bob.

DR. CALIFF: I guess maybe the best I can say is I'm no less reassured by these data than any other hypertension database that we've seen. I think it's practically -- you know, I think patients expect their doctors to know whether the treatments they're giving actually benefit the patients, and we have no knowledge one way or the other for this drug or the other ones that we've looked at for hypertension.

CHAIRPERSON PACKER: But that's actually not the question.

DR. CALIFF: Well, but reassurance has to be in the context of what's the risk relative to the benefit.

CHAIRPERSON PACKER: Okay.

DR. CALIFF: So I'm not reassured.

CHAIRPERSON PACKER: Okay. I understand. JoAnn.

DR. LINDENFELD: Yeah, I'm mildly reassured that there won't be a high incidence of serious liver toxicity. I think, of course, the question is what is the incidence that we have to be concerned about, but I'm mildly reassured by this data.

On the other hand, I think this population of patients that we studied was also a relatively low risk hypertensive population, and I'm worried. I don't think we know if low risk hypertensive patients also have a lower risk for liver toxicity or if it's truly idiosyncratic. So I'm just very mildly reassured.

CHAIRPERSON PACKER: Marv.

DR. KONSTAM: I'm not reassured. I mean, I guess my entire uncertainty around the approvability of this drug relates to how concerned I should be about the LFT abnormalities. If I am concerned about those LFT abnormalities, I am not reassured by the level of lack of severe liver disease that we have in the data set because I think we could have a significant problem there and not see it in the

present data set.

CHAIRPERSON PACKER: Udho.

DR. THADANI: As I said earlier, I'm somewhat reassured that there were not clinical cases of liver toxicity -- liver disease, but with one caveat. In this trial, they did the enzymes very frequently, and the fact that the liver enzymes were up, the patients were stopped, and I don't know what would have happened to those patients if you continued that without following the same rules of the study trial.

So, you know, we're not talking about death or liver disease. In this particular trial there were no actual liver disease problems, but what would happen to the patient if you did not stop it? And I don't think I heard any even from the experts. I don't think the experience is there, although they were 67 percent normalized, but, say, if it was three times, four times, would they go into fulminant liver problem? I don't know.

CHAIRPERSON PACKER: Ileana.

DR. PINA: I share what Udho was saying. I am not reassured from the data that I'm seeing. The population studied may not be the population that we see in the post marketing type of population.

We've been told by the liver experts that elevations of five times or higher should make us be concerned. Many of the patients were dropped when they got to three times higher. So I don't know what would have happened to those patients had they continued.

The one reassurance that I have is that some patients returned back to baseline doing absolutely nothing, but I wonder if those blips were caused perhaps by some other factor and not necessarily by the drug because we see this clinically a lot.

CHAIRPERSON PACKER: Dan.

DR. RODEN: I'm reassured, but my level of reassurance is really sort of going to be difficult to distinguish from no effect at all. I think that you can say that there's not going to be a huge incidence of acute liver failure with this drug. I think you can say that, and beyond that I think that I don't have anything new to add to all of the issues that have been discussed already.

Except I would say one thing, Ray, and that is that we should just stop using the term "idiosyncratic" to describe these reactions. That just means -- there is a mechanism. We just don't

know what it is, and that, I come back to my sense of scientific frustration again because that's a word that I really object to because it just says we're ignorant.

CHAIRPERSON PACKER: Barry?

DR. LIPICKY: Do you have an alternative word?

DR. RODEN: No.

DR. MASSIE: I would say I'm somewhere between mildly and moderately reassured echoing the reasons that Cindy and others have stated. I should point out, and maybe this is getting into Rob's territory, that there were 13 deaths in this experience. That's a lot of deaths. This is not a low risk population. That's one out of every 300 people in their trials. So I really think this is a general question. This is not so much a liver function question.

CHAIRPERSON PACKER: I guess I'm mildly to moderately reassured only because I think it's better to see no clinical events than to see clinical events. It may not be the level of reassurance that everyone is seeking, but I think it's nice to see that there weren't any cases.

All right. The Committee vote on that one

was six to five, six meaning that six members believed that there was some reassurance even though it might have been mild. Sometimes I can't believe the kinds of votes we take.

Okay. There have been scattered post marketing reports of clinically significant liver disease convincingly attributed to some of the sartans. Should these reports be treated as drug specific or do they suggest a class effect?

Dan got into this earlier. Udho, what do you think?

DR. THADANI: I think what we have heard from the experts we'll have to think they're drug specific. Metabolites are different, and I think unless we have a clue we can't say they are class effects. I would say it would have to be each individual drug read could be different because of either the metabolite or the paired compound because to my judgment what I've heard is not a class effect as a drug specificity.

So the answer is drug specific.

CHAIRPERSON PACKER: Okay. Dan, did you want to have anymore comments on this?

DR. RODEN: I mean, I guess if there were a drug, if there were a class effect from whatever

mechanism, then this is what you'd expect to see. So it doesn't -- I don't know whether I like the wording, but they're certainly compatible with the idea of a class effect, and my frustration was before, again, nobody seem to have any handle on the mechanism whereby a class effect would or would not arise.

I'm not sure I like the wording of the question.

CHAIRPERSON PACKER: Here's the concern about the --

DR. RODEN: No, no, I --

CHAIRPERSON PACKER: -- concept of class effect has -- is not only an issue related to what do the data show. I think it puts the Committee in a position of having to judge whether whatever labeling is created for this drug will be different than labeling that exists or may be created for other sartans.

So the question here is a generic issue, in part, but a specific issue in others because it says, "Should the existing reports of clinically significant liver disease with this group of antihypertensives be treated as drug specific or do they suggest a class phenomenon?"

And I understand intellectually we don't

want to say "class phenomenon."

DR. RODEN: No. That's not quite what I said. What I said was that if there were a class effect through whatever mechanism, then this is what we would expect to see, and perhaps my difficulty with this question is that there have been 13 cases now, Bob, and out of several million patient year exposures. So if in a year from now or six months from now there are 1,300 cases and they include all three, perhaps four, depending on what we do with this drug, available AT1 receptor blockers, then I think the question will have answered itself.

So at some point the agency tracking the data will come to some level of comfort. Now, sort of quoting -- this is the way Bob Fenichel would -- come to some level of comfort and say this is a class effect or not, and I don't think we have those kinds of levels. I don't.

DR. FENICHEL: Well, let me just get back to some grounding in reality with the numbers. There are not enough people in the United States to have 1,300 cases, you know, if the incidence rate is the same across the class between now and a year from now because there aren't that many people getting treated with these drugs, and we're talking about incident

rates on the order of one per million.

You can't do it. The question is -- I mean, the analogy which perhaps should be brought, you know, back to public recollection is if you look at the ACE inhibitors, there is now labeling language in each of the ACE inhibitors that points out a shared int hat case mechanism understood or at least mechanism theorized, but I should say mechanism theorized.

There is a mechanism theorized for anaphylactoid reactions when people have bee sting therapy, bee sting desensitization and may be tolerating that well. An ACE inhibitor is introduced, and then there is a definite incidence of angioedema, of anaphylactoid reactions.

Well, that is a very rare phenomenon. It's happened, I think, three times that's been reported, and when an ACE inhibitor was inadvertently reintroduced and the person had been tolerating this bee sting desensitization fine, and then -- but it certainly is not something we know about all the ACE inhibitors. It seemed prudent to stick it into labeling because we do believe that it is related not to some mysterious property of the specific molecules with which it is reported, but rather to the fact that

the ACE inhibitors are all bradykininase inhibitors.

Now, I don't know that that is true. Bradykinin levels were not measured in those patients. They're rarely measured in anybody. How much sureness about mechanism do we need before we give this kind of advice to people who are looking for what drug to remove when a liver problem develops and one of several drugs may be responsible?

I don't think there is any simple answer, but to say that almost solipcistically that every piece of data stands on its own, every molecule is distinct from every other, that's not fertile.

DR. RODEN: No. So I think that if your question is given a patient who develops an elevation in a transaminase level and they're only taking an AT 1 receptor blocker and a benzodiazepine, then I would implicate the AT1 receptor blocker.

PARTICIPANT: That's a class judgment.

DR. RODEN: I understand that, but that's because the only other class drug has been cleared by the liver experts.

So if there is a class action, the data are what one would expect.

CHAIRPERSON PACKER: The problem with the word "class phenomenon" is it implies a greater

understanding of mechanism than we have.

DR. RODEN: Right, exactly.

CHAIRPERSON PACKER: And I think it may be better to reframe the question. Should these reports be regarded as drug specific or should they be characteristic of the available sartans?

Because if one says class effect, one assumes that one actually understands how a sartan by what it does can cause liver injury.

Dan, am I summarizing that correctly?

DR. RODEN: Yes.

DR. FENICHEL: Okay. I think that that is well taken, and let me rephrase what I think was the intent of the question, and Ray may want to comment on this, but it seems to me the intent of the question was we now have some data that come entirely from losartan and valsartan because they're out there. Should new sartans, about which there is no hint of serious liver toxicity -- irbesartan, for example is out there. Well, it hasn't been out there very long. Should irbesartan mention that this is something seen with other agents in the class or is that no more relevant than that liver toxicity is seen with dilevilol or isoniazid?

CHAIRPERSON PACKER: Barry.

DR. MASSIE: I think the important issue -- I'm glad you raised the analogy to the pril group because the neutropenia there is more, I think, analogous to what we see.

I hear a "no."

DR. LIPICKY: I mean only from -- there's only one place where neutropenia was seen, and that was with captopril. The reason that the neutropenia is in all of the labeling is because in the captopril circumstance it was very clear that there was a patient population that could be studied where one could have an incidence of neutropenia sufficiently large to clearly rule out that the new drug causes that problem, and all of the people developing the ACE inhibitors refused to take that challenge, and we said, "Okay. Then you can have neutropenia in your labeling."

DR. MASSIE: I understand.

DR. LIPICKY: So it is not an analogous circumstance from a regulatory point of view, nor is it an analogous circumstance because in this case you can't identify how you can get liver disease. So you can't study a population where the incidence might be very high.

DR. MASSIE: Okay. Let me take that

comment back, but I think there is something. I guess my feeling is we don't understand mechanism. I guess in this case we're far from understanding mechanism. If there are convincing cases with two drugs that have this action, I'm beginning to say, "Show me. Prove to me that other agents of this class do not have the action."

At some point when there's three sartans that cause liver failure, and we've excluded other things that cause liver failure, tox., alcoholism, and other things, then I think that the balance begins to shift, and if the agency becomes convinced that there are three different agents that do this, I think one has to begin to put into the labeling some concern that many agents with this action have caused liver dysfunction, and as a result of that, you need to be concerned that if your patient gets liver dysfunction, it may be related to this drug.

I don't think the enzymes that we're seeing here weight one way or another. I think what you now should be on is alert status, and one more agent that does it makes me think that there is some action of statins that raises concern --

PARTICIPANT: Sartans.

DR. MASSIE: Sartans.

CHAIRPERSON PACKER: Okay. I think everyone on the panel wants to say something, but probably the best way to say it is in answering specifically going through the question.

Let me also for the record simply say that the vote on the previous question about reassurance was seven to four, seven gaining some reassurance about the absence of clinically apparent liver disease.

Why don't we -- the question to the Committee is: should the reports of post marketing clinically significant different liver disease be treated as drug specific -- and I'm revising this question after recent discussion -- or do they suggest a characteristic, a side effect which may characterize many members of the sartan class?

That, I think, gets away from the bias towards identifying a mechanism because we can't do that.

Barry, let me ask you to begin -- I'm sorry. Udho, please begin.

DR. THADANI: I think the fact that in this database there's no cases of liver toxicity or clinical toxicity, it's very difficult to be absolutely sure, and the fact that you're seeing only

in the post marketing database which you haven't seen. I think at the moment my feeling is that we should say that it has been reported with the two statins which are out there.

CHAIRPERSON PACKER: Sartans, sartans.

DR. THADANI: Sartans which are available. So it could be drug specific, but the fact it happened to two, I think one should raise at least the suspicion level that one has to watch very closely with other sartans that will be coming up.

CHAIRPERSON PACKER: Okay. So that there --

DR. THADANI: There may be some class effect, but I'm not actually sure because --

CHAIRPERSON PACKER: I really want to avoid the term "class effect." I think what we've heard is the more precise term, which is that this might be characteristic of many members of the sartan group.

DR. THADANI: I don't think you have enough data to say that.

CHAIRPERSON PACKER: More than one.

DR. THADANI: It was reported with more than one. There's two at the present time. That's all you could say. Experience with that is very

limited.

CHAIRPERSON PACKER: Okay. Barry. We're going to go down this way, right.

DR. MASSIE: I think I pretty well said I think we're at the status where there may well be such a characteristic effect of this group of agents, and for me it would take one more agent to make more statements, more strong statements.

CHAIRPERSON PACKER: Dan.

DR. RODEN: Whatever Barry's vote was, it was my vote, too.

CHAIRPERSON PACKER: Ileana.

DR. PINA: I would keep it drug specific at this point. I'd need to see more cases than the other sartans now available to really say that it extends across.

CHAIRPERSON PACKER: Marv.

DR. KONSTAM: Yeah, I would keep it drug specific. I don't see any significant support at this point either on the basis of uniformity of action or on the basis of mechanistic concept that would make me suggest even that it was a class effect.

However, I would say that it might be prudent nevertheless in labeling to make some comment to say other drugs of this class have shown this. I

wouldn't object to that kind of remark.

CHAIRPERSON PACKER: Okay. I guess I'm a little bit confused. What I thought I heard Barry and Dan say was they considered this to be a characteristic of more than one member of the class. Ileana said she disagrees with that. I think that that's what you said, and you're saying that --

DR. KONSTAM: To answer the question, the question asks drug specific or group specific, and I would stick to drug specific at this point. I don't know what it means or how it helps to say we've seen this with a couple of drugs. I don't see how that helps.

I think the question is going to be: do we see any evidence or any rationale for attributing this to the class? And at this point the answer is no.

CHAIRPERSON PACKER: The rationale for the question, I think, to the Committee is that as we go forward through the questions, the Committee is going to be asked to recommend a decision about the approvability of tasosartan; and if that is yes, the labeling for tasosartan; and any statements in that labeling that pertain to what data exists about LFTs, and whether those abnormalities are -- does that

labeling now mention any other abnormalities with other sartans?

Because if it is entirely drug specific, then such labeling need not consider that.

DR. KONSTAM: Well, I just guess I have to expand on my answer. I think unless you have either evidence or mechanistic rationale, you cannot jump -- you should not jump to say that either a benefit or an adverse effect is class related, and I don't think we have either of those.

And so I don't see any evidence for saying that there is an adverse class effect here. I would though add one little caveat, that I wouldn't see anything wrong -- and somebody can say there might be something wrong -- with putting on labeling of newly approved sartans, a comment that says some other sartan caused this, although we don't know that that's a class effect.

I wouldn't see any problem with that even though we don't have any evidence for it being class effect. Does that make sense?

CHAIRPERSON PACKER: Yes.

JoAnn?

DR. LINDENFELD: Yeah, I think I agree with Marv. I wouldn't be quite willing to say yet

that this is a class effect, and I also think from the data that this drug has more problems -- I'm convinced that it has more problems at least with elevated liver function tests than the other sartans.

CHAIRPERSON PACKER: Rob.

DR. CALIFF: I pretty much agree with Marvin. I think there is a solution to this problem, but hopefully we'll get to that before dinnertime.

CHAIRPERSON PACKER: Yes. Lem.

DR. MOYE: Well, to the extent that this question is hypothesis generating, I would say yes. The question is a relevant one, is what was found with this drug, raised the issue, the possibility of a class phenomenon.

If the question is can we draw the conclusion that this is a -- I'm sorry. I can't keep track of the right phrase. I'll just say the class phenomenon -- if the question is can we draw a conclusion, then my answer is, no, we can't.

CHAIRPERSON PACKER: John.

DR. DiMARCO: Well, Bob's presented information that there is liver disease in two drugs which have significant post marketing data. The other two drugs, including this one, we don't really have that large a body of data. So we can't really exclude

that they're not going to show the same frequency.

So I think that if your statement is characteristics or is a characteristic shown by several members of this class, I'll agree with that, yes.

CHAIRPERSON PACKER: Cindy.

DR. GRINES: I agree. I agree with John's comments.

CHAIRPERSON PACKER: Okay. I think that regardless of how the individual votes came out, the consensus is that the present phenomenon about liver function, clinically significant liver disease, to this point in time should be viewed in accordance with the drugs to which they were reported, but, in fact, a pattern may be emerging, and that pattern may be important with respect to all members of the class, and the data right now are not available to provide any guidance on this. I think that's a fair statement.

Number four, in the absence of reported cases of clinically apparent liver disease, what is your interpretation of the data related to observed elevations of hepatocellular enzymes in patients in control trials of tasosartan and the other sartans?

Udho.

DR. THADANI: I think there's no doubt that the liver function test or the ALT abnormalities occur, which we heard from the experts and my own judgment indicates some liver damage, and I think this is true when the data was provided from the FDA database on other sartans, as well, that it's not just unique to this. The only thing is probably the incidence is higher than the other drugs supported, and the reason possibly could be --

CHAIRPERSON PACKER: That's the next question.

DR. THADANI: Okay, and so it's there. Now the only question is what is the significance in patients who discontinued it. What would have happened to them I still don't know. So that's part of this question, too, because it said what is your interpretation.

So the interpretation is, yes, that these liver function abnormalities are real, and they are in sartans more so here, and the problem is the patients who dropped out because of this. What's the significance of this? Again, we don't know because of the absence of disease.

CHAIRPERSON PACKER: Okay. Ray, maybe we can ask for some guidance here. It's clear from the

way that this question is phrased that you anticipated that the Committee may have been quite reassured by the absence of clinically apparent liver disease, and this question is being asked to explore, well, with that degree of reassurance how worried are you about the abnormal transaminases that have been reported in the database.

Since this Committee is uniformly not very assured about this, is there -- and presumably the increase in LFTs is considered by this Committee to be a real phenomenon -- can we go on to question five?

DR. LIPICKY: Yes. Question four was to ask whether you thought it was a real phenomenon.

CHAIRPERSON PACKER: Right. Does anyone disagree that this is a real phenomenon?

(No response.)

CHAIRPERSON PACKER: Five, patients who withdrew from clinical trials of tasosartan are much more likely to have been receiving tasosartan than placebo. This sartan controlled difference in withdrawal rates was larger with tasosartan than with the other sartans. Was the unusually large difference probably the result of chance? Was it instead more likely to have been a consequence of tasosartan investigators' unusually frequent assays of hepatic

enzymes? And does it instead suggest tasosartan is more hepatotoxic than the other sartans?

And Bob.

DR. FENICHEL: Yeah, I just realized that in wording this question I did a grave injustice to the sponsor, and I really want to make this plain. The first sentence of the question should have read, "Patients who withdrew from clinical trials of tasosartan because of liver function abnormalities," and then the rest of it follows, but the statement as now given is flat out false.

CHAIRPERSON PACKER: Okay. Thanks.

So now having seen a higher incidence of LFT abnormalities resulting in withdrawal, what is the explanation for it?

And the three possibilities that exist -- and let me just present them again -- chance; two, sampling and/or duration -- that's not mentioned here, but I think that that's part of sampling -- and, three, that there's a difference between tasosartan and other sartans with respect to their predilection for increased LFTs and/or hepatotoxicity.

Udho.

DR. THADANI: I'm glad Bob stood up because if you look at the withdrawal rate, overall is

not different between placebo and the sartans. So I think that's true for this drug.

Now, there is no doubt in my review of this of the fact if you're going to sample patients at every week you're going to have some more abnormalities in the test, and that has something to do with it, although not knowing the investigator threshold.

The problem is if you don't have a definite cutoff at three times you have to withdraw and leave to investigator judgment, as it showed some of the patients are going to be stopped even when it's twice normal. So I think that had something to do with it.

Whether that explains the difference in the incidence, you know, in this versus other drugs has quite relevance, and same could be true with the longer exposure as well. So from my reading, I think both had some -- quite a bit of role to play. Unless you do have comparison with frequent labeling with a comparative drug, you can't answer the absolute question, the last part, does it suggest.

So I don't believe that the data I've seen that I could conclude this is a larger incidence, although if you look at the post marketing phase or

the open label studies where the frequency of measurement was probably every three months, as we've been led to believe, or not every week, in some of the studies the incidence was somewhat higher than reported.

So I think those are my remarks.

CHAIRPERSON PACKER: I guess to look at this question, and, Ray, there's a possibility that members of this Committee will not be able to pick one of these three answers or may want to pick more than one or may want to say that they either need more data or just don't know. So I guess we need to include that as possibilities.

DR. LIPICKY: I guess so, but I'm not sure why there's some difficulty with it. In four you basically said you're sure there is a phenomenon documented in the data. This simply is asking that same thing sort of, you know, is there a phenomenon documented in the data, but it's coming at it from the point of view of dropouts, and it's asking about placebo controlled trials and positive controlled trials and whether the dropout rates in those trials, in fact, differentiated tasosartan from placebo and/or the positive control.

And then it asks -- and maybe the thing to

do is to say yes or no to that, and then to ask the question: is there some non-tasosartan property that could have caused it to be differentiated? I mean that's all that that's asking, I think.

CHAIRPERSON PACKER: Marv.

DR. KONSTAM: You know, Ray, the sponsor is claiming to have done an analysis that indicates that all of the difference between LFT abnormalities and, therefore, to some extent the dropouts is explainable on the basis of the higher sampling rate of LFTs.

DR. LIPICKY: No. What they're claiming is that they look like the sartans.

DR. KONSTAM: Right, right.

DR. LIPICKY: Across studies and stuff like that.

DR. KONSTAM: Agreed.

DR. LIPICKY: They do not claim that their studies did not differentiate tasosartan from placebo on the basis of --

DR. KONSTAM: Okay. Agreed, and we're saying -- I'm sorry.

DR. LIPICKY: Okay?

DR. KONSTAM: I agree.

DR. LIPICKY: And nor do they claim that

it did not distinguish tasosartan from the positive control trials.

DR. KONSTAM: Agreed. But so the question relates to differences between tasosartan and other sartans.

DR. LIPICKY: Correct.

DR. KONSTAM: And so in that regard the sponsor is suggesting that it's explainable on the basis of the sampling rate.

DR. LIPICKY: Right.

DR. KONSTAM: When someone asked you, you know, does the agency concur with that analysis, your answer was we really haven't done that analysis sufficiently to concur or not concur.

DR. LIPICKY: Well, no, and there was an unspoken answer to that also. I don't care.

DR. KONSTAM: You don't care?

DR. LIPICKY: Yeah. I'm only concerned with whether in this set of data tasosartan distinguished itself from something.

DR. KONSTAM: Well, but --

DR. LIPICKY: I don't care whether in going across studies --

DR. KONSTAM: But in my mind --

DR. LIPICKY: -- it makes much difference.

DR. KONSTAM: Well, but I think this gets to the heart of this question because in my mind and maybe other members of the panel, there is the possibility that the distinction, apparent distinction, between tasosartan and losartan, for example, is a function of differences in the protocol design, and I'm not sure about that.

Now, that's not --

DR. LIPICKY: You mean across studies, not within the studies.

DR. KONSTAM: Correct, correct.

DR. LIPICKY: Right. Well, cross-study comparisons is not what this question is directed toward.

CHAIRPERSON PACKER: Okay. Let me -- there are two databases that pertain to this question. First is a database consisting of placebo controlled trials with tasosartan and with other sartans.

DR. LIPICKY: Right.

CHAIRPERSON PACKER: And that database in order to answer this question, one would be mentally comparing the placebo corrected event rates on tasosartan versus the placebo corrected event rates on other sartans, and if one does that analysis, Marv's point pertains.

There's another database that the sponsor has presented which the FDA has not seen, which is a direct comparison of tasosartan and other sartans, which is not placebo controlled.

DR. LIPICKY: Right.

CHAIRPERSON PACKER: That database then could be used to answer this question as well.

DR. KONSTAM: But it's a small n. But that database has a small n relative to the entire tasosartan database.

DR. LIPICKY: Right.

CHAIRPERSON PACKER: All right. So do you want us to use our judgment as to which database to use or would you like us to focus the direct comparisons?

The advantage of the direct comparisons is that they are direct comparisons and don't require -- they correct for all of the assumptions in sampling and duration, but they're small.

The placebo controlled is a larger database, but there are different trials, maybe even different patient characteristics, and it's hard to compare across trials, and everyone knows the problems in doing that.

So do you want us to use our judgment

between those two databases in answering this question?

DR. LIPICKY: Sure.

DR. KONSTAM: Well, that then comes back to my point, which is that I don't think we have the data to answer it.

DR. LIPICKY: Fine.

(Laughter.)

DR. LIPICKY: I mean that's an answer.

DR. KONSTAM: Or the analysis to answer it.

DR. LIPICKY: Right. That's an answer.

CHAIRPERSON PACKER: Okay. Let me try to make life easy here. I'm going to try. How many members on the Committee think that the observed difference in the withdrawal rates between tasosartan in its placebo controlled trials and the other sartans in their placebo controlled trials is a result of chance?

DR. LIPICKY: Why don't you take them one at a time?

CHAIRPERSON PACKER: One at a time.

DR. LIPICKY: Placebo controlled and then the other is not placebo controlled.

DR. CALIFF: I think I've heard the panel

say that we don't have the data to answer the question that you asked. We just don't know.

DR. THADANI: We haven't seen the other database.

DR. LIPICKY: Well, but I guess I don't understand that answer. That answer says that the medical review was wrong, that there was not a differential dropout rate between placebo and --

DR. KONSTAM: No, you're asking a different question than the one Milton just asked. Your question is within the placebo controlled trial with tasosartan is there a difference in the dropout rate.

DR. LIPICKY: That is what this question is oriented toward answering.

DR. THADANI: No, no, it says other trials.

DR. MASSIE: This is two questions.

DR. KONSTAM: Right. If you ask us one question at a time, I think we can --

DR. LIPICKY: Well, that's what --

DR. KONSTAM: I thought Milton did ask one specific question, which was across drugs, and I think that the panel feels that there's not enough evidence to draw.

The conclusion about tasosartan versus placebo would be a different question, and it may be worthwhile answering that.

CHAIRPERSON PACKER: But the conclusion about tasosartan versus placebo is apparently not being asked because it is a phenomenon which has been observed. In other words, let me try to summarize what I think people are saying.

Tasosartan has more LFT abnormalities than placebo, period. There are more withdrawals because of tasosartan because of LFT abnormalities than placebo, period.

The question now is whether the LFT abnormalities, particularly those leading to withdrawal, which were -- if you look at that number, it is higher than the number of LFT abnormalities leading to withdrawal in the other sartan databases.

DR. THADANI: Un-huh.

CHAIRPERSON PACKER: Okay. Is that a phenomenon which is related to sampling and/or duration, or can you conclude or is there evidence to suggest that there is actually a true difference between tasosartan and other sartans in terms of the predilection to cause LFT abnormalities? Right, Ray?

DR. CALIFF: And I think everyone has

agreed with everything you said when you posed the question, and the three possible answers, yes, no, or we can't answer it because we don't have enough data.

CHAIRPERSON PACKER: That's correct, and let's do that.

DR. CALIFF: Right.

DR. KONSTAM: Can I just say one difference? There may be enough data if the analyses were done. In other words, it might be possible to look at the various data sets of the various sartans and do modeling such as the sponsor did or some more detailed analysis to shed light on this question. It won't resolve it completely, but it might be possible to do that with the data that exists.

CHAIRPERSON PACKER: Charlie Ganley?

DR. GANLEY: Yeah, I may be able to shed some light on losartan's frequency of getting labs, and I gave the information to Bob. I'm not sure if he included it in his document, but in their active and placebo controlled trials, blood tests were usually obtained in the treatment period either at the middle -- if it was an eight week trial, it would get it at four and eight weeks. It was never done on a weekly basis. So it was either done two times, for example, in an eight week trial or at the end of the trial.

In the open label studies, there was really no difference. I had talked to Dr. Klaje about it. There was no difference in the frequency of obtaining labs in the open label studies.

CHAIRPERSON PACKER: Okay. I think we have the question to the Committee, and the question to the Committee is: there is an observed dropout rate from LFT abnormalities in the tasosartan placebo controlled trials which is numerically larger than the dropout rate for LFT abnormalities in the placebo controlled trials with other sartans. What is the explanation or what do you think is the explanation for this difference?

Is it the play of chance, you know, these differences can occur? Two is do you think that it's because of the difference in study design. Three, do you think that tasosartan is truly more likely to cause LFT abnormalities, specifically those requiring withdrawal, than the other sartans? Or, four, you don't know.

Okay, and we'll take a vote, and let's start with Barry.

DR. MASSIE: I think the answer is at least in part it's due to the study design, and I don't know whether the drug is more hepatotoxic than

other drugs because I can't distinguish it from the play of chance.

CHAIRPERSON PACKER: Dan?

DR. RODEN: I agree with Barry.

CHAIRPERSON PACKER: Ileana?

PARTICIPANT: Whatever that vote was.

CHAIRPERSON PACKER: He agreed with Barry. Barry -- I think to summarize what Barry has said is that he is persuaded that part of it may be related to design issues, and the other part he is uncertain about. It may be chance, it may be numbers.

Did I say that correctly?

DR. MASSIE: Yeah. I guess that I tried to vote on two questions. One, I'm convinced part of it is due to the design, but the more important question you're asking all of us is is it hepatotoxic, and my answer is I can't tell from the data available.

CHAIRPERSON PACKER: Okay, and Dan said he agrees with Barry.

Ileana?

DR. PINA: I agree with Barry, too.

CHAIRPERSON PACKER: Udho?

DR. THADANI: As I said earlier, I think it's probably study design. You could address that issue easily if you could look at how many withdrawals

occurred at week four, week eight in the two databases. I'm sure there are statistical way to look at it, and if you find the withdrawal rate is much higher in the first four weeks, then you could say it was the study design. If it's not, then you could come to the conclusion it would be the drug, and this only applies to placebo control.

Now, if you look at the open label studies, then what we have been given is I think it seems to be a bit higher level. Whatever the reason I don't know. Again, we have to look at other database.

CHAIRPERSON PACKER: Marv?

DR. KONSTAM: I'm just going to leave it at I don't know.

DR. LINDENFELD: I agree. I just don't think we have the data to know.

DR. CALIFF: Ditto.

DR. MOYE: The best I can say is study design.

DR. DiMARCO: I think the data are not comparable. So I don't know.

DR. GRINES: I think the study design plays an important role, but I'm not 100 percent convinced.

CHAIRPERSON PACKER: Okay. I think the answer is that the Committee is uniform in saying that there may have been or some members are convinced there is a contribution of study design, but there is a big unknown factor which weighs heavily on the minds of all members of the Committee. No member of the Committee specifically believed that tasosartan was likely to be more hepatotoxic than other sartans.

Number six, assuming that tasosartan's antihypertensive efficacy is beyond challenge -- we as a Committee should assume that -- should tasosartan be approved for the treatment of hypertension, and if not, what sort of new study results should provide sufficient reassurance to permit approval?

Let us leave the second part aside. We need a vote on antihypertensive efficacy. We need a vote on approvability. Generally speaking this is a yes or no vote.

DR. THADANI: Regarding that --

DR. RODEN: May I ask a question of the agency? If we believe that this compound has a potential for hepatotoxicity and that potential is probably no better or no smaller than the now newly recognized potential potential for other drugs of similar mechanism of action, are we obliged -- I mean,

how do we factor that into the decision to recommend approval or not?

Are we holding the same --

DR. LIPICKY: I can make --

DR. RODEN: -- standard as before or --

DR. LIPICKY: I can make it fairly simple if you'd like.

DR. RODEN: That's the best way.

DR. LIPICKY: I think that if there is suspicion that there may be real hepatotoxicity that is tasosartan, that's the thing that you're considering. You're not considering whether you want to take losartan off the market. Okay? You're considering whether you want to approve tasosartan.

That there's some real chance of hepatotoxicity, my thought would be if I were you that I would say it is not approvable on that basis.

Now, I point out that a number of years ago when lobetalol was approved, the Committee members were fully aware that it was a hepatotoxic, and said, "Approve it, but draw bloods once a month and measure enzymes, and if enzymes go up, stop it."

The scenario at that time was that that was a totally new chemical entity that was a beta blocker/alpha blocker, and it was one of the more

recent new innovations in antihypertensive therapies. So that's sort of what surrounded that scenario.

And so I guess the third alternative is to not just say draw samples, but to tell the agency they ought to put this in a black box, and that's a big deal because then all promotion -- you know, it can't hand out pencils and little note pads. You have to give full labeling with all advertising, and you put the black box in the labeling, and then there's no casual promotion.

CHAIRPERSON PACKER: Ray, as I understand it, the purpose of question six as opposed to question seven, seven allows the Committee to explain. If the vote on six --

DR. LIPICKY: Right.

CHAIRPERSON PACKER: -- were to be yes, seven allows the Committee to then say, "Yes, but."

DR. LIPICKY: Right.

CHAIRPERSON PACKER: But you can't get to seven unless you think that --

DR. LIPICKY: Unless you do six, but I was just trying to make the decision making simple so you knew you could say yes to approve and then do something later, or if you really thought there was a problem, to say no to approve, or, in fact, you could

say yes to approve and you don't think there's any problem at all, and there'd be no labeling at all.

The Advisory Committee that looked at dilevolol before the agency acted in its wisdom said, "Don't put anything in labeling on the liver at all."

CHAIRPERSON PACKER: Marv.

DR. KONSTAM: Milton, I'd like to suggest that actually we do consider both parts of question six together, and the reason is, you know, in my thinking and maybe other panelists I think the issue of approvability or not approvability ought to carry with it some kind of notion of, well, what would you advise if it were not approved.

If the answer is, "I have no idea," I think that's different than if you had some kind of thought about what would make it approvable, and I'd like to see that discussion together.

CHAIRPERSON PACKER: You see, the problem with separating the questions is that it doesn't allow for a very important discussion to take place, which is, I think, the discussion that Rob would like to have, which is is this the kind of database that one should be presenting for the approval of an antihypertensive drug, period.

Now, Rob hasn't said that, but he has said

everything but that, and I think that there is a real important lesson to be learned by separating these two. One can be assured that, given the tenor of the Committee's deliberations, that seven will not be nothing. Seven will be something, and I think seven will be something that will vary according to the Committee's opinions.

But, no, six only says what additional evidence if you say no. So what really this should be is six says should the drug be approved. Six (a), which is the sub-question, is if not, what else do they need to do, and seven really is 6(b), which is if yes, what does the labeling say, which addresses all of the other issues about labeling, post marketing studies, et cetera.

You need to separate the two questions.

Udho, yes or no?

DR. THADANI: I want to make some clarifications. There's no doubt the drug is antihypertensive. So if you're just approving the drug for lowering the blood pressure, the answer would be yes, but we don't have anymore data. I think that's Califf's point.

Now, so I think it's approvable, but I'll have to put a lot of caveats to it.

CHAIRPERSON PACKER: This question only works if you say yes or no. You can discuss anything you want before yes or no, but it has to be yes or no.

DR. THADANI: So you want the answer first and then the discussion?

CHAIRPERSON PACKER: You can do it any order you want.

DR. THADANI: Okay. So I think I'd like to start with the discussion. I think you'll have to put a lot of issues. From my review the drug does lower blood pressure. We don't have any idea about the mortality effects or morbidity effects. It did not cause hepatic dysfunction, but I'm worried about the fact that it had a normal liver function test which in the protocol were done on a weekly basis, whatever the issue is. So I think we have to --

CHAIRPERSON PACKER: Okay. That's question --

DR. THADANI: So the answer is approvable.

CHAIRPERSON PACKER: That's question number seven.

DR. THADANI: Okay, okay.

CHAIRPERSON PACKER: Question number six is: do you recommend that the drug be approved for the treatment of hypertension, yes or no?

DR. THADANI: I'm going to say yes.

CHAIRPERSON PACKER: Cindy?

DR. GRINES: Yes.

DR. DiMARCO: Yes.

DR. MOYE: No.

DR. CALIFF: Can I have a moment?

CHAIRPERSON PACKER: Yeah, you can say anything you want as long as you vote yes or no.

DR. CALIFF: I'm going to vote yes, but the only reason is because this is every bit as miserable as every other antihypertensive database that we've seen.

DR. MOYE: Well, then why are we compelled to repeat the mistakes of the past?

DR. CALIFF: Well, I want to comment on that. I think what the Committee has said after all this discussion is that we're convinced that there is LFT abnormality. We don't know the clinical significance of it, and we don't even know if it's different than the other sartans that have already been approved.

As a matter of public policy I'm generically opposed to punishing an individual entity at an arbitrary point in time unless there is a general policy decision made that equally affects

people that are in a very competitive business environment.

To the general question of should we change the rules for hypertension approval, the solution to this problem is obvious, that if you did an outcome study and showed whatever the size it took that you reduced total mortality, stroke and heart attack, any rate of LFT abnormality would be okay if in the balance it was outweighed by the benefit in terms of reduction of the reason that we use the drugs in the first place.

Lacking that in this case, as in all others, I would vote yes.

CHAIRPERSON PACKER: JoAnn.

DR. LINDENFELD: I'm going to vote yes.

DR. KONSTAM: I'm going to vote no, and I would say, first of all, that I'm not convinced that based on what we've see, that it's a uniquely efficacious antihypertensive agent. So it may be, but I'm just not convinced of it from the data that we see to this point.

And in light of that, I continue to be concerned with the LFT abnormalities, and I'm going to slip in a comment on 6(b) because it goes into my rationale about voting no, which is if I saw a

convincing trial with a large enough n that indicated that the signal of LFT abnormalities was no greater with tasosartan than it was with, say, losartan, then I might not be reassured that there's no significant hepatotoxicity, but I would be reassured that the signal is no different than other sartans, and that would, based on the experience that exists out there with other sartans, would permit me to think of approvability.

So my answer is no.

CHAIRPERSON PACKER: Ileana.

DR. PINA: I'm going to vote yes, and I'll save my comments for when we come to question seven.

CHAIRPERSON PACKER: Dan.

DR. RODEN: Yes.

CHAIRPERSON PACKER: Barry?

DR. MASSIE: I'm going to vote yes, as well. Just a couple of comments. This is a little bit going against what Ray's instructions to us as a jury in the beginning because I have a lingering doubt that it might be more hepatotoxic than other agents, but it's a real lingering doubt, and I'm really concerned about Bob's elegantly phrased paragraph on perverse incentives, and in that sense I agree with Rob's comments about trying to maintain a constant

standard.

In fact, if we want to know about LFTs in sartans and we discourage their measurement, we might not get the answer until we have a lot of people who are dead.

CHAIRPERSON PACKER: My vote is yes actually for reasons very similar to Rob's, and I think that the concept of creating perverse incentives here is an important issue.

DR. KONSTAM: Can I comment on that? I think if you encouraged more direct comparative studies, I think you would not get into the problem of adverse incentives. I think if we had a bit enough -- I mean, my only problem about the losartan comparison is that it wasn't big enough. So if you had enough direct head-to-head comparison, I think in this sort of situation where you have other agents in the same class and there is a possibility that you're overseeing it because of a difference in the protocol, you could solve that problem by doing head to head comparisons.

CHAIRPERSON PACKER: Yeah, but that solves only one dimension.

DR. KONSTAM: Well, but it's an important one.

CHAIRPERSON PACKER: The real issue here is is this drug hepatotoxic, not is it more hepatotoxic than any other drug, and if it is hepatotoxic, how does that factor into your calculation of risk to benefit relationships --

DR. KONSTAM: I agree.

CHAIRPERSON PACKER: -- for lowering blood pressure.

DR. KONSTAM: I agree, but the issue before us is a signal. Okay? It's not clinical hepatotoxicity because we don't see any clinical hepatotoxicity. All we see is a signal, and we're not sure what the signal means.

And if we knew that that signal were no higher than the signal that really exists for other drugs that have two million patient-years, then that would make me more comfortable that the signal is not that important.

DR. LIPICKY: Well, we'll need to take this up sometime, I guess, in the near future, but I don't understand what people are talking about because, you know, this business of comparing drugs in this area, you know, are 40 and 80,000 patient trials, and on top of that, there's no positive control that I can know of using.

I guess 25 milligrams of reserpine once a day and 200 milligrams of hydrochlorothiazide would be a good positive control, you know, and so it's unclear to me exactly what people are referring to or what the allusions are toward.

I understand what the orientation is and why one wants it, but I don't think you can find out whether this liver toxicity is real or unreal and whether it's like other sartans or not like other sartans outside of, you know, a very, very large control trial, some 20, 40,000 patients, I should imagine.

CHAIRPERSON PACKER: Yeah, I actually think that that relates to number seven. So let's move to number seven and I think we'll answer your question.

And the vote was nine to two in favor of approval for hypertension.

Okay. Question seven can be quite long and time consuming, and I just want to remind the Committee that the cafeteria closes at two o'clock.

(Laughter.)

CHAIRPERSON PACKER: So there are many components to number seven, and let me say that there is a component of post marketing study. There is a

component of monitoring, and there is a component of language about the effect on the liver, which may or may not refer to other sartans, which is the specific question for number eight.

Let's take those in reverse order, and what I really would like the Committee first to say is what should the labeling say about the effect of the drug on the liver specifically with respect to tasosartan or with respect to other sartans. Let's not deal with monitoring, and let's not deal with post marketing studies.

Ray, your question was on post marketing studies or conceptually even premarketing studies if the Committee felt it was necessary.

DR. LIPICKY: Well, no, I think you've answered that.

CHAIRPERSON PACKER: Well, we said yes.

DR. LIPICKY: You've already said approve it.

CHAIRPERSON PACKER: We did say that.

DR. LIPICKY: You didn't say wait.

CHAIRPERSON PACKER: That's correct.

DR. LIPICKY: So I think this is post marketing.

CHAIRPERSON PACKER: Okay. Udho.

DR. THADANI: Yeah, I think there's little doubt that tasosartan does produce abnormalities on the liver functions as by ALT and AST do increase in patients exposed to this drug,a nd the placebo controlled studies, patients were discontinued from the medication because of LFT abnormalities, i.e., levels two or three times normal, and so the labeling will have to say that, that the drug causes abnormalities in enzymes, liver enzymes, which necessitated discontinuation of the drug in X number of patients, and that has to be followed in the instructions to the physicians who are going to prescribe it. So I think that should go in the labeling as far as I'm concerned.

CHAIRPERSON PACKER: Barry.

DR. MASSIE: Yeah, I think we did vote that this drug does seem to be associated with more abnormalities of liver enzymes than placebo, and I think that needs to be in the labeling as a result.

I would also say that in the relatively limited experience, there's no evidence of clinical liver disease, and then I would add another sentence which says that other sartans have been associated with hepatic failure and sometimes fatal, and I would put all of that in the labeling.

CHAIRPERSON PACKER: But, Barry, if you say that, that other sartans have been associated, you're doing two things. One is you're taking the threshold for Bob Fenichel's survey up to the level of reality, and --

DR. MASSIE: Well, I think it has to be confirmed. I'm sorry. None of us has seen the data that Bob is talking about.

If the agency is convinced that other sartans have been associated with liver failure, I think that belongs in the same paragraph of labeling. If the agency is not yet convinced of that, then it shouldn't say it.

CHAIRPERSON PACKER: Other discussion on this issue?

What I'm doing is as everyone's speaking formulating certain points that everyone would like to see, and then we'll take a common vote on all of that.

So far the points that would be included in labeling would be that the drug increases LFTs and would mention how frequently; two, that in the clinical trials done to date there have been no signs of clinically symptomatic liver disease; three, that there have been reports of clinically significant liver disease with other sartans, if that's confirmed;

and I'm going to anticipate this, that data are lacking at the present time that despite the absence of clinically significant liver disease, that this drug is not hepatotoxic or different in its hepatotoxicity from other sartans.

DR. THADANI: Also I said that the drug was withdrawn in a certain number of patients because of liver function abnormality.

CHAIRPERSON PACKER: Yeah, okay.

DR. THADANI: That has to be stated, I think.

CHAIRPERSON PACKER: Okay. That would be in the initial line.

DR. THADANI: Right, yeah.

CHAIRPERSON PACKER: So let me make sure that I have all of these points. First, that the drug has been associated in increase in transaminases which have led to withdrawal of a certain percentage of patients; that these increases in transaminases have not been associated to date with clinically symptomatic liver disease. However, the date are lacking as to what the effects of this drug will be on the risk of clinically significant liver disease in a broader population or with longer experience or in real life situations. One can craft the language in

a regulatorily acceptable fashion.

That there have been reports of clinically symptomatic liver disease with other sartans, and the data are not available as to whether this drug is any different than the other sartans in that respect.

DR. THADANI: I think you probably want to put another caveat. In the patients in whom the drug was not withdrawn, it has not been associated with liver disease.

CHAIRPERSON PACKER: Oh, the goal here is not to wordsmith.

DR. THADANI: Okay. Very good.

CHAIRPERSON PACKER: I just want to hit the highlights.

DR. DiMARCO: I think that Udho is bringing up a point, that you have to mention two factors. One is are you going to monitor for these, and what do you do if you get a sign, and I think so you have to mention --

CHAIRPERSON PACKER: Yeah, yeah, yeah.

DR. DiMARCO: -- that some of these are transient.

CHAIRPERSON PACKER: That's the second question, second question. Okay?

DR. DiMARCO: But you have to say that

some of these may be transient and resolve on their own, whereas some may persist.

CHAIRPERSON PACKER: Okay. I'm going to try again. Maybe I'll succeed. Yes, Ileana?

DR. PINA: I would add actually the percentages if possible of elevations because some clinicians may see two times elevations and say, "Well, I wouldn't consider that significant," and somebody else may. So I would specify the level of elevation.

CHAIRPERSON PACKER: Okay. Let me try again. I'm looking up and down.

That there have been reports that in clinical trials with this drug there has been a certain incidence of LFT abnormalities; that in, let's say, the majority of cases the LFT abnormalities were a certain height, three times greater than normal; that in the majority of cases these increases were transient, but in some cases led to withdrawal of the drug, in a certain percentage of cases; that there were no signs of clinically symptomatic disease. However, there have been reports of clinically symptomatic disease with other sartans, and the data are not available to distinguish this sartan from other sartans in terms of whether the risks are

greater, the same, or less.

DR. THADANI: That's okay.

CHAIRPERSON PACKER: Does anyone disagree with that?

(No response.)

CHAIRPERSON PACKER: Let's go on to the next question. Monitoring: what will we recommend for monitoring?

Does anyone think that no monitoring should be done?

(No response.)

CHAIRPERSON PACKER: Okay. Does anyone want to propose, Udho, a monitoring schedule?

DR. THADANI: I think I'd really like to see the -- I think you have to look at the database, how the patients were withdrawn, at what week, because if you go by the study design and the placebo controlled study monitoring, you have to say it's every week because, you know, we paid a lot of attention to it. Now you live by it, and I don't know if I saw the enzyme level twice or three times normal at week one I might withdraw. It might be a blip, but I don't know.

So I think I would really like -- I haven't seen the detailed data, but each week of

enzymes, and given the database, you're almost stuck here that it should be frequent monitoring because I really don't know.

I may be wrong, but I think if they could say that LFT abnormalities at month one are no different than at week two or month two and three, then I think FDA should be given some leeway to adjust to that.

CHAIRPERSON PACKER: As I understand it, the FDA in the past has been very nonspecific about its monitoring guidelines and has used the word "periodically."

DR. THADANI: Yeah, but I --

CHAIRPERSON PACKER: To describe monitoring.

DR. THADANI: Yeah. My concern here is that there were some patients that were withdrawn, and the withdrawal rate probably is slightly higher, and that was driven by the LFT abnormalities, and I don't know if LFT abnormalities at month one-two versus week one and two. Then I think one would like to look at the database and decide on that and just rather than showing a very weak statement, do whatever you want. I just want more reassurance the patients who are withdrawn wouldn't run into trouble because that's the

last thing a physician wants to do, is let the patient develop jaundice. It may be a minority, but I think one should put a caveat there as far as I'm concerned.

CHAIRPERSON PACKER: Ileana?

DR. PINA: I think the reality is that the physicians are not going to monitor this frequently, and they're not going to give an antihypertensive agent to a patient who's otherwise doing well and bring them back every week. I can just see the health care organizations telling you that you can't do LFTs on a weekly basis.

But I do think that we can include the timing after dosing or after exposure to the drug that the LFTs were most likely to be elevated, and then allow the clinician to do a serum transaminase at that time and allow the clinician the free rein to do so.

But I think we should give them an approximate time at which the elevations were seen, whether it was six weeks, eight weeks or three months after exposure to the drug.

CHAIRPERSON PACKER: Again, for the sake of time let me suggest the following. Since it appears as if from the clinical database that exists, as well as some of the post marketing data that the period of vulnerability here is within the first two

months or is it longer or do we not know?

DR. THADANI: I think it is time dependent from the database we have seen because your incidence on open label was a bit higher. I realize there are problems there.

CHAIRPERSON PACKER: Yeah.

DR. THADANI: So not only the -- it's duration dependent, too, because the studies do not show as much. So I think it's both time dependent there as well.

CHAIRPERSON PACKER: Okay. Ray?

DR. THADANI: So I think it would be nice to know from the database.

DR. LIPICKY: It really does depend on the specific drug that you're talking about, and it's not clear to me since we haven't seen any evidence of liver disease in this data base that there is any basis for, if you want to be data dependent in your recommendation, that there is any basis for making a recommendation.

If you don't want to be data dependent, you can make a recommendation.

DR. THADANI: You only brought in the patients who were dropped. You don't know whatever happened to them had they not been dropped.

DR. LIPICKY: I just said there's no data --

DR. THADANI: No data.

DR. LIPICKY: -- upon which you can base your recommendation.

DR. THADANI: Sure.

DR. LIPICKY: You have to make it data independent.

CHAIRPERSON PACKER: Barry, then Dan.

DR. MASSIE: Yeah. I missed my chance to raise my hand and say I didn't want monitoring. I don't know how we can recommend monitoring here. I would like to recommend a post marketing surveillance study that includes measurements in, you know, a certain number of patients that we could then associate with some sort of clinical outcome, a large number.

But to pick a time and say, "Draw LFTs," based on what we know here, I don't know how I could recommend that.

DR. PINA: I want to clarify. I'm not saying put in there, "You must draw bloods," or, "you should draw bloods." I would just give them a time period based on the data, and then let the clinician.

I agree that I think we need post

marketing studies.

DR. LIPICKY: But what data would you use? We have no people who got clinically sick, and you all are saying approve it because you don't know if the liver enzyme elevations mean anything. So what data would you use?

DR. PINA: I would use the elevation of ALT, the three plus where our consultants here told us that they may start to be concerned.

CHAIRPERSON PACKER: Ray, what do you want to hear from us in this regard? I think it sounds as if what we would like to be able to do is to inform physicians about what is known about the time course of this.

DR. LIPICKY: Fine. I think we have heard enough to be honest.

CHAIRPERSON PACKER: Okay. Good.

(Laughter.)

CHAIRPERSON PACKER: Post marketing studies. How many of you would suggest that there should be a post marketing study? Does anyone say that there should not be a post marketing study?

DR. MASSIE: Can I ask what the post marketing study would accomplish?

CHAIRPERSON PACKER: What would a post

marketing study accomplish? Well, depending on how it was designed, it could define the incidence of LFT abnormalities in the general population, and it could follow up on those abnormalities and see the extent of clinically significant liver disease with a very large n.

DR. MASSIE: I think that's a reasonable answer. On the other hand, I think it will be very difficult to convince any reasonable IRB that a protocol whose sole design is to find out how often a potentially fatal drug effect occurs should be conducted, and I would be interested to know people's thoughts about what should go into a consent form.

"We want you to take this drug because we want you to participate in a study to tell us how often this drug produces a potentially fatal abnormality."

So I think that the goals of the post marketing study need to be pretty explicitly defined and ought to include some sense of efficacy, as well as collecting data by the way on safety. And we're missing data on both of those.

DR. KONSTAM: Yeah. You know, I'd agree with the efficacy point, but I think that we have a lot to learn about what the meaning of these LFT

abnormalities --

DR. MASSIE: Yeah, but I don't think you can get people to consent to a study whose goal is to say, "How often does your SGOT go up or ALT go up, you know, threefold or eightfold or tenfold?"

DR. KONSTAM: You can't get a consent for that?

DR. THADANI: I think Dan's point is well taken because if our IRB looks at that, they'll think, well, you guys have gone crazy because --

DR. MASSIE: Well, how about --

DR. THADANI: -- there is not denying there is not any evidence.

DR. MASSIE: -- Marv, to ask how often people drop dead during quinidine therapy?

CHAIRPERSON PACKER: Okay. Let me -- okay. Let's try to move forward. Rob.

DR. CALIFF: I would say the real issue here as it should be for any medical therapy is what benefits are there to the patient of the treatment and what are the risks, and right now we have a drug which has not been shown to have a shred of benefit to the patient for things that --

DR. LIPICKY: That's absolutely incorrect, Rob, just totally and absolutely incorrect.

DR. CALIFF: What patient benefit has been noted --

DR. THADANI: It lowers blood pressure.

DR. CALIFF: -- here?

DR. LIPICKY: It has lowered the blood pressure.

DR. CALIFF: And if you die --

DR. LIPICKY: And that is good for people.

DR. CALIFF: It's always good for people to lower the blood pressure?

DR. THADANI: Yeah.

DR. LIPICKY: It has been in 27 trials, placebo controlled compared across every class of agent that you wish to name.

DR. CALIFF: And if I bled you into a trash cash till your blood pressure dropped, that would be good for you or I gave you arsenic and your blood pressure dropped, that would be good for you?

DR. LIPICKY: Well, you know, you can put it in those terms, right? But there has never been a trial that has measured morbidity and mortality that has lowered blood pressure that has not found a treatment benefit.

DR. CALIFF: Well, I've got one trial that's soon to be published where the drug that

lowered the blood pressure more was associated with worse outcomes than the drug that lowered the blood pressure less. So --

DR. LIPICKY: Well, okay. I'd be happy to look at it.

(Laughter.)

DR. CALIFF: The point I'm trying to make is in general we prescribe treatments to have patients live longer or feel better, and you have endorsed that for almost every other aspect of cardiovascular disease at least, and in this case we have no direct evidence. How about that? No direct evidence.

DR. LIPICKY: That's 100 percent true.

DR. CALIFF: All right. So it seems like that the study, as the other drugs in this class are currently doing, should be addressing the question of how do you put potential hepatotoxicity in the context of directly measured patient benefit, and from that perspective, if you did a trial that was large enough to demonstrate a reduction in death and stroke, whatever the rate of hepatotoxicity is within that, if the overall effect is a patient benefit --

DR. LIPICKY: Yeah, but -- but --

DR. CALIFF: -- then you have a balance in favor of --

DR. LIPICKY: Fine. A large enough study to detect a change in stroke, say, compared to what?

DR. CALIFF: Well, that's where someone could be innovative. It could be compared to a thiazide.

DR. LIPICKY: Fine. So let's compare it to a thiazide. So this would be a positive control trial.

DR. CALIFF: Right.

DR. LIPICKY: It would follow the usual rule that have been enunciated, that is, you cannot have less than X treatment effect lost.

DR. CALIFF: Something like that.

DR. LIPICKY: Fine. Can you define the treatment effect for thiazide?

Okay. You haven't got a positive -- there are bunches of trials, but I dare you to produce the trial or even two trials where we'll be able to say we can rely on this treatment effect.

DR. CALIFF: And my point is we do a lot better coming to a consensus on what we think the treatment effect is and doing an adequate size trial than we are just throwing these molecules out to the public and letting whatever happens happen.

It's not -- I mean, we don't have a

perfect scientific way of defining the treatment effect of the currently effective antihypertensives, but to say because we don't have that we're going to do nothing I think is not a very responsible --

DR. LIPICKY: That's fine, but again, I think that this whole issue needs to be taken up some time when --

CHAIRPERSON PACKER: I think that's a great idea.

DR. LIPICKY: -- when the entire morning can be devoted to it.

CHAIRPERSON PACKER: Great idea. Let me ask the Committee though as a follow-up. There are two types of post marketing studies that have been proposed in the last five minutes, one which is a very large incidence and follow-up survey of LFT abnormalities, but focused on LFTs.

The second is a true benefit-to-risk trial which assesses morbidity/mortality and I don't want to get into how that needs to be done, which puts the LFT issues into a direct clinical perspective, not an assumption based surrogate perspective.

So we have already said that we'd like to recommend post marketing trial. Everyone agreed with that. The question is what kind. So the first one is

LFT safety based study, and the second is a true clinical benefit-to-risk assessment.

And let us take a vote quickly through the Committee as to which you would prefer, and, Cindy, why don't we begin with you?

DR. GRINES: I'm not sure that just monitoring LFTs is going to give us anymore information because we already have 4,000 patients in the database that have LFT measurements. So I'd lean more toward one that could accurately measure clinical outcomes, although I'm not sure that we need to look specifically at death and stroke. I thought the biggest issue was whether there was any hepatic failure.

CHAIRPERSON PACKER: John?

DR. DiMARCO: I think you could do it one of two ways. You could either do a very large trial and just look for clinical signs of hepatic failure and forget other endpoints, or you could look at some other population, such as a heart failure population, and more carefully look for both a heart failure and other outcomes because that would be an easier trial to do and would be a logical extension for this drug.

CHAIRPERSON PACKER: But outcomes or safety?

DR. DiMARCO: Both in that second trial.

CHAIRPERSON PACKER: Okay. Lem.

DR. MOYE: Yeah. If we are to be comforted in the end that this drug is -- the changes this drug is producing in liver function is benign, then I think that we need two things. We need to assure ourselves that we understand the true prevalence of the changes, number one, and, number two, we have to know what the implications are for the changes that we do see, which means linking the short term changes to long term hepato sequelae, and I don't see any way other than a large post marketing trial to answer those questions definitively.

CHAIRPERSON PACKER: Rob?

DR. CALIFF: I mean, I think my view is pretty clear that there needs to be a clinical outcome trial, and I would think to really nail down the exact incidence of hepatic clinical injury would take even a larger trial than the clinical outcomes study since we already know the rate is going to be quite low of clinical events.

You know, the real issue for me is putting the hepatic injury into perspective of what the drug does to help patients.

CHAIRPERSON PACKER: JoAnn?

DR. LINDENFELD: Yeah, I think a clinical outcome trial would be very valuable. I think that it should definitely include women and the elderly in a high percentage who have a bigger risk.

CHAIRPERSON PACKER: Marv.

DR. KONSTAM: Well, you know, I'd like to see this company do a trial focusing on safety with regard to LFT abnormalities and relative to the surrogate of blood pressure. I think that with regard to -- I agree with everything that Rob has said, that a true outcome study is what we need.

I'm not sure what we're voting on, however. I'm not --

CHAIRPERSON PACKER: We've been asked as to what post marketing studies we would recommend to this company, to the FDA for this company.

DR. THADANI: For hepatic enzymes.

DR. KONSTAM: Yeah. I'm not prepared to recommend to the FDA with regard to this company that they be asked to do the definitive trial that Rob wants done. I'd pull back on that particular recommendation.

I'd like to see that study done. I'm not sure that we need to lay it on this company.

CHAIRPERSON PACKER: Udho.

DR. THADANI: If you're addressing specifically the hepatic issue, since there was no case of hepatic clinical toxicity in 4,000 patients, and Bob Fenichel told us there are two patients who have died out or 13 in several million. I think in order to address that issue, you need a very large sample size, more than hundreds of thousands of patients. So I don't think you're going to address it.

Obviously there will be vigilance to report those patients.

If you're really worried about the toxicity on the liver enzymes is more than your other sartans, then I think you could do a comparative study in a large enough database. They're shown at 200 patients. Maybe they should do a few thousand and show there's no difference. Then perhaps we'd be convinced there is no difference between the drugs. That's all you could do.

CHAIRPERSON PACKER: Ileana.

DR. PINA: Yeah, I would like to see a safety trial, and I echo what Lem has said. I'd like to see that these changes that are noted in the ALTs do not bear any clinical significance for the patient population.

CHAIRPERSON PACKER: Dan.

DR. RODEN: Well, I'm going to reiterate again one more time. We're talking about a surrogate in terms of safety, and we're talking about a surrogate in terms of efficacy.

I would love to see a safety trial. I don't think such a thing is ethically defensible. So I think the only way to collect the safety data is within the context of an efficacy trial. How such a trial should be designed is not very clear, but an efficacy trial, as well as post marketing surveillance which I presume will happen.

CHAIRPERSON PACKER: Barry.

DR. MASSIE: Yeah. I think this is a very difficult question. The question is what's more important or do we want to recommend two things. If we want to know about the liver function, we need a huge trial, and not liver function because I don't care much about liver function. Liver disease is going to take a huge trial.

If we want to know comparative liver function with other sartans, a smaller comparative trial which would give us some minimal -- it would exclude a certain level of clinical liver disease if you had 10,000 patient, 5,000 on losartan and 5,000 on

this agent. You would find out if there's a difference in LFTs, and you'd rule out some huge rate of clinical liver outcomes, but not any, not the type that Bob has come up with in the post marketing area.

I would tend to go toward that one. As far as the clinical outcome study in hypertension, it's something that it's likely the company may want to do to get on the map as the fifth sartan, but it won't answer the liver function question in any meaningful way.

So, you know, basically those are the options. I don't see how we or probably the agency can mandate any of this, except to continue to keep close track on liver outcomes in this population treated with this and other drugs of this type.

CHAIRPERSON PACKER: My own view is similar to Barry. We really have a split vote on the kind of post marketing with about half of us, in fact, six favoring outcomes and five saying that safety should be the primary focus, whatever guidance you get from that.

And I think there are issues related to design which we have not even touched upon which we should touch upon at some other time.

We're going to skip question number nine

because I really think we don't have time for it, and it isn't particularly specific to this drug, but I think we need to look at question eight, and we have already recommended in the labeling for tasosartan that some mention should be made about LFT abnormalities and/or clinically symptomatic disease with other sartans. Does that mean that the other sartans should have that labeling?

And Udho.

DR. THADANI: Obviously I think the fact you have to say the liver function test abnormalities have been reported and give the incidence as it is provided in this handout, and also I think if the FDA is convinced that there are 13 cases of actual disease and two deaths, I think that information should be updated.

I think because you have the data, you don't want to run into this hassle of one year from now then there were not only two deaths. There might have been 50 deaths. So I think you should update that information with those drugs where it has been described, and just put in the other ones which is not know.

So I think, yes, it should be updated.

CHAIRPERSON PACKER: Okay. Let me for the

sake of time simply try to make this a yes/no question. Should the information that we've discussed be incorporated in the labeling of other sartans? Yes or no? Udho says yes, and, Barry, we'll begin with you.

DR. MASSIE: It's very hard to vote without having seen Bob's data. I think if the agency is convinced that these other -- that sartans, two, right now individual ones and when the third one comes, that sartans can cause liver toxicity, clinical liver disease, that that should be included in the label, but I can't tell them whether they are convinced yet or not.

CHAIRPERSON PACKER: Well, I think that the label --

DR. MASSIE: I think the rest of this stuff on the LFTs peculiar to this drug, it's very hard to put that in the label in any other drug.

This has gone off. I think it's very difficult to put all the things we carefully went through into any other drug, but when, I think not if and I suspect when, we get enough cases of clinical liver disease involving more than two drugs that it ought to go in there.

CHAIRPERSON PACKER: I think the labeling

that Udho was referring to would go something like it would cite the specific incidence of LFT abnormalities in clinical trials with that specific sartan.

DR. LIPICKY: Well, but that's fine. they didn't distinguish themselves from placebo, and I would argue against that because I don't like to put all kinds of garbage into labeling that has no sense.

DR. THADANI: It's more than the placebo. These are placebo controlled, right?

DR. MASSIE: But there are so many agents in which they measured it once and they didn't see much. I think there you have a perverse incentive, that if you're going to compare a drug that measured it every week for 16 weeks with an agent that measured it at the end of a 12 week study. I don't know how you can do that.

DR. THADANI: But surely you could say there's no difference between placebo controlled trials, and yet you are seeing some hepatic --

DR. LIPICKY: What do I want to put garbage into the labeling for?

DR. THADANI: Because the hepatic incidence of liver failure deaths. That's the issue now.

DR. LIPICKY: Whoa, whoa, whoa. You mean

the post marketing reports? You don't know anything about that. You haven't even seen it. So please don't recommend that we --

DR. THADANI: No, no, no. That's what I said. After you're convinced. I didn't say you have to put it in. If you are convinced you're getting reports and you're absolutely sure there were no other cause, I think there should be some -- if I'm prescribing the drug, I ought to know at least this could happen. That's all I'm saying.

DR. LIPICKY: So then the other sartans would have labeling that would say there have been reports of X number of people who have gotten sick from liver disease, but nothing ever happens to liver enzymes in controlled trials.

DR. THADANI: Well, if that's what you --

DR. LIPICKY: Is that what you want to put into labeling?

DR. THADANI: Well, if that's what the data would suggest that at the moment.

DR. LIPICKY: Well, I mean --

DR. RODEN: Well, you can say that the predictive value of serial routine monitoring of liver function tests is not known or is not established or --

DR. LIPICKY: Right, and in the end --

DR. RODEN: -- or is, in fact, nonexistent.

DR. LIPICKY: And then another section in the animal pharmacology set says it was also clean in animals, and that has no predictive value either.

DR. RODEN: Yeah, it's a situation where --

DR. LIPICKY: Well, why am I putting all of this garbage in?

DR. RODEN: I don't think you need to.

DR. LIPICKY: Yeah.

DR. RODEN: All you need to say is there are rare cases of sporadic -- I mean assuming that the review of the data shows it -- that there are rare cases of sporadic serious liver disease. You might want to say something about the symptoms so the guy who's reading the package insert knows that these symptoms are things that they should think about as a problem with liver disease, and leave it at that.

CHAIRPERSON PACKER: There's also another issue that if you're going to put this in labeling, are you going to tell people to monitor for it. I'm sorry I mentioned that.

DR. RODEN: No. No.

CHAIRPERSON PACKER: No. I'm sorry?

I guess what we are saying is when sufficient data becomes available in the post marketing surveillance to say things that can be said that they will be said.

DR. LIPICKY: Yes.

(Laughter.)

CHAIRPERSON PACKER: And since the present --

DR. LIPICKY: That's good guidance.

CHAIRPERSON PACKER: What's that?

DR. LIPICKY: That's good guidance.

CHAIRPERSON PACKER: Yeah, and since the present labeling of tasosartan that we recommended refers to the other sartans, I guess we are not unfairly biasing the situation in a way that would make us uncomfortable.

Having said that, does anyone have any other additional modifications, comments, or recommendations?

(No response.)

CHAIRPERSON PACKER: If not, we are recessed, and we will reconvene at 2:15.

(Whereupon, at 1:41 p.m., the meeting was recessed for lunch, to reconvene at 2:15 p.m., the same day.)

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

(2:26 p.m.)

CHAIRPERSON PACKER: Can I ask everyone to take their seats?

We're going to begin this afternoon's session. The session is a general discussion about the evaluation, development, and approval of intravenous drugs for the treatment of heart failure.

The schedule that you have before you is in error. There will be no formal presentation by Sanofi.

We do have in addition to the panel on the podium two invited experts, who will be nonvoting: Dr. Lynne Stevenson from Brigham Women's Hospital in Boston and Dr. Christopher O'Connor from Duke University in Durham.

Barry Massie is a temporary voting member this afternoon, as he was this morning.

Although generally speaking we do not reserve time for public comment in the afternoon session, there are those who are interested in IV inotropic drugs, their use and development, and some of them are here with us today, and one of them, because of flight schedules, will not be able to be here for the entire afternoon session and has asked

for an opportunity to make a brief comment before we begin.

Dr. Silver.

DR. SILVER: Thank you, Dr. Packer, Dr. Lipicky, and members of the panel.

My name is Mark Silver. I'm professor of medicine and Director of the Loyola University Heart Failure Center and Associate Director of the heart transplant program at Loyola.

Like many of you, I spend my time caring for patients with advanced heart failure and those awaiting heart transplantation, and I want to thank the panel for bringing to light this discussion on the use of inotropic agents.

I believe the reality is that when these drugs were approved we did not and could not envision what heart failure would be like in 1998. Patients awaiting heart transplantation for months being supported by continuous use of inotropic agents, heart failure being the lead cause of admission for patients over the age of 65 with a fixed and sometimes punitive reimbursement schedule.

Therefore, I think we really have at hand an eclectic and outdated and inadequate database to answer the questions regarding inotrope use, and I

really just wanted to make the comment to urge this panel to help in the development of proper questions and trial designs to answer the questions that we have today and for the future.

Thank you very much.

CHAIRPERSON PACKER: Okay. Thank you very much.

This afternoon's session does not have formal presentations as part of. The division has asked the Committee to consider a broad range of topics related to development of IV drugs for heart failure, and those topics are embodied in the questions which have been distributed to the Committee and is available to the audience.

I want to draw your attention to the first paragraph of these questions. The division wishes to draw the Committee's attention to issues that arise during the development and evaluation of intravenous medications for the treatment of heart failure. Such a medication may sometimes exist in an oral, but sometimes in an intravenous formulation.

Sometimes the intravenous formulation will stand alone, as in the case of dobutamine. Sometimes it will be coupled with an oral formulation, as in the case of amrinone and milrinone.

Now, development of the oral formulation may be concurrent with that of the intravenous formulation or the oral formulation may have been developed earlier or later. In either case the oral formulation may or may not turn out to be useful. That is, the oral formulation may eventually be demonstrated to carry a survival benefit, a symptomatic benefit, both or neither.

Now, the division would like to remind us that there are four scenarios in which one can apply an intravenous preparation and can be a target for drug development.

First, when a patient is temporarily unable to take a medication by mouth, the intravenous formulation will make continued therapy possible by bridging the gap of a small number of missed oral doses, possibly doses of a medication different from the one being pursued for approval.

Second, when a patient sustains an acute decompensation of heart failure, the intravenous formulation will be used for a day or two in the intensive care unit.

Third, when myocardial dysfunction in a patient with or without heart failure develops during cardiopulmonary bypass, the intravenous formulation

can facilitate the weaning from the bypass pump.

And fourth, when the patients are more or less stable, the intravenous formulation will be used intermittently or continuously for maintenance or for prophylaxis against deterioration, and this represents the four settings in which intravenous therapy can be reasonably used, and not all of these settings were anticipated when many of the drugs that are presently approved for intravenous use were made commercially available.

Now, in general, intravenous drugs for the treatment of heart failure have historically been approved after adequate demonstration of dose dependent and appropriate hemodynamic effects, generally speaking a decrease in filling pressures or an increase in cardiac output or other effects in patients with acute or chronic heart failure, and in making these decisions, the division has made several assumptions.

First, that the drug would be used only occasionally in any given patient; and then for no more than a day or two, always when the patient was hospitalized for the treatment of severe acute heart failure.

Second, that although standard hemodynamic

changes cannot be defined, that is, one cannot specifically identify what drop in left atrial pressure is always desirable, a clinician may be able to titrate a drug through its effect on hemodynamics by monitoring some other physiologic variables or clinical variables so long as there is a predictable relationship between dose and the hemodynamic effect, not that the same dose will have the same effect in every patient, but at least the useful dosing range can be defined, and dose response relationships for the various hemodynamic effects can be at least qualitatively predicted over the specified range.

A third assumption. When a safe and effective chronic oral regimen has been defined, the concomitant target hemodynamic changes have been described because it would make sense that these same changes are appropriate in acute and chronic heart failure and could be a target for intravenous therapy.

And fourth, the fourth assumption, when no oral regimen exists, the short term hemodynamic effects are suitable surrogates with short term symptomatic benefit, and that no formal estimate of the mortality effect needs to be obtained beyond whatever point estimate it incidentally obtained, probably with wide confidence intervals, from the

hemodynamic trials.

So now we are being asked by the division the following question: should we reconsider the current guidelines for the development of an intravenous drug for the treatment of heart failure, and in particular, are you satisfied with the validity of the assumptions which have guided the approval of intravenous drug therapy to date?

So that is the questions which are being posed, and what I would suggest is that what we should begin with is a general discussion about how the field of intravenous therapy for heart failure, one, may have changed and, two, which assumptions in particular are assumptions that may no longer be considered to be valid given the change in our perspective over the last ten to 15 years.

The last drug, I think, approved for intravenous use for heart failure was milrinone in 1988.

DR. LIPICKY: I believe so.

CHAIRPERSON PACKER: So it's been ten years.

Nitroprusside was approved in 1991.

Okay. Marv, let me ask you to begin and review the first assumption or, for that matter, any

assumptions that you would like to identify as being assumptions that you think may no longer be valid in terms of the evaluation process.

DR. LIPICKY: Milton, before you start that discussion, you wouldn't have to have that discussion if people didn't want to change the guidelines.

CHAIRPERSON PACKER: I'm sorry?

DR. LIPICKY: You wouldn't have to have that discussion if people did not want to change the guidelines.

CHAIRPERSON PACKER: That's right.

DR. LIPICKY: So --

CHAIRPERSON PACKER: Okay.

DR. LIPICKY: -- maybe people think they're fine.

CHAIRPERSON PACKER: Well, we have heard the assumptions which underlie the present guidelines. Does the Committee believe that these assumptions are all still reasonable?

And, Marv, why don't you begin to address that question? And if they are not reasonable, why are they not reasonable?

DR. KONSTAM: Well, I mean as Dr. Silver pointed out, there certainly has been an evolution of

practice, and I think that as these drugs were first conceptualized to be used in the intensive care unit for acute exacerbations of heart failure, there has certainly been an evolution or a movement toward other uses.

I think that this first came about with the view that short term use of inotropic agents could -- particularly dobutamine in the early '80s -- could result in improvement in clinical status that could be sustained for some time, and that from there came the viewpoint that exists that there might be a role for intermittent use of these agents in order to achieve a long term benefit.

No, I mean, I think that we really need to revisit all of the assumptions. I think the first question relates in my mind -- and I don't know what you want to do, Milton, in terms of going through these or maybe I just could make some comments --

CHAIRPERSON PACKER: I think general comments first would be appropriate.

DR. KONSTAM: Yeah. You know, I mean, I think to me there are -- I could divide the questions into two. To me, first of all, the question is let's assume for the moment that you are going to use an intravenous agent with inotropic capacity for short

term use. Why are you using it, and what kind of effects would you like to document in order to prove efficacy? That is, do we accept the fact that certain hemodynamic measurements are acceptable surrogates to acute short term improvement in clinical status, yes or no?

And if the answer is yes, well, what exactly do we want to see in terms of efficacy that might represent a surrogate toward a short-term improvement in clinical status?

I guess that's one set of questions, and then second set of questions really relates to long term use, whether it be continuous or intermittent, and therein I think we would wind up, I believe, all agreeing that the goal should be clearly improvement in long term outcomes.

And I think the question before us would then be: do we have any evidence for a particular agent that there is an improvement in long term outcomes, and what should be the criteria there?

So I think that where we are in the state of the art as I understand it for approvability of intravenous agents falls far short of what we need to develop, and I think that clinical practice -- said another way -- I think clinical practice has gotten

far beyond the regulatory process.

And why don't I stop there?

CHAIRPERSON PACKER: Okay. Ileana, just some general comments?

DR. PINA: I think in the years that I've been taking care of heart failure patients our practice, as Marv has just said, has evolved. Patients look clinically very different than they did ten years ago, and I think our approach has become perhaps a bit more sophisticated, a bit more physiologically based, and so our therapies and our approach to therapies have changed.

We see a very large and rather ill group of patients that are maintained on inotropes sometimes for many, many months at a time waiting for hearts, and because of the UNOS criteria for what constitutes a status I patient, and these patients fit that definition, we need to keep them in the hospital at this time on inotropes or with a ventricular assist device pending transplantation.

There are patients, however, that are extremely ill, but that are sustained in an inotropic agent and very often now being sent home, and it's not just happening in Philadelphia. It's happening everywhere in the country, sent home on inotropic

therapy, and we often see that as a last resort to make the patient comfortable and allow them to be at home with their families rather than being tied to an IV tube inside the hospital.

And this, of course, brings out a whole other set of issues of end of life care, et cetera.

So I think we've seen such a change in the way that we approach heart failure from the days that these drugs were approved and discussed that I see it as a wonderful thing that we're sitting here together and going to revisit this issue and hopefully set down some new suggestions for guidelines as to the use of these agents.

CHAIRPERSON PACKER: Barry.

DR. MASSIE: Yeah, I think, you know, what the division does and, I guess, what this group discusses in approving a new drug or a drug for a new indication, I guess, is defining three things. One is whether the drug is effective for that indication; the second, the safety and of course the relative efficacy to safety; and third is the dose of the drug to be administered for those indications.

And I think as we move beyond the original idea that we had a treatment that for a short, intermediate period of time would sustain a patient

until either the condition passed or an oral regimen was developed to accomplish the efficacy goals has moved on, and we really -- I'm not sure for some of the uses that we currently have evidence for efficacy, knowledge of safety or really information about the appropriate dose to be using in those settings, and so I think it's quite appropriate to revisit these issues and see if we can define that or if we can define how it can be defined in the future.

CHAIRPERSON PACKER: Okay. Having said that, let us now as a panel go through the assumptions and see if any of the present assumptions are still valid or perhaps all of them are still valid, but why don't we go through them selectively?

Let me emphasize the intent here is to get through most of the questions, probably until about question six or seven, within a very short period of time. So we're not really talking about extensive discussion unless such discussion is warranted.

Let me ask -- we'll just go through. Does anyone in the panel still believe that the assumption that an IV drug will only be used occasionally for a day or two, that that assumption underlying the evaluation approval is still valid?

(No response.)

CHAIRPERSON PACKER: Does anyone in the panel believe that a clinician who has somehow decided on target hemodynamics can approach those target levels by dose titration so long as there's an orderly relationship between dose and effect?

The concept here is the rationale behind evaluating or requiring that up to now that dose dependency be established because one could not identify a target hemodynamic dose.

DR. LIPICKY: Milton, before you get to that part, I know I'm not part of the panel, but I'd like to defend that first thing, okay, that first assumption, and by nobody saying that that was still valid, does that mean that if I were going to develop an IV inotrope and I developed a one or two dose regimen for a patient and showed that whatever it was you're supposed to show under those circumstances, that this panel would tell me to go home? I cannot get that approved?

CHAIRPERSON PACKER: No, I think that --

DR. LIPICKY: I mean, there's nothing wrong with that as a goal.

CHAIRPERSON PACKER: Well, I think that what the panel is saying is that's not the only way that IV drugs could be approved, so that the

general --

DR. LIPICKY: Right, but the --

CHAIRPERSON PACKER: -- so that the general concept that one has a blanket approval of an IV drug for, quotes, heart failure --

DR. LIPICKY: Okay. So the lack of supporting that statement was not that that is not okay.

CHAIRPERSON PACKER: It's just not the only perspective that one can take of IV therapy.

DR. LIPICKY: Okay, but I guess it would be good to know whether the statement has any validity, okay, because you know, it could be that that would not be a valid thing.

CHAIRPERSON PACKER: I think the sense is that although IV drugs can be given for a short period of time and that a sponsor can request an approval for short term therapy for a day or two, it would need to clearly define that that's what it was doing because right now the original assumption that that was the only thing on the menu is no longer necessarily valid; that there are other ways that IV drugs can be used.

DR. CALIFF: I think what Ray is asking is even if that was the case, is it necessarily the case that because the other assumptions here are true for

one or two days, that that would be a valid route to approval.

CHAIRPERSON PACKER: You mean --

DR. CALIFF: In other words --

DR. LIPICKY: Right.

DR. CALIFF: -- let's say that it was not ever going to be used more than one or two days.

CHAIRPERSON PACKER: Would that be reasonable?

DR. LIPICKY: Right. That as a developer, I would never intend it to be used in any other way except one or two days. I can't control what doctors do once it's approved.

DR. CALIFF: I mean my interpretation of that question is are the surrogates that are listed in the rest of this reasonable predictors of whether well intentioned clinicians are helping or hurting the patients they're treating.

DR. PINA: I don't think it's the statement in itself. I think it's the statement sounds like it precludes the use for more than a day or two. In other words, it is not a desirable thing to accept --

DR. LIPICKY: No. That's incorrect. That's not the way to read it. The statement says

just what it says, that is, it's okay to do that, and if that's all you do, you develop a drug to be used that way, that would be okay. What would you need to do to develop a drug and that's what it would be labeled for, as opposed to it being an assumption that that data would then allow you to use it for an eternity? Okay?

That's not the implication of those words.

CHAIRPERSON PACKER: Right. The implication of the words is that a sponsor could pursue this if it wanted to, and that would be one path to approvability.

DR. LIPICKY: Right.

CHAIRPERSON PACKER: Okay. Lynne.

DR. STEVENSON: I'd just like to emphasize what Marv said at the beginning, which is the issue that we really do distinguish between acute therapy of symptomatic heart failure in the hospital and chronic therapy of a patient out of the hospital.

I think the big changes that have occurred over the last ten years are that we've found that some of the therapies that work acutely do not work chronically, and conversely, that some of the therapies that work well chronically are very difficult to institute acutely.

So I would suggest as we proceed that we bear in mind those two indications differently, and while one drug might seek to get both of them, that it would not be assumed that one leads to the other.

CHAIRPERSON PACKER: Okay. Let me try to -- because much of these subsequent questions after this focus on the issue of endpoints, measurements, and clinical settings which would constitute approval, and so that the discussion that, Rob, you're suggesting that we might have or, Ray, you're suggesting we might have now actually is something that comes up in just another question or two.

This is really more to identify which of the working assumptions you have had up to now we think require additional discussion.

DR. LIPICKY: Oh, okay.

CHAIRPERSON PACKER: So does anyone think that the first assumption is still valid, and -- Udho?

DR. THADANI: I think the first assumption is still valid because at least we get patients in the CIC who are sick enough they may require for two or three days, and then they could go home. So I think the way it stands, there are hospitalized patients that say you can use it occasionally in any given patient. It doesn't say how often. It doesn't talk

about chronic, and I think it's a very reasonable thing to do.

And there are patients who really are in Class IV that are on everything else you can have them on, and they're not even on the list yet, and they can go home. I've seen those patients. So I think that's still a valid assumption, at least in my judgment.

CHAIRPERSON PACKER: I think that the target here, the way this question is phrased, is I think a question that defines the basis of regulatory action of IV drugs, and I think that perhaps a better way of getting through this question is to have the panel elucidate which assumptions may no longer be as valid now as they were in the past.

Clearly, I think we've heard already that the concept that a drug would necessarily be used for a day or two in a hospitalized patient with acute heart failure, well, that's certainly an option, but it's not the only option available to clinicians when the IV drug is made available for commercial use.

And we can discuss the interaction of short term and long term use in a little bit.

The question as to -- the second question, which is whether the identification of a dose response relationship is a good way of obtaining information on

the efficacy of a drug. Up to now the efficacy of a drug for IV therapy has been defined not based on symptoms, not based on events, not based on clinical endpoints, but has been based on the surrogate of showing a dose dependent effect in hemodynamics.

Is that an assumption that we would like to continue to have dominate the thinking of the approval process?

Marv?

DR. KONSTAM: Milton, I'm not sure. I wonder could we just take half a step back? I know we're not making too much progress, but I think maybe -- and just refocus on what it is we're aiming at here, and maybe we could then go back through these or maybe we need to reword these a little bit.

You know, it seems to me that, you know, as Lynne was saying, that there may be a role for -- there is a role, I think, for intravenous inotropic agents acutely, and then the question is going to be if there is such a role, then what should be the basis of approvability for that purpose, for that indication, for short term use for patients who have acute clinical exacerbations of heart failure.

And then the second issue is what should be the basis of approvability for these agents if they

were to be used differently from that, that is, chronically whether intermittently or continuously.

It seems to me that those are the two sets of questions. I would not try to sort of pigeonhole us into saying that --

DR. LIPICKY: But 1(b) is pertinent to each of the considerations that you wish to consider. What 1(b) says is that you know something about the drug and you ought to define it --

DR. KONSTAM: Right.

DR. LIPICKY: -- in terms of the relationship between dose and its hemodynamic effects.

DR. KONSTAM: Right.

DR. LIPICKY: And that that's important. That's applicable to each of the specific circumstances you want to discuss, and you will get a chance to.

DR. KONSTAM: Right.

DR. LIPICKY: The question now is: is that statement true or not true?

DR. KONSTAM: So let's take it in the simplest sense. Let's say that -- maybe to clarify, so if a company were seeking approval for a drug for short term use in hospital in a patient who had manifested acute clinical exacerbation of heart

failure, would it be sufficient for approvability to indicate improvement in hemodynamics with a dose response relationship? Is that a reasonable --

DR. LIPICKY: Yes. Would that be a part of the basis for approvability?

DR. KONSTAM: Part of the basis.

DR. LIPICKY: Because in each other circumstance there will be more and less information that will be needed.

CHAIRPERSON PACKER: I have a sense from reading the subsequent questions that the purposes of this review would be best served by skipping this question.

DR. KONSTAM: Okay.

CHAIRPERSON PACKER: And going on to question number two because I think that we are already well into the concept of what the different settings are. We are well into the concept of what measurements could be made and what measurements might be important in the evaluation of a drug.

And what we may do, Ray, is come back to one at the appropriate time.

So we have in the preamble defined a number of clinical situations. The first one is acute decompensation of, you know, acute or chronic heart

failure.

The second is weaning from cardiopulmonary bypass.

And third is chronic heart failure.

And we are going to go through a series of questions first to identify which assessments can be made, can be made, and secondly, which assessments are important for the program an for an approval by the FDA.

So the first question, in the setting of acute decompensation, acute pulmonary edema, and chronic heart failure, which of the following assessments can be made in a clinical development program?

And, Barry, do you want to take this?

DR. MASSIE: Sure. Well, I think that, in fact, to some degree each of these assessments can be made. I guess that's independent of how many are practical to be made.

Hemodynamics has been the standard and can clearly be measured for acute short term therapy. Symptoms can be measured. Morbidity, I guess, in this case might be not terms of hospitalizations but time in the hospital or time in the intensive care unit, and survival also could be measured, probably not very

practically in the numbers.

I would add to this that measurements such as renal function, which to some extent is connected with the ability to achieve hemodynamics in terms of diuretics would be something that one would also want to measure.

And then, of course, this is not safety issues, but there are safety things you would want to measure at the same time.

CHAIRPERSON PACKER: Okay, Barry. You've identified hemodynamics, symptoms. I guess to a certain extent renal function, I guess, is one type of evaluation of morbidity.

DR. MASSIE: And then one type of evaluation of hemodynamics one might also say, something like that.

CHAIRPERSON PACKER: Okay. You've said that you think that conventional measures of hospitalizations doesn't apply here because of the short term infusion?

DR. MASSIE: Well, they're in the hospital.

CHAIRPERSON PACKER: Right.

DR. MASSIE: In this particular indication, they're in hospital. Well, I'm assuming

that we are following on the more traditional thing. If this is not being done in hospitalized patients --

CHAIRPERSON PACKER: The assumption here is a hospitalized patient.

DR. MASSIE: Right, and I forgot to measure, but certainly blood pressure to some degree is another hemodynamic measurement that is not listed there, but one would want to look at.

CHAIRPERSON PACKER: Okay. Barry, let me --

DR. MASSIE: If you're in the hospital, clearly one way of getting at -- boy, this goes on and off -- is length of hospitalization and length of time in the intensive care unit, are measures that have some clinical meaning, as well as economic meaning.

CHAIRPERSON PACKER: Okay. Barry, the Committee has had distributed to it a protocol that Chris O'Connor and his colleagues have developed and are conducting now at Duke which actually deals with the setting of acute decompensation, but measures morbidity in a somewhat different way. It measures morbidity -- the therapy is given short term, but morbidity is measured during a follow-up period of two months after a short term infusion.

Chris, do you want to -- the protocol has

been distributed to the Committee, but do you want to outline just the overall way that the protocol is designed and its objectives?

DR. O'CONNOR: Sure. Thank you, Milton. I appreciate the opportunity to speak to the Committee.

This protocol concept really came out of a joint effort between the sponsor and academic steering committee, many of whom are in the room and some on the panel, concern that there was not much data looking at acute decompensation heart failure in the treatment with inotropes or inodilators.

So a trial was designed to look at the inodilator milrinone in a randomized fashion versus placebo in patients with acutely decompensated heart failure with the primary endpoint to look at total hospital days within 60 days, and that was hospital days due to cardiovascular events.

So not only did it take into account the hospital day duration of the acute decompensation, but also rehospitalizations that occurred within the next 60 days, and this was a trial that looked at a 48 hour infusion of the therapy versus the infusion of a placebo in a blinded fashion.

CHAIRPERSON PACKER: Okay. So, Barry --

Chris, why don't you stay up there for a moment? -- Barry, this is a trial in which the drug is infused short term, but morbidity is measured over a 60 day follow-up period. Morbidity is not necessarily measured during -- a measurement of morbidity is not restricted to the time of the infusion, but includes a period of follow-up of 60 days.

So I guess if this protocol is any example of what can be done in the setting of acute decompensation, one could conceivably measure rehospitalizations after a therapy designed for short term treatment of acute decompensated heart failure.

DR. MASSIE: I should indicate that I was part of the panel that helped design that study, and therefore it's not surprising that I'll say I think that's a good idea and another approach. I think that either approach would be something you'd want to look at and both approaches. Obviously the morbidity in that hospitalization, but certainly a follow-on issue of morbidity measured that way and presumably survival if the numbers of patients are big enough is also a reasonable way of assessing this.

But as a single exposure, I would also be happy to see that you could effect the short term morbidity as well.

CHAIRPERSON PACKER: Rob.

DR. CALIFF: I think if we come back to simple concepts, and again, the broken record here, if we give drugs to make people live longer or feel better, then you have to define whatever period of time you define as feeling better. You know, it could be the short term. One would wonder about whether it would be worthwhile to give a drug that made people feel better for a day and then they felt worse or were more likely to die.

And that's really why the 60 days was put in there after considerable discussion, is that the feeling was that it would only be worthwhile if the benefit was at least not going in the wrong direction over a period of time that was meaningful to a patient.

So it's kind of getting back to the feel better or live longer concept.

CHAIRPERSON PACKER: Again, this question is really directed toward what can be measured, not what must be measured, not what's the basis for approval, and not what's the primary endpoint. What can be measured, and I guess what we've done is identified two ways one can measure morbidity short term and during a period of longer term follow-up even

if the therapy is given short term.

Udho.

DR. THADANI: I think that your protocol probably doesn't address this question because here the acute decompensation is due to acute pulmonary edema, and I don't think --

CHAIRPERSON PACKER: No, no, that's for example.

DR. THADANI: Okay, but the way I was reading, because most of the patients if they're in shock are excluded, and the decompensation heart failure is a very different definition.

I have patients who get a lot of edema. They're not responsive, and they're short of breath on minimal exertion. That's one decompensation, but if I see a patient with acute decompensation who's actually going to lie flat, he's going to get something to improve his condition in that next 21 to 24 hours. I want him to be able to sit up without being short of breath.

Obviously the surrogate endpoint, what he does in the next 20, 30 days, is important, but I think to me acute improvement is important. Mortality is an issue which you can address later. If patient, you know, is four below, he can't even lie flat, and

whatever you're giving, whether it's nitroprusside or whether you use inotropic agents to improve his function and he can breathe well, I think that's an important marker.

Whatever happens subsequently may be relevant to us, but for that particular patient, I think that's relevant as well. So I think you have to, again, perhaps have two dissociations here, what we're talking about: really acute decompensation or relative decompensation where the patients are in the ward and we drag them into the unit to do certain things.

DR. O'CONNOR: Well, I think you're correct in part in that the acute shock patients are excluded from these patients, but nonetheless, these patients are sick, and the protocol doesn't exclude the use of other therapies that can treat acute pulmonary edema.

DR. THADANI: Say if you had a patient with pulmonary edema. You're not going to withhold -- you're not going in with placebo. At least I won't. I don't know. You might. I don't think any IRB committee is going to allow you doing that.

DR. O'CONNOR: They can get other IV medications.

DR. THADANI: Sure.

DR. O'CONNOR: And you can get a balloon pump if --

DR. CALIFF: Yeah, there are nitrates, lasix, morphine, all kinds of good treatments for pulmonary edema.

DR. THADANI: They're on ACE, they're on diuretics. With acute decompensation with pulmonary edema, how are you going to withdraw it? I don't know how we can.

CHAIRPERSON PACKER: That's not the issue. The issue is what can be measured, and if we want to know how it's done and what's prespecified and what the primary endpoints are, that's a little bit later on. The question is what can be measured.

DR. THADANI: I think what you can measure acutely is how the patient does. Does he leave the unit? To me that's very critical at that point, and then the rest is secondary.

DR. KONSTAM: Milt, let me follow up on Udho's comments, and let me just say that I really applaud this protocol. I mean I think it's exactly the direction -- it's an important direction to go, and I applaud the investigators for heading in that direction, of really trying to measure outcomes in

association with acute hemodynamic studies.

But just really to say what Udho is saying maybe in a different way is that I'm not sure it's a meaningful question, Milton, to stop it by saying can you measure it. Yeah, you can measure anything. You can measure mortality. You can measure anything you want.

I assume the question is asking for meaningful measurements, and I think that in that light, I think one has to say: okay. What is going to be the significance of this measurement? And let's stop and think about it for a moment.

Because you may be blinding the treatment, but if you are not -- and I don't think you can -- fully control all other treatments, then you have to say, well, if in fact an intravenous inotropic agent is achieving a hemodynamic benefit, perhaps improvement in renal blood flow and perfusion, you may be accelerating diuresis, and then the control group is very likely to wind up being managed differently because of the effect of the treatment.

And, therefore, I think, you know, just maybe to second the spirit of what Udho is saying is that this measurement can be done, but it's going to be ladened by the necessity of the clinical

circumstance with a lot of complexities, much beyond what we're used to in looking at long term outcome trials that we've seen, you know, in other domains.

So, yes, you can measure it, but you're going to hit a lot of problems.

CHAIRPERSON PACKER: Okay. We'll get into some of these in a little bit because we cover each of these settings again in a more definitive and hierarchal fashion.

JoAnn?

DR. LINDENFELD: Well, I think that I would say the same thing. This was a good study, and these are some of the things we need to know. At least we're measuring a definite outcome here, and even if the other treatments are different, I think at least we'll have data to look at.

So I think this is a good study, and I think this is something that should be measured. Will you be better for two months or in two months? I think that's something that's important to tell patients, and I think this is one of the areas, this short term therapy, that's changed a lot in the last ten or 15 years.

An awful lot more patients are being brought in for short term therapy. We're going to

tune you up, and I think this is one of the biggest changes, and this is just where we need some more data. Does this really do any good?

CHAIRPERSON PACKER: Okay. Again, we'll get into the what is valuable issue in just a moment.

Let's move on to question three. JoAnn, do you want to take this one?

In the setting of weaning from cardiopulmonary bypass, which of the following assessments can be made? And I understand that that sounds like an overly simplistic way of looking at it, but in some cases the measurements the can't be made.

DR. LINDENFELD: Right.

CHAIRPERSON PACKER: And this may actually be an example.

DR. LINDENFELD: Well, I think symptoms probably can't be made in this setting, actual symptoms within patients on cardiopulmonary bypass, but certainly hemodynamics can be. There would be a number of morbidities, time to weaning from bypass, ventilation time, ICU stay. All of those things could be easily measured, and certainly survival.

CHAIRPERSON PACKER: Okay. So that everything but 3(b) can be measured?

DR. LINDENFELD: Right.

CHAIRPERSON PACKER: Okay. Fourth -- okay. Barry.

DR. MASSIE: I was just going to say in the morbidity, I guess clearly you would want to look at assist device need as well.

DR. LINDENFELD: Right.

DR. MASSIE: In addition to ventilation.

DR. DiMARCO: But actually to some degree even symptoms can be measured because you'll want to look at the outcome. You might have something which weans people from bypass, but they have poor neurologic function, and so you may want to look at something two days later or three days later as an outcome and then evaluate symptoms at that time.

DR. CALIFF: There's a great analogy actually in the pediatric ICU data with weaning from ECMO where there are agents that will improve the weaning from ECMO but actually leave more kids with a disability or not getting out of the hospital.

So it seems like even in this case to ignore symptoms would be a big mistake.

CHAIRPERSON PACKER: Okay. Many of you have mentioned various measures of morbidity, and they seem to be varied depending on the clinical setting. We've heard mention of number of hospitalizations,

length of hospitalizations, length of an ICU stay, use of interventions, use of devices, need for emergency care.

There's a whole host of definitions of morbidity, and one of the things that seems to characterize heart failure is that since the sequelae of heart failure are so varied, I guess you could define morbidity in a variety of different ways.

Is there any guidance that we can or should give to sponsors in their pursuit of how to try to identify what is a reasonable measure of morbidity in a given clinical situation? Because, God, I don't know how many measurements have been made, how many ways it has been measured, but it would probably be fair to say that in almost every clinical trial everyone measures it differently.

Is there a right or wrong way of measuring it? I don't think that that's the case, but is there a better or worse way or is it really entirely up to the sponsor? Can the sponsor simply define morbidity in the way that it thinks would pick out the best or most favorable aspects of the drug, or do we think or should the agency think that some measurements of morbidity are better than others?

DR. MASSIE: I think Rob brought up an

excellent point. One measure of morbidity or symptoms is what you can do when you leave the hospital if you leave. I mean obviously if you die, that's an important outcome. If you leave the hospital but you're hemiplegic or you end up not being able to go home but rather to a nursing home, et cetera, that's a different type of morbidity.

I think I'm not sure when we get to assist devices and ventilators. Those are cost issues as well as morbidity issues, but I guess if you go on an assist device but you leave the hospital quicker and leave the ICU faster, then it's not morbidity. It's cost.

There's an intersection there. I guess you really need to look at those factors in looking at morbidity, but the end is, I think, the most common denominator is how quickly you get out of the ICU and how quickly you get out of the hospital and what your status is when you leave the hospital.

CHAIRPERSON PACKER: Ileana?

DR. PINA: Yeah, I would like to ask Ray is there currently a list of items -- I'm sorry. Is there currently a list of items that you would consider valid to assess morbidity? Does the agency currently have something, a working definition of

morbidity?

DR. LIPICKY: No.

DR. PINA: You know, we've discussed lots of morbidity items. I keep coming back. Every trial that is now looking at rehospitalizations. Rehospitalizations and length of admission continue to come back as a very important item of morbidity because it also translates, as Barry was just mentioning, into cost.

Exercise function is also something that doesn't get measured often after a hospitalization, especially if the patient is going to be rehospitalized again, but that can offer a very objective sense of functional capacity, which also has a correlation not only to morbidity, but also to survival.

So I would look at some very tangible aspects and give a list, a basic list of what can be considered items to be looked at for appropriate assessment of morbidity.

CHAIRPERSON PACKER: I think the problem, Ileana, that we might have with exercise is that although it might correlate with things, the question that arises is what is it actually a direct measure of, and this has been a pretty interesting discussion

primarily in the area of oral drug development, and I think the answers are not entirely clear right now because clearly one would like to -- if you're going to actually say that something is beneficial, you want to actually measure that as directly as possible.

And I guess the closest thing that has come forward is that exercise tolerance is more closely related to symptoms, and although it may predict morbidity and mortality, it actually isn't a measure of morbidity and mortality.

Would you agree with that?

DR. PINA: I would agree with that in general, but I think that as an event of morbid capacity, the inability to do anything is part of this patient's morbidity profile.

I've been waiting for somebody to also enter the quality of life issue in here, which is one of the hardest things to measure, and I mean we've argued at this in committee after -- not these Committees, but other committees -- as to how do you assess quality of life, and for some of these limited patients, quality of life may be something very simple and very basic as being able to do activities of daily living.

Now, how do you measure that? That is an

exercise function, and I don't mean by exercise everybody has to be on a treadmill.

CHAIRPERSON PACKER: I think maybe one thing we probably need to define is what we mean by morbidity. I think that the way that we're using that term is that symptoms or clinical status or quality of life -- and I'll group those together -- are measurements that you can make of a patient at any time you choose, whereas morbidity is the occurrence of an event of the disease's choosing preferably or the physician's response to a disease's choosing, but can only be measured at the time that it occurs and cannot be measured at a time that the protocol prespecifies.

Is that reasonable?

DR. MASSIE: No. I mean one exception. I guess the word "disability" pops in. You can measure disability at the time you leave the hospital. It will be, you know, a measure of the impact of the disease process and the treatments on morbidity.

I mean it's really the opposite of symptoms, and I think particularly when you talk about coming off of cardiopulmonary bypass, disability at the end of that hospitalization may be a very important measure.

So may I toss that into the morbidity equation, too?

CHAIRPERSON PACKER: Rob?

DR. CALIFF: Well, I mean, it seems like your array is, again, remarkably simple, and it's a definition that you're focusing on, which are difficult. I mean, you've got death and you've got bad things that happen to people that they wouldn't like to have, and hospitalization represents that, and you've got how you feel.

The dimensions that I think are important are, first, the more likely it is that you can measure the endpoint in every patient, the more clear the result will be. So death is good for that reason and hospitalization is good.

And one of the problems with quality of life is that there are many people in whom you just don't get the measurement at the time you want it, and you're left pretending like those people didn't exist or imputing some value or doing something. No matter what you do, you can't get out of the problem.

But the other aspect of the endpoint which I think is very important that this Committee could be helpful on is cause specific versus all cause. I think that the standard now in every field for

mortality is all cause, but what tends to happen in heart failure trials I've noticed is heart failure specific, hospitalization or morbidity, and that has an attraction because it's more powerful, but what if you had a drug that was better for heart failure but caused other problems? You wouldn't pick it up in the endpoint.

CHAIRPERSON PACKER: Yeah, Rob. In fact, I think that's why there is more and more movement in the area of heart failure to go to a less cause specific approach. I agree with you that that has been the way it has been done, but I think more and more there's an appreciation for how limited or even occasionally misleading that could be because a drug could reduce hospitalization for heart failure, increase hospitalizations for other cardiovascular reasons. Perhaps digitalis is an example of that, and clearly, if being in the hospital is a bad thing, if your total hospitalization risk is not affected, but your hospitalization risk for heart failure is reduced, I'm not certain there's much to celebrate if the goal is keeping the patient out of the hospital.

So I think that in all of these morbidity measures it's not only what one should be measuring, but to try to make it as general as possible to

eliminate the possibility that one is getting only the answer one is seeking instead of a complete picture.

Ray?

DR. LIPICKY: Well, but I guess the farther you get from morbidity and mortality -- and I'm not going to try to define morbidity for the moment -- is to closer you get to patients feeling better, and the one disturbing part of everything that's going on in the cardiovascular area is that that doesn't seem to matter anymore. Okay?

And knowing that patients feel better is less and less investigated and, in fact, has all of the problems that exist, you know, with quality of life and symptom evaluation and all of that sort of stuff.

And is it time to give that up?

DR. CALIFF: Well, I'd like to comment on that because we've done a lot of work on quality of life in various types of heart disease. I really think it is fair to characterize heart disease for the most part as a chronic disease punctuated by episodes of feeling bad, but in between which most people actually feel pretty good.

So if you measure, it's very hard to measure differences in quality of life, particularly

with global measures.

Then you can pick out particular elements of quality of life scales and find differences, but when you ask for overall quality of life, it's mostly dominated by the person's personality and other aspects of their life and not their disease.

DR. KONSTAM: Well, you know, Rob, heart failure though is the one condition in which that might be a little different as compared to acute ischemic events. I mean heart failure, of course, is associated with exacerbations, but is also associated with chronic persistent symptoms.

So, you know, I think conceptually there's a circumstance where answering Ray, you know, we really should be looking at how patients feel, and I think we have been getting away from it, but not because people are feeling it's not important, but more because of a frustration that we don't know how to measure it.

DR. CALIFF: Well, is it that we don't know how to measure it or that a lot of studies have been done and they've all been negative?

DR. KONSTAM: Well, I think the frustration is or the feeling is that we're not sure how to measure it, and perhaps part of the reason for

that is that there's been an inconsistency of findings, and there has not been one quality of life instrument that has been universally documented or accepted to clearly do the job.

So I don't think it's a movement away. I think it's a frustration that we're not sure we know how to measure it.

DR. LIPICKY: Well, but it does lead to the kind of model in your head that Rob just stated, that is, that although you're sick with congestive heart failure so that you're not normal and you're not feeling well, that level of sickness is relatively unaffected by anything you do, and that all you do is change the number of episodes where you need sudden attention.

But the problem is is that really true or is it that one, as you said, doesn't know how to measure symptoms and can't tell whether there is a difference in the treatments.

DR. KONSTAM: Well, I mean, I think we could ask the panel, but I think that there will be a feeling that quality of life -- I think people will answer you in the affirmative, that knowing how people feel chronically and looking at health related quality of life is extremely important, and I don't think the

panel would want to leave you with a sense that we don't think that's important.

I think that there's a tremendous uncertainty in the field about how to measure it. That's all.

DR. O'CONNOR: Well, certainly in acute heart failure, right? I mean if you can't tell that people get better, I don't know where you can tell, right? I mean is that not so, or is it that you can't tell the difference from placebo because all kinds of other things are going on?

See, I'm not sure I understand what anybody is talking about at the moment, including my self.

DR. MASSIE: Well, I was going to say if you give an IV diuretic in a person with upper pulmonary edema and they diurese five pounds and they're not short of breath anymore, I think we can get that answer. I guess it's more when you get past that acute improvement, dealing with the vagaries of up and down in the Class III patient that's much harder.

DR. LIPICKY: Well, okay, but here part of this stuff is acute. Okay?

DR. MASSIE: Should be able to do it.

DR. LIPICKY: Should be able to do it you think, tell whether people really get better.

CHAIRPERSON PACKER: I think you should be able to do it, but I'm wondering whether one would really bother. I mean I understand that there are reasons to measure quality of life, and I think I am particularly understanding of that for a sort of chronic, symptomatic disease, but in acute heart failure, a patient comes in with acute pulmonary edema, and just suppose you had a drug that got them out of acute pulmonary edema in five minutes instead of an hour. I just made that up, and the patient really went from being in pulmonary edema to being totally comfortable.

I'm not certain I would bother to measure quality of life scales in something like that.

DR. KONSTAM: Well, you just did, didn't you? I mean I don't understand what you're saying. You just made a quality of life judgment.

CHAIRPERSON PACKER: I made a symptom judgment.

DR. KONSTAM: Okay, right.

CHAIRPERSON PACKER: I didn't make a quality of life judgment. I didn't ask the patient --

DR. KONSTAM: Well, what's the difference?

CHAIRPERSON PACKER: -- what the impact of his lack of symptoms were on his ability to carry out activities of daily living.

DR. KONSTAM: I think we're quibbling. I think we're quibbling. I think we're talking about symptomatology, and in the chronic setting we call that health related quality of life, and in the acute setting we call it symptoms. I think we're talking about the same thing.

DR. CALIFF: Well, now you're getting me worked up. I want to quibble with you a little on that one.

(Laughter.)

DR. CALIFF: Symptoms and global quality of life can be quite different. You may have a miserable patient for other reasons who gets better with regard to his heart failure, but hates being alive just as much. In fact, we have many examples of that.

They're both important. I don't think either is unimportant.

DR. KONSTAM: Yeah. Well, we should probably cut this discussion short because as we keep going, we're going to wind up diverging.

CHAIRPERSON PACKER: Okay.

DR. KONSTAM: But let me just say that I guess I would say my view of this is that health related quality of life is the only thing that's important other than keeping the patient alive, and that symptomatology is one of the major drivers of health related quality of life, and that's the way I would say it.

CHAIRPERSON PACKER: Okay. Why don't we go on to question number four? And let's see. In patients with chronic heart failure -- these are out-patients -- which of the following assessments can be made, and let me take the prerogative of saying in oral therapy we know that the answers here are we can measure hemodynamics. We can measure symptoms. We can measure morbidity. We can measure survival, and my guess is if we can do that with an oral drug, we can do that with an IV drug. These measurements can be made, and I can't see, unless there's anyone that would disagree with that, why we would have to spend anymore time on this question.

DR. THADANI: The question is should you make them.

CHAIRPERSON PACKER: That's next. That's the next series. That's the next series.

So, Ray, the answer is that we are

providing to two, three, and four -- is, in fact, in all of these settings all of these measurements can be made. Even in the setting of weaning from cardiopulmonary bypass, you can make a measurement of symptoms a couple of days after surgery, and now you want to have us evaluate which of them should be made and which should matter.

DR. LIPICKY: Right.

CHAIRPERSON PACKER: And we're going to do that in each of the clinical settings that we've just discussed.

What might be the primary endpoints, any of the four that we've talked about or others, of trials designed to support approval of an IV medication used when the patient sustains an acute decompensation of chronic heart failure?

This is the clinical setting, acute decompensation of chronic heart failure. Generally speaking, we are talking about the IV drug being used for a day or two in the hospital, short term therapy, and what should be measured? What should be the control treatments, and what should count in terms of approval?

So that's the basis of this question, and, Barry, do you want to take first shot at this?

DR. MASSIE: Yeah, and I think we've sort of had this discussion in a sense, and I think Chris O'Connor's protocol gives you some idea of the heterogeneity of time points in which you could look at it.

I think that if we're really specifically looking at this setting, somebody comes in sick enough to require an intensive care unit admission, that perhaps hemodynamics is a valid measurement. If it's somewhat less than that, I think that's not a valid measurement of what goes on, and then again, symptoms, morbidity, and mortality are also important, and I think we have to open up our time windows.

I think certain if they're on the far sick end, how quickly they get out, that time counts, but if they're Class III patients, they probably wouldn't get into an ICU anymore, I guess is one way of looking, but if you are going to take people who aren't barely surviving and aren't really needing to be in an ICU, then I think you have to look longer out, and I like the Chris O'Connor protocol.

CHAIRPERSON PACKER: Okay.

DR. MASSIE: But hemodynamics, I think, is the one we have to be most careful at looking at because they're appropriate measurements in a very

narrow range of patients, I think, and I'm not sure that that constitutes the vast majority of people who are admitted, quote, unquote, with decompensated heart failure.

CHAIRPERSON PACKER: Okay. Barry, up to now the approval process for acute decompensation of chronic heart failure or just acute heart failure, with the concept of short term IV therapy, this approval process has had as its primary endpoint hemodynamics.

DR. MASSIE: Right.

DR. LIPICKY: You already said that's fine.

DR. MASSIE: But, no, I don't think --

CHAIRPERSON PACKER: Well, you did say that.

DR. MASSIE: It is fine, but I think the important thing is even in those studies that up until now have gotten these drugs approved, probably most of those patients don't meet my narrow range of where it's a valid measurement of outcome in the study.

In other words, because we enroll patients in those trials, and we've often brought in Class III patients who were out of the hospital to come in and get 42, 72 hour infusion of a drug and show that it

improved more than placebo or equally or more than a comparator. Those are people who wouldn't have gotten into ICU if they weren't in a protocol.

So I think we have to --

DR. LIPICKY: So as long as they're really sick, hemodynamic measurements are okay --

DR. MASSIE: I think they're --

DR. LIPICKY: -- as a basis for approval?

DR. MASSIE: Right, but I think there's very little -- because those patients are so hard to deal with and so many of them mandate active therapy even of this type of therapy, it's a little bit hard to study those. So I really do think that in the types of patients who have gotten IV drugs approved before we have to look at broader measurements of outcome than we have.

CHAIRPERSON PACKER: Barry, let me just focus this a little bit. The Committee has previously said that one can measure hemodynamics. One can measure symptoms, morbidity, and mortality, and you're saying that, yes, you can measure them, and I understand you would measure them, but if a drug didn't affect symptoms or morbidity or mortality, but did affect hemodynamics, you would consider that to be all right?

DR. MASSIE: I would consider it all right only in a very narrow range of patients who are not usually part of the package that gets these drugs approved. So I guess you're sort of forcing me to say we should measure other things and show they get better, too.

DR. LIPICKY: Don't let them.

DR. KONSTAM: Yeah. Can I --

DR. LIPICKY: You're okay.

DR. MASSIE: No, I'm not sure I'm okay because I've done enough of these trials myself to know that we're not collecting the hemodynamic data in the people in whom it's meaningful.

DR. KONSTAM: I'd like to help Barry out here.

DR. MASSIE: Okay. I always appreciate it.

DR. KONSTAM: Because, Milton, I think there is a movement of this discussion in a certain direction which in large part I agree with, but you know, let's focus on this acute/severe exacerbation, which the most simple example is acute pulmonary edema, and I think here I'd like to introduce or save perhaps or mention the concept of an instrument drug perhaps, and also say that we could well come to the

conclusion that pulmonary capillary wedge pressure is a useful surrogate for the driving force that results in acute pulmonary edema.

So that if even sticking to our guns and saying the only thing that matters is getting the patient well and improving their quality of life and getting them out of the hospital, reducing hospitalizations and reducing mortality, we might at the same time say, "Okay, but if we know the drug is safe and if we know that it achieves an acute reduction in pulmonary capillary wedge pressure, that that might well be an acceptable, valuable surrogate in the circumstance of acute/severe pulmonary edema."

CHAIRPERSON PACKER: Marv, I understand what you're saying, but most people with acute pulmonary edema hopefully are not swanned.

DR. KONSTAM: That's okay.

CHAIRPERSON PACKER: No, no. You know, we give them whatever we need to give them, and it works.

DR. KONSTAM: Right.

CHAIRPERSON PACKER: So that the number of people with acute decompensated heart failure that actually get a Swan Ganz Mather (phonetic) are actually people who are not only in pulmonary edema, but hypoperfused.

DR. KONSTAM: Right.

CHAIRPERSON PACKER: That is, they're more along the lines of cardiogenic shock --

DR. KONSTAM: Okay.

CHAIRPERSON PACKER: -- than they are acute pulmonary edema.

DR. KONSTAM: Right.

DR. LIPICKY: So what?

CHAIRPERSON PACKER: And you're saying that in -- I think what you're saying is in that patient population, you would use hemodynamics because the pulmonary edema population actually doesn't get invasive measurements in the first place, in general.

DR. KONSTAM: Just a minute.

DR. LIPICKY: But they could for a study.

DR. KONSTAM: For a study. They could for a study.

DR. LIPICKY: They don't have to come implanted in order to be involved --

DR. KONSTAM: I mean, I guess the question is going to settle into -- Milton, I think what you're driving at asking is: are there any circumstances where we would accept hemodynamic measurements alone as the basis for efficacy as we have in the past, or should we not do that anymore?

And I'd like to hear more discussion about this, but I'm at the starting point where I would like to rescue hemodynamics a little bit in the setting of patients with acute clinical exacerbations of heart failure. I think that there is a place for approvability on the basis of acute improvement in hemodynamics based on what we know in terms of the pathophysiology of heart failure.

You know, I think I'd like to see the exact circumstance, but I'm not willing to abandon that as a possibility as the basis for approvability.

CHAIRPERSON PACKER: Udho.

DR. THADANI: I think, you know, I beg to differ with you that I think it could be a surrogate marker. In 1998, or we used to put a lot of swans. Now it's very rare a patient gets swans unless he's hypertensive. You know, you can get them out of the hospital. When you're talking about acute decompensation, you have read Chris' protocol. Most of the patients have more edema, they're a bit more short of breath. We do swan just to put them in the study. They may not be realistically acute decompensated.

Acute pulmonary edema is a different issue. So I'd like to see the symptoms improving,

too. You know, if you have a chest X-ray full of fluid and you can see in the chest X-ray the fluid goes away, that's your clinical marker, but usually the patient always feels better. He can sit up.

Most of the time when you're saying blood pressure goes down, so does the patient's improvement in acute situations.

DR. KONSTAM: Udho, let me --

DR. THADANI: I'm not sure that we want to take just hemodynamics alone.

DR. KONSTAM: We're talking about a trial design for the basis of approvability. We're not talking about necessarily saying everybody comes in --

DR. THADANI: You're talking about acute decompensation. So I think you'll have to make sure the patient has come to you because of symptoms. He doesn't come to you to tell you his cardiac output is low. He can't walk or he's symptomatic. So I think you have to go on symptoms. You can't just say, "We don't care about your symptoms, you know. We're going to just increase your cardiac output, lower your wedge pressure, and we are happy with it."

So I think the two have to move together.

CHAIRPERSON PACKER: Rob?

DR. CALIFF: I can't believe this. I

really can't. I mean how many more examples do we have to go through of surrogate endpoints before we catch on? It seems like a virus that people have caught in their brains where they are compelled to find these surrogate endpoints.

I mean if people really feel better when you lower the wedge pressure, then ask them if they feel better, and if they say they feel better, you can do a very small trial and get the answer.

But perhaps even more importantly, you know, many of us were involved in a trial of acute heart failure where we improved the hemodynamics and we killed people.

DR. KONSTAM: Which trial was that?

DR. CALIFF: The first trial, flolin. It's a prostacyclin type drug. It lowers the wedge pressure. It improves the cardiac output. It was for acute decompensated heart failure.

DR. KONSTAM: Wait. No, Rob, that was a home infusion. That was not -- it didn't kill people during the first 12 hours of administration. We have to be clear.

DR. CALIFF: Well --

DR. MASSIE: It was chronic home infusion.

DR. CALIFF: Okay. It's a little murkier

than that.

DR. KONSTAM: No, no. Wait. Hold on a minute, Rob.

DR. CALIFF: Yeah?

DR. KONSTAM: Now, I don't know how we're going to end up in this discussion, but my starting point, which I'm willing to listen to somebody dissuading me from it, is that there is a difference between asking for approvability of a drug for, let's say, one hour, let's say, to achieve a specific hemodynamic endpoint, which I believe is strongly associated with certain clinical morbidities. There's a big difference between that and saying, "What should be the goal when we're switching or talking about using an agent for long term use?"

I would like to ask the panel: do we really want to totally move away from that? Are we going to say the drugs that have hemodynamic benefit and that might be used for an hour, let's say -- one extreme -- that there is -- are we willing to totally move away and say, "No. Every time we're going to raise the question of approvability for that agent, we need to document the effect on long term mortality in that agent"? That's the question.

DR. CALIFF: Well, no. If you take out

the term "long term," if you take out the word "long term," then that I would --

DR. LIPICKY: Or even short term.

DR. CALIFF: -- I would take the opposite point of view.

DR. LIPICKY: But -- but -- but I think the way to look at it is in this setting now, okay, we'll take the population Barry likes, you know, drowning people, high filling pressures, low profusion, okay, not making urine, and involve them in a trial, and you might have to put some catheters in because they don't come that way, right?

And then you do a placebo controlled trial on top of all background therapy, right? Now, the issue is let's say you document that there is appropriate hemodynamic changes, but you cannot document -- and that the appropriate hemodynamic changes are there as a function of placebo and drug, but you cannot document as a function of placebo and drug symptom benefit, but, in fact, compared to baseline everybody improves.

So you measured symptoms, and indeed, everybody got better, right? But you can't tell drug versus placebo. Maybe it numerically leans. Okay?

But, indeed, the hemodynamics are very

clear. They're very appropriate. So the question here is not that you wouldn't measure symptoms or you wouldn't measure anything else. The question is: what's the primary endpoint? And could you only get something approved in this circumstance if, in fact, for symptoms you had to beat placebo or for symptoms you had to, in fact, have a shorter stay in the ICU or for symptoms you had to have a shorter -- a longer life? Excuse me.

DR. KONSTAM: Well, let me say about that that I think under those circumstances it may be very difficult to design a trial and achieve a result that clearly documents the difference in symptoms, and this relates really back to my comments with regard to Dr. O'Connor's trial where let's take an example of where you wanted to study the effect of nitroprusside in acute pulmonary edema, and you were going to give it for an hour.

And the issue then would become in that patient are you able to fully control everything else going on such that the treatment is identical in both the treatment group and the placebo group, and if you could, then maybe you ought to be able to demonstrate a difference, and in fact, you'll show that you're winding up having patients die because you're

withholding therapy.

But if you're not going to withhold therapy, then it's very likely that the placebo patients will wind up being treated differently because they're going to be getting more diuretics, let's say, for example.

So I guess my answer to your question is not the lack of desirability to document the benefit on symptoms and quality of life and important outcomes. It's just that in those settings of acute exacerbation, it may be very difficult to design a trial and achieve documentation of those endpoints that you really would like to see.

And I think I continue to be willing to accept under those circumstances what I know about the pathophysiology of heart failure, and if I have a trial that lowers wedge pressure, I might be willing to accept that.

DR. LIPICKY: Well, I'm on your side, but in particular, if -- and then we come back to 1(b) -- if you know over what dose range you can affect those pressures --

DR. KONSTAM: Yes.

DR. LIPICKY: -- and you know what kind of doses you ought to use, where you ought to start and

where you ought to end, that would seem to me if there was just a yes or no answer, that is, yes, I can affect wedge pressures, but you hadn't the foggiest notion whether it took a milligram or ten grams; you gave both, and they both gave you something. Okay? That I find unacceptable.

DR. KONSTAM: I agree.

DR. LIPICKY: Okay. So at the moment you and Barry have painted a picture where in one clinical setting, in particular, if you could demonstrate dose related hemodynamic effects, even though you don't know what good the hemodynamic effects are and even though you know that any given dose won't give you the same hemodynamic effect in every patient; if you demonstrated that, that that would, in fact, be the basis of approval.

It doesn't say you would not measure other things, but if the other things did not differentiate themselves from placebo, it wouldn't matter, and I suppose -- and then, in fact, just having a point estimate for mortality, you know, taking the point one step further, in the trials that demonstrated the dose related hemodynamic effects, clearly you would have had the ability to observe on an intention to treat basis who died and who didn't die.

But since it's not a trial designed to evaluate that, it probably would not be suitably powered to draw any conclusions relevant to that, but at least there would be a point estimate.

So you guys have staked out a position for saying that would be okay.

CHAIRPERSON PACKER: Let me see if I -- I'm fairly certain I understand it, but I want to have Rob respond to this specifically.

Ray's summary clearly states that everyone on this panel would want for an acute drug for acute heart failure, short term drug for acute heart failure, to encourage sponsors to measure everything, and even though some of the measurements or conclusions from those measurements may be grossly underpowered because they had wide confidence intervals, we would still want to know, and we would probably not be underpowered for symptoms.

DR. LIPICKY: Yeah.

CHAIRPERSON PACKER: But even if the drug didn't beat placebo on symptoms, you would, Marv, say that was all right, and the major reason that you would say that it was all right is not because you don't think symptoms are important, but because you think that the acuity of setting forces the clinician

to compensate in treating the control group in order to make sure that everyone has improved symptoms at the end of an observation period.

So that although symptoms are nice to measure, when you measure them, if you measure them long enough into the course of an acute exacerbation, you may be reflecting not only the effect of treatment in the active treated group, but the effect of additional interventions in the placebo group so that the physician makes certain that everything comes out equal at the end.

That's what you say before.

DR. KONSTAM: That's close enough.

CHAIRPERSON PACKER: Okay. Rob, what would you say to Marv's concerns? Because he's basically saying that he's not advocating the surrogate. He's just saying that he loves symptoms and would love to see that the drug beats placebo on symptoms, but you can't get there from here. So he doesn't want to hold the sponsor to doing that.

DR. CALIFF: It's ironic, isn't it, that the guy that just stood up for symptoms and quality of life is now saying we don't need them? It shows how complicated this is.

DR. KONSTAM: It's complicated, isn't it,

Rob?

(Laughter.)

DR. CALIFF: But I think we've learned that we can do clinical trials in complicated, life threatening diseases if we develop the clinical ambiance and fortitude to answer the question because what happens is we do these sort of -- the word that comes to mind I wouldn't use in public -- we do these sort of weak studies. We open the door, and then before you know it, we've gotten the drug being used all over the place based on, you know, little studies with nicely funded investigators talking about how we can use the drug for all of these other indications.

I don't think that heart failure is the only problem where people get treated differently in Group A versus Group B. It seems to me that the major question in this decade and in the future is not how does the drug do in the setting of a physiology experiment. The question is: does the drug add patient benefit to the standard treatment for the disease?

And so from that perspective, I would argue that if you add the new drug or a placebo on top of what the doctors otherwise do and the patients don't feel any better or live any longer, why do we

need it? Why would you want something like that on the market?

Wouldn't it be better to require that the sponsor and the investigator show that you actually improve the patient? Then when it got on the market, we'd actually have something that we could have confidence would be beneficial.

DR. LIPICKY: Then you'd have nothing on the market.

DR. CALIFF: You mean historically we would?

DR. LIPICKY: Well, in the future.

DR. CALIFF: Well, I don't know. I mean maybe it's -- I'm hopeful that milrinone would be shown to have this beneficial effect.

DR. LIPICKY: Well, yes, sure.

DR. CALIFF: We'll know in about ten months.

DR. LIPICKY: Sure.

DR. CALIFF: But what if we find it has a detrimental effect? Then we will have really done a service, wouldn't we, instead of just using hemodynamics?

DR. LIPICKY: Yes. No, I understand, but see, I mean, the scenario you paint is certainly very

reasonable. You know, you don't want to open the door and all that sort of stuff, but it's not clear to me that the only time that one can think about approving something is if, in fact, it is better than those things that are standard, and in fact, better than on top of all of the standard things.

I think that that is really a burden on the development process that although, you know, it's not too hard to defend that, okay? It just doesn't seem like that's a reasonable thing. It seems like it's too demanding, and I thought you just voted this morning for saying that since you guys are such slobs, continue to be slobs, did you not?

DR. CALIFF: No, no. I hope that we'll actually soon have a major meeting about hypertension where we actually require some --

DR. LIPICKY: Yeah, but --

DR. CALIFF: -- evidence.

DR. LIPICKY: -- until then you say, "Behave like you have in the past."

DR. CALIFF: I'm not for -- I'm not for arbitrary punishment of individual people or companies, but I am for trying to improve patient outcome, and it seems like we have a chance to take a step in that direction in this case.

DR. LIPICKY: Well, but you can. I mean, there isn't any reason if you designed a trial like we're talking about. This is the acute setting, placebo versus drug and so on. You could discover that this on top of everything makes people really feel much better. You know, feel better.

The question is if you did not find that and all you found were dose related hemodynamic effects, whether that would be good enough. It would not preclude finding something that was better, but you're saying that it would not be okay if it was the same, but had hemodynamic effects on top of everything else, that that would not be good enough if there was no clinical benefit that you could associate with it.

And that seems rather strange to me. I don't understand that. Why do you say that?

DR. CALIFF: Because I thought we approved drugs because they improved patient outcome.

DR. MASSIE: Maybe I can respond. I think we're getting in a rut here because I think in defining this population we've defined it away. I think I agree with what Marv said, I said, and that Ray is saying, and Milton reiterated. This would be okay in this population.

I have never seen this population studied,

and it never will be studied, because by the time you get informed consent, they've diuresed a liter or else you're a lousy doctor, and then all of a sudden they're transitioning into a group that is not -- a hemodynamic endpoint is no longer sufficient.

And I bet if I went to any NDA for any inotropic drug, especially the ones I participated in, none of the people who have been enrolled meet these criteria. They are people who have the same hemodynamics sometimes as people in acute pulmonary edema. They have wedge pressures of 35, but they signed an informed consent form. They often waited a day to be admitted to the ICU, and then they got titrated up, and they had these hemodynamic effects.

And I'd ask Ray if in those patients you show dose related hemodynamic effects and you lower the wedge, are you going to approve them for the indication of acute heart failure?

DR. LIPICKY: Well, that was 2(c).

DR. MASSIE: Right, but I'm saying that --

DR. LIPICKY: Rather than 1(c). That was, in fact, the question that was directed --

DR. MASSIE: But those were the people who have always been --

DR. LIPICKY: -- toward --

DR. MASSIE: -- studied for 1(c).

DR. LIPICKY: That was the question directed toward is there some difference between hemodynamics and chronic heart failure and affects, you know, dose related hemodynamic changes and acute heart failure. My anticipation was you would say no, and that if you were willing to accept hemodynamics in the acute decompensated setting, you would be willing to do the same in something short of that.

DR. MASSIE: Well, maybe it's time to move on because there's disagreement among everybody up here that we would not be willing to do that.

DR. LIPICKY: Well, I haven't heard that agreement.

DR. CALIFF: For 5(a), I would agree, but 5(b) and (c), it's a weak step to continue to take a surrogate for such an important disease.

DR. LIPICKY: Yeah, okay.

CHAIRPERSON PACKER: Let me try if I understand. The reason that you would vote yes for 5(a) is because of the concept of a bridge. So that there is no -- why is the bridge acceptable?

DR. CALIFF: That reaches a threshold for me. You know that the drug is beneficial. At least when it's put in the blood stream by a different route

it's beneficial.

CHAIRPERSON PACKER: Okay. Let me see if I can summarize this here. There is a desire to gain more information about clinical measures when evaluating the effects of short term therapy for acute exacerbations of heart failure. That is a message this Committee wants to deliver.

Applications, the evaluation of IV drugs has generally ignored symptoms and morbidity or point estimates of survival, and the message we want to send forward is: don't ignore these anymore because we would like you to measure them.

The question that the Committee has been grappling with is, okay, so you measure them. What will we hold you to if you come back and show that what we have asked you to measure isn't distinguishable, isn't the basis of distinguishing your drug from placebo, and there is a difference of opinion in the panel as to what that means in the setting of acute heart failure, but as Barry made the point, that is not a disease that is studied.

DR. LIPICKY: Well, that's what Barry says.

CHAIRPERSON PACKER: I think that's true.

DR. MASSIE: Maybe we could take a poll of

the panel here since I recognize at least six or so people have participated in trials of drugs looking for an indication for acute heart failure. What proportion of the patients they put in have acute heart failure?

DR. THADANI: Yeah, I think that the thing is if somebody is in pulmonary edema, nobody goes in the trials. You may say anything. You know, most of the physicians are not going to put anybody in pulmonary edema on a trial.

CHAIRPERSON PACKER: Lynne.

DR. STEVENSON: I do think, however, that there's a large population of patients who have symptoms at rest who are not in danger of dying in the next couple of hours or needing to be intubated, but who have significant symptoms at rest that can be relatively rapidly relieved with acute therapy, and I think those patients often get into trials.

Their symptoms by and large I would maintain are related to their hemodynamic abnormalities, specifically their filling pressures, if they're short of breath at rest. If you relieve those filling pressures, you will relieve their dyspnea. It may not be immediately. It may be the next day, but I think you will find a concordance

between symptom improvement and the hemodynamics in this population.

I think it's a fairly large population. I do think if you have people who are more severely ill than that, it will be hard to show a difference with placebo because, as Marv indicates, you'll have to add other therapies, and for instance, if you have someone who's very dyspneic, you may add morphine, and they might feel just as good as the patient who got the drug, but that's obviously not the point of what we're trying to do.

So I think it is a large population. Hemodynamics matter, and symptoms will follow the hemodynamics, and all I think we need to do for the acute setting is just demonstrate that there is not an unacceptable incidence of adverse events like morbidity and mortality. I don't think we need to put a benefit.

DR. LIPICKY: Lynne, how do you know that people get better in acute pulmonary edema from what you do?

DR. STEVENSON: Because they feel better. It's not always immediately because --

DR. LIPICKY: Why wouldn't --

DR. STEVENSON: -- there may be other

things happening.

DR. LIPICKY: -- you know that if, I mean, for a new drug?

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

DR. LIPICKY: Do you have any placebo controlled trials that evaluate current therapy?

DR. STEVENSON: No.

DR. LIPICKY: No. So, again, how do you know it works?

DR. STEVENSON: I know that medicines that take the filling pressures down make people less dyspneic.

DR. LIPICKY: How do you know that? Rob says that's not true.

DR. STEVENSON: I know that.

(Laughter.)

DR. LIPICKY: Well, he says it isn't.

DR. STEVENSON: We could fill this room with patients up to the ceiling who felt better as soon as their wet pressure came down.

DR. THADANI: I don't think Rob said it's not true. I --

DR. LIPICKY: Rob says that's a surrogate.

DR. THADANI: No, no, but you're treating the patient with symptoms. His symptoms got better if

he can --

DR. CALIFF: But if they get better, you just have to ask them if they got -- "Are you breathing better?" And they'd say, "Yes," and then you'd have your answer.

DR. LIPICKY: Well, no, I understand, but again, then you're into symptom evaluation, new drug versus placebo, on top of all of the positive -- all of the things that people have to do. So it seems entirely possible to me that you could end up with the drug that, in fact, affects filling pressures fine, but you would not be able to develop an instrument that would be able to evaluate symptoms that would detect on an intent to treat basis placebo versus drug.

And consequently, you could not hope to use that as a basis for approval even if it worked unless you did a set of sequential trials where those were the first trials one did and then one could start eliminating the other common therapies and get that through an IRB and finally get it down to placebo versus new drug along.

Then you might be able to evaluate symptoms and expect to win, and what I guess I'm not comfortable with is the thought that one would need to

win to be approvable in that setting.

If one did that, I mean, obviously that'd be just terrific, and then there would be no discussion, but I think the issue was do you have to.

CHAIRPERSON PACKER: Well, one thing just to comment on what you said, Lynne, by the way, when you measure morbidity and mortality and you say you want to do that to rule out harm, realizing that given the power of trials and the confidence intervals, any effort to reasonably rule out harm is equivalent to a full evaluation of that drug in a two-sided manner.

DR. STEVENSON: Except that I think when we're talking about someone who has serious symptoms at rest that we're trying to relieve, we might accept a much larger confidence interval --

CHAIRPERSON PACKER: I agree.

DR. STEVENSON: -- in terms of is mortality increased by seven percent, by nine percent. Depending on how sick he was when he came in, I might be happy to accept that.

CHAIRPERSON PACKER: I think that's a very valid point.

Okay. I'm sure that the Committee realizes that the reason these discussions are taking place is because there are IV drugs that are under

development right now, and it's likely that within the foreseeable future we may see some of these come to the Committee, and so we will have this discussion again, and I think it would be fair to say that the discussion will be an interesting one and will probably highlight some of the points that have been raised here, but that sponsors who are embarking on an IV development program now should keep in mind that not all of the answers are in, and they should endeavor to measure as many clinically relevant endpoints as possible and, in fact, try to design their trials in order to distinguish active therapy from placebo on these clinical measures.

There's no reason to measure them unless you want to distinguish your drug from placebo. So there's a challenge to go forward and try to do that to the best of your ability, and if you don't do that, then the Committee will be happy to tell you what it thinks at that time.

I think we should skip number six and move on to number seven. It's the same question for number five. What are the primary endpoints of trial to support approval of an intravenous medication to be used intermittently or continuously for maintenance therapy, and what would be the control and the three

cases which are listed in the questions?

And let's see. Who wants to take that? Barry.

DR. MASSIE: Well, now we're obviously dealing with a population that's not as sick as either that narrow acute population or the people that I think Lynne is dealing with at least when they're in their Class IV symptomatic at rest situation, and I think there I think we know that we can and ought to measure some sort of clinically relevant endpoints.

I think it's also -- the safety requirements, I think, need to go up if this is planned to be given more than 48 hours or cumulatively over many hours over a period of time because I don't really know how toxicity in these drugs evolves. I'm fairly convinced that it's not necessarily limited to that period when the patient is exposed to active medication, and that there may be chronic changes that happen in the myocardium, as suggested by some of the chronic trials.

So I think there we need to look at measurements of symptoms and measurements of morbidity and get an estimate of mortality. I don't think we have to show that we improve mortality, and as Ray says, we may even prove that we don't improve

mortality, but that we improve morbidity and symptoms in a way that it's an acceptable tradeoff.

There are some subsets there. What happens if the oral formulation exists? If the oral formulation has, in fact, been shown to be effective in accomplishing these endpoints, I'm not sure why the patient would need the IV formulation intermittently on top of that unless its substitution during an NPO period, which I think is probably a trivial question we don't need to look at.

PARTICIPANT: IV diuretics.

DR. MASSIE: IV diuretics. Yes, that's true, but -- and there may be limits to dose response range of oral therapy that would require a whole different package of studies to show that you wanted to go higher up on the dose, and then that might be reason for going to intravenous therapy.

I think the standards become a little higher when we know that the oral formulation is either ineffective or unsafe. Then that estimate of harm that you need or harm ruled out that you might need in another setting would have to have narrower confidence limits, I would think, because one would have to wonder whether or not, again, chronic exposure even if given intermittently to a drug can cause harm.

So I think there are many. We've talked about all the endpoints. We probably don't need to fine tune them, but they should include measurements of symptoms, and they should include morbidity, and they should include some estimate of mortality even though it may not be an improvement.

CHAIRPERSON PACKER: Barry, if I hear what you're saying, I think what you're saying is that if a drug is going to be used long term, that the measures used to evaluate efficacy should be similar whether that drug is an IV drug or an oral drug. Is that fair?

DR. MASSIE: I think so, although mortality, as Ray points out, has become our major standard for long term, chronic exposure of drugs, and I don't think it need be in those settings and certainly need not be necessarily in this group of patients either. We just need to know what it does and so we can describe it.

CHAIRPERSON PACKER: But that's the same for oral. In other words, you don't have to show an oral drug prolongs life. You just have to evaluate what it does to survival, and if you show that you make people feel better and you do that to an extent in which the effect on survival is acceptable, then

that would be compatible with an oral drug, and I guess what you're saying, an intravenous drug as well. It wouldn't be different.

Marv.

DR. KONSTAM: Yeah, Milton. I just want to say that more strongly. You know, I mean, I think that the issue of route of administration, you know, is in my way of thinking the least consequential thing that we should be thinking about and is driven by practicality, you know, of whether the patient can or cannot take oral or actually whether or not there is an approved oral agent is the thing that tends to drive it in practice.

I think if you're going to administer a drug chronically, whether it be continuously or intermittently, for long term management of heart failure, then I think we are evolving standards of approvability related to clear-cut outcomes, and I see no reason to hold an agent to a different standard because it may or is often administered intravenously as opposed to administered orally, and I just don't think it matters.

So I think that we need to look there. We clearly need to look at hard outcomes, and I think preferably survival, but there may be circumstances

where survival is neutral, but we need then to look at morbidity outcomes.

CHAIRPERSON PACKER: JoAnn?

DR. LINDENFELD: I would just second what Marv said. I think that the standards have to be the same.

CHAIRPERSON PACKER: Ileana, any -- agree? Agree.

Lynne?

Anyone disagree with the fact that the standards should be the same for a long term therapy regardless of the route of administration?

(No response.)

CHAIRPERSON PACKER: Okay. That leads us actually directly to question nine. Having said that in the future you believe that therapies being evaluated for long term IV use, either intermittent or continuous, should meet the general guidelines for what is now looked at as long term oral use, realize that that is a prospective opinion.

And the question is: how much of that conclusion should be applied to what is already on the marketplace? Because there are IV drugs approved for use in heart failure, and there are -- and some of those drugs, although not evaluated for intermittent

or continuous IV use, are being used intermittently or continuously long term, and there are trials using oral formulations of these drugs long term that have raised concerns.

So the question is: is the opinion of the panel regarding future development -- how should that be applied to drugs which are already concluded with their development to date and are already on the market? And the concern has specifically been raised about the safety and efficacy of long term IV therapy, either intermittent or continuous, given the experience with these drugs long term in oral trials.

Can we have the projector up? Is that possible? Okay. That would be great.

The Committee has received a copy of a review entitled "The Evaluation of Long Term Treatment with Cyclic AMP Dependent Positive Inotropic Agents," and what we want to do is present the main conclusions of this review and, in addition, to have members of the panel comment on this because it is pertinent to the overall discussion as to the approvability and labeling of IV drugs for heart failure.

Just so that the audience is aware of what the conclusions of this review are, and we just have a few overheads that highlight the main parts of this.

The main goal of this review was to obtain evidence from controlled clinical trials concerning the efficacy and safety of long term positive inotropic therapy for heart failure.

Next.

And in order to do that, the following methods were employed. All trials that evaluate drugs with positive inotropic properties that were dependent in part or in whole -- that should be "whole" -- on cyclic AMP were evaluated, and the reasons is that all of the drugs presently approved for IV use for heart failure for short term use are, in fact, cyclic AMP dependent.

The trials were -- the trial had to be double blind, placebo controlled with a parallel group design. Trials that were a crossover or withdrawal were generally excluded.

Could we go back for a second, Ray?

And the trials that were included in this review were those of three months in duration because that's generally the duration of trials that the Committee sees for long term therapy as a minimum.

There was no attempt to validate the results. In some questions the results were questioned by the Advisory Committee.

There was no attempt to correct for P values for multiplicity of endpoints or treatment or analyses, and the review contained 23 trials with seven orally active drugs. The list of drugs is shown above, and that includes drugs that are beta agonists. Xamoterol has beta blocking properties, as well, but is commonly put into this category.

Phosphodiesterase inhibitors, such as milrinone and enoximone, and drugs which have a phosphodiesterase inhibitor action, although they have other actions as well, that may or may not be more or less important than their effects on phosphodiesterase, and you can see the number of trials with each agent on this slide.

DR. CALIFF: Now, before we see the results, don't all of these drugs lower the wedge pressure?

CHAIRPERSON PACKER: All of these drugs lower the wedge pressure.

DR. CALIFF: Okay.

CHAIRPERSON PACKER: Actually, Rob --

DR. CALIFF: I just wanted to be clear about this.

CHAIRPERSON PACKER: If I remember correctly, almost all of these drugs increase cardiac

output and lower systemic vascular resistance as well.

DR. CALIFF: Just what you want in a short term drug.

CHAIRPERSON PACKER: Just the type of person you want to -- just the type of thing you wanted to bring home and put under your pillow, right.

Okay. These are the overall results of the 23 trials. What I've listed here are not the results of 23 trials, but in each case, in each of these seven drugs, there was one large, definitive trial.

Frequently it was the last trial performed with these drugs.

(Laughter.)

PARTICIPANT: Funny how that happens.

CHAIRPERSON PACKER: Well, you know, large, definitive trials are commonly the last trial performed with the drug. So one shouldn't reach any conclusions from that necessarily.

In any case, we have the effects in this trial on mortality in the first column, the effects on morbidity in the second column. Morbidity here is defined as hospitalizations or when that data weren't available, number of dropouts generally for worsening heart failure, and the effect on symptoms, by the way

not necessarily in this definitive trial. Sometimes there were smaller trials that were part of the package.

And you can see that the trials -- that in every single case, every single one of these seven drugs, there was a definitive trial that showed that the drug increased mortality, and in almost all of these trials, the trial was actually designed to evaluate the effects on mortality. That was the primary endpoint. The trial achieved that primary endpoint by showing an adverse effect of drug therapy on mortality, and in all of these trials there was an adverse effect on morbidity.

And despite the fact that there's a common assumption that these trials generally showed an improvement in symptoms, this was not a consistent feature of these trials. Most of these trials showed very weak or equivocal evidence for symptom relief, and in the trial which showed the most definitive evidence for symptom relief, for example, pimobendan or flosequinan, the symptom benefit was short term only and disappeared over long periods of observation.

In five of the trials the trial was stopped by the Data Safety Monitoring Board because of the adverse effect on mortality, and in three trials

an analysis specifically in Class III versus Class IV heart failure showed a worse outcome in Class IV.

I have to emphasize that most of these -- all of these trials enrolled very sick patients, patients who generally were much sicker than the patients who were enrolled in the exercise trials with these drugs. Most of these patients had Class IV heart failure, had repeated hospitalizations for heart failure.

Next.

The overall conclusion to the review. First, efficacy. Although some studies have reported a favorable effect, this favorable effect was usually not the primary endpoint of the trial and was not supported by changes in other endpoints.

More importantly, trials that reported favorable effects were almost always carried out in Class II and III patients. There has been no evidence from any of these trials of a favorable effect in trials of Class III or IV patients, and with the exception of two trials where a favorable effect was seen at two to four weeks and then disappeared. The majority of trials showed an increased risk of hospitalizations over the long term.

Next.

Conclusions about safety. All the drugs in this review, all cycle AMP dependent positive inotropic agents were associated with increased risk of death. In most cases the adverse effect was observed in the trial that was specifically designed to evaluate the effects of treatment on mortality. Concerns were large enough to lead the Data Safety Monitoring Board to stop five of the seven large scale trials and let the sponsors terminate the development of all seven drugs.

Next.

The mortality risk was not necessarily apparent early in development when there were very few events. In most cases the dose associated with increased risk was not the highest dose evaluated. In most cases it was 50 to 75 percent lower than the highest dose that was evaluated in the controlled clinical trial, and in trials that evaluated more than one dose, all the doses that were evaluated were associated with increased risk, and when the trial did report symptomatic improvement, this was seen after the dose was associated with increased risk of death.

And patients with Class IV heart failure in many of these studies appeared to be at particularly increased risk.

Next.

Let me just conclude by turning attention to specifically intermittent therapy. Everything in the previous couple of slides was on oral therapy. As far as I can tell, there are four trials of intermittent inotropic therapy that have been placebo controlled. They're listed here.

The Bental trial at the bottom is really the first author is Ellis, just for clarification.

You'll notice that all of these trials use dobutamine. None of them used any other IV drug. All the trials were small, ranging from 19 to only 60 patients, and they gave dobutamine, in general, 48 hours per week for varying lengths of therapy. Two trials evaluate patients for about six months.

Next.

Now, I've summarized here the mortality results from these four trials, and let me emphasize that the Ellis trial is not included here, one, because the report had no mortality data in it, and, second, it used the one dosing regimen which was different than the other three trials. It used 24 hour infusions every two to three weeks. The other trials used weekly infusions.

And you can see the data comes directly

from the reports. We don't know how much of this is intention to treat and how much complete follow-up there is, but you can see that in the Dies trial, seven -- these are all one-to-one randomizations -- in the Dies trail, seven deaths on placebo, 13 on dobutamine.

Let me emphasize that two of these deaths were in patients who were crossed over to dobutamine. Crossovers were allowed in this trial.

In the Erlemeier trial, one in each group, one death.

In the DICE trial, three deaths on placebo, five on dobutamine, but three patients in dobutamine were transplanted urgently.

The conservative estimate totaling only the events that you see -- this is intention to treat -- 11 deaths on placebo, 19 on dobutamine.

The alternative regimen, which is to exclude the two deaths that crossed over and to assume that the three urgent transplants would have died -- these are not necessarily valid assumptions -- nine deaths on -- nine events on placebo, 22 events on dobutamine.

This needs to be taken into consideration that the number of events for analysis here is quite

small, but the trends are not encouraging.

Next slide.

And need to be taken into consideration that if one cuts -- looks at the results of the PROMISE trial, not the overall results, but the results at 15 days, and I chose 15 days here not because it was arbitrary, but if you look at the package insert for milrinone, it specifically states that there was no adverse effect of milrinone in the PROMISE trial at 15 days, and there were 12 deaths on placebo, 16 on milrinone, and of course, as you all know, when the follow-up was continued, this drug was associated with a significant increase in mortality during long term therapy.

Questions on this part of the review?

DR. RODEN: Milton, with such small numbers, are the groups balanced at baseline?

CHAIRPERSON PACKER: The problem is that the only data we have on these trials -- interestingly enough, almost none of these trials have actually been published as full length papers. In the four trials that you've seen, three are only available as abstracts and have never been translated into full length publications.

The only trial that has been translated

into a full length publication is the Erlemeier trial. That only had 20 patients with one death in each.

DR. RODEN: And the other question is, at the risk of being obvious, what do these people die of?

CHAIRPERSON PACKER: They died. The problem with trying to classify deaths in heart failure is that all of us who have been on mortality classification committees realize how difficult the process is.

Let me say that the data from the abstracts or from the one paper never made clear what they died of. In the oral trials, attempts were made to determine sudden death versus pump failure, and in reality, depending on the study you look at, you can find an increased in sudden death, and in another trial increase in pump failure death. There's no consistent pattern.

DR. RODEN: So your thoughts of a mechanism might be that arrhythmias might be one cause and then sort of, for lack of a better term, sort of flogging a dead horse is another?

CHAIRPERSON PACKER: I think the conclusion I would feel comfortable with is that we have a lot of trouble translating a description of

what happens around the time of death to an understanding of the mechanisms of what is occurring. I think that would be the only conclusion I would feel comfortable with.

DR. DiMARCO: Milt, on those four IV trials that you talked about, were those done out-patient basis or were they in-patient? If they were in-patient, why don't we have more information about the mechanisms of death?

CHAIRPERSON PACKER: The implication from the trials is that they were all out-patients. It isn't clear in many of the cases whether the infusions were always given in a sort of supervised setting or not. I think that you can tell from the literature summaries which are included in the handout we have preciously little data as to how this was done or what was done.

DR. DiMARCO: So that, in fact, it might be possible that if we take Dan's hypothesis that arrhythmias contributed to some of the excess mortality, that if it was done in a setting where the arrythmia could be handled either with an implantable defibrillator or in a monitored setting, that we might see some symptomatic benefit and no increase in mortality.

CHAIRPERSON PACKER: Well, I think that's possible. Again, assuming --

DR. RODEN: Assuming those arrhythmias could even be handled.

DR. DiMARCO: What's that?

DR. RODEN: Not every arrythmia is handleable.

DR. DiMARCO: Okay, but assuming if you had monitoring and you, you know, stopped your infusion at some point in time if you noticed some change in pattern, you might be able to do it.

CHAIRPERSON PACKER: The impression I get, John, is that, first of all, we don't know. We just don't know. The impression I get is that there was no particular pattern of the timing of deaths to the timing of the infusions.

Now, I did not see any data that indicated, for example, that there was a -- that the difference between two treatments was entirely due to sudden death, and the sudden deaths occurred during the infusion of the drug. That kind of data is not available.

So we can't conclude one thing or another. Let me emphasize: number of events, very small; classification of deaths, very difficult; and we don't

even have full reports in almost any of these trials.

Rob.

DR. CALIFF: Just a couple of comments. One is I think it's worth emphasizing again how infrequently negative trials get published. There's one that you know of quite well that we're still waiting to see. So just a comment there.

But, I mean, it's a real -- if you think about our national system of dealing with this issue, you've got practitioners out there unaware for the most part of very important studies that should affect the way the patients are treated.

The second comment, and Chris may want to say more about this, in the database of the first study we've had a chance to look at the observational view of out-patient dobutamine. One of the puzzling findings that we had was that there was a detrimental effect of the prostacyclin analog, in general. It was very evidence in Europe, but not so evidence in the United States, and the question was whether that was because the United States was using the IV out-patient therapy better or whether there was something wrong with the placebo group in the U.S., and the big difference was a very high rate of the use of dobutamine in the placebo group.

And it turns out in the analysis that IV dobutamine is associated with a substantial increase in the risk of death and certainly no improvement in quality of life in that study with a fairly large sample size.

So it's not definitive information, but it very much supports what you've shown here.

CHAIRPERSON PACKER: Ileana.

DR. PINA: I just want to underscore in these trials that you showed here how very different the monitoring system was, if we even know, how poorly electrolytes were perhaps followed, which may be the substrate for arrhythmic deaths, if that's the mode of death, and how little firm data we really do have and perhaps need it.

CHAIRPERSON PACKER: Barry, I know you wanted to add some comments as well. So we'll ask Barry to proceed with his comments.

DR. MASSIE: Yeah. Could I have that carousel of slides? I just wanted to particularly comment on something related to mechanisms other than arrhythmias. So let me go through most of what I was going to show.

This just makes one point that Milton touched to. Can we focus that somehow? Could you

focus that? Yes.

This is the differential of mortality in the PROFILE, the flosequinan trial of Class III and IV patients, and I think you can see that it really is the Class IV patients that were at highest risk. This is mortality increase.

The same, although not quite to the same extent, was true with milrinone in PROMISE, and again, the people who are most likely to treated with IV therapy, I think, are those that are more severe.

The other point I wanted to amplify that Milton made before talking about mechanisms a little bit is the dose dependence of these. Where several doses have been looked at, either directly or indirectly, it's always been the case where the toxicity comes out at a higher dose than a lower dose.

My concern about intravenous therapy is that we don't know what dose we're giving, what's high and what's low, and in this whole different approach to therapy, we need to have some information about what the appropriate dose is.

Now, getting to -- let's skip that -- the issue of arrhythmias, the study that was most accurately looked at in terms of chronic therapy for arrhythmias was the PROMISE trial with milrinone, and

this was a study that we did looking at holter variables, which we know are not good surrogates for ultimate arrhythmic death, but in fact, nearly the entire excess mortality in the PROMISE trial was at least classified by the event committee as being sudden.

So there's no doubt that arrhythmias are important here, but even as the small intravenous experience Milton alluded to suggests, where there were three people in the dobutamine infusion who went on to urgent transplantation, that may not be the entire issue, and that's what I wanted to say just a couple of words about.

This is a trial from an abstract that hasn't been published as a paper that we did participate in, as well, and this was an interesting design where a group of people was randomized to be treated with either milrinone or digoxin over a six month period. This is oral therapy.

At the end of that six month period, there was hemodynamic measurements before, and then there were hemodynamic measurements at the end of the six month period, but these measurements were performed 48 hours after the drug was stopped.

So I think the important finding here is

that at the end of six month exposure to milrinone, there is a significant change in hemodynamics that was not seen with digoxin, at least by some parameters. The cardiac index had fallen by 12 percent from pretreatment, the stroke volume index also by 12 percent, and the pulmonary capillary wedge pressure had gone up.

The same findings were not found when digoxin was removed, and although we know the pharmacokinetics of digoxin are such that maybe there is some residual digoxin effect, this deterioration during treatment or best observed when the treatment itself is withdrawn so the deterioration of cardiac function during chronic exposure is important, and actually Milton reported this with amernone, as well, earlier.

So what could this mean? I think that this is our own data, and I apologize. It's not published, but this shows something that I think is relevant to at least intermittent intravenous infusions.

This is one hour of infusion of dobutamine at a dose of 20 microgram per kilogram in pigs, and what we're looking at is a group of controlled pigs normalized for baseline at the end of 15 minutes, at

the end of one hour of infusion, and then one hour after the infusion was stopped, and in this preparation things deteriorate over time. It's an open chest pig model, but look at what happens to the normal controls when the drug is withdrawn, and even more so when we have hypertrophied pigs, which is what we're studying.

And the other evidence which I think is interesting, again with dobutamine, looking above inside a solid calcium transients and below developed pressure in perfused rat hearts. This is baseline, but fourth returns far below baseline. Again, one hour of exposure to the drug.

Well, can we make anything -- oops. I'm trying to move forward here -- of this information? And I want to go back, I think, to this slide, and there's some interesting information that Milton provided me from his as yet unpublished profile experience, which I think is helpful and actually coincides with observationally what has been seen with some other inotropic agents.

This was a trial, as you remember, that was stopped by the Data Safety and Monitoring Committee because of increased risk of death in the treated patients, but I think wisely this group

decided to look at what happened in the 30 day period of withdrawal from therapy.

And remember the excess mortality in the Class IV patients with flosequinan was substantial, suggesting at the end of the trial that perhaps the placebo group patients left behind should have been sicker.

But during the 30 day period of withdrawal, you can see worsening heart failure. Hospitalization for worsening heart failure, ER visits for worsening heart failure, the need for ID diuretics, the need or perceived need for IV positive inotropes were all greater when flosequinan was withdrawn.

And I think that's very important because it suggests that there's something about chronic exposure that causes deterioration of underlying cardiac function, and I guess we can end by talking about what those might be.

I think there's well documented evidence that chronic exposure to catecholemines desensitizes contractile proteins. It should be a short-lived effect, not one that would explain 30 days of increasing risk when drugs are withdrawn after chronic therapy, but that could be a reason for decline in

contractility.

Energetic imbalance, or as Dan said, flogging a heart in terms of its energetic requirements. We have beta receptor down-regulation could play a role. Neurohormonal activation and its consequences could play a role, but it could be that this chronic exposure is causing accelerated cell death either by necrosis mechanisms or apoptosis mechanisms.

I don't think we understand this phenomenon, but I think it says that monitoring a patient during an infusion is not necessarily going to guarantee us that chronic exposure can be safe.

So let me stop there.

CHAIRPERSON PACKER: Questions for Barry? Udho.

DR. THADANI: Barry, a lot of the data you've shown is based on the oral long term studies in which the patient is like a dead horse analysis that I think Bob mentioned before because their hearts are sick and you can flog them long enough and perhaps there is cardiotoxicity and withdrawal because they still need the inotropic support. You withdraw it and, you know, they fall apart.

Can you apply, given that very little

database on the IV drugs we have seen, where most of the trials are not published, can one be sure that the short term is harmful?

The reason I'm asking this now, because most of the patients were on transplant lists. In order to get into priority lists, all of them are on IV inotropes. Otherwise they do not get on the transplant list.

So if you're going to tell somebody that, you know, IV inotropes are bad, you're going to have all of the transplant surgeons coming after your life because all those patients are going to be denied transplants, at least the priority list.

I'm sure in your part of the world, the same as in Oklahoma at the moment. So is there any data in those transplant patients who are on inotropes versus who are not for the same -- I'm sure there are a lot of people in big transplant centers to say that the mortalities really increase. I know that's not a perfect experiment, but there must be some data out there to show those people are just flying like flies -- dying like flies.

DR. MASSIE: Well, I think -- let me make a couple of comments, but then turn over the answer to that to the people who are better qualified than I am

to address what happens during chronic exposure while awaiting transplant.

First of all, I think that none of these data tell us that chronic inotropic exposure makes the heart worse for sure. I think they raise important questions, and I think I really second what the Committee has been saying all along, is that we need to know what happens in an objective manner, you know, following chronic exposure no matter how it's given, and whether that translates to four hours a week, four hours a month or whatever, we need to understand that before we recommend giving it in that way.

I think that the transplant group is unique, but what we do see is as long as you're receiving the agent, you seem to be better off than when you're not receiving the agent after you've been exposed chronically. So it's not a situation where it will be easy to uncover, and if these patients deteriorate during chronic exposure awaiting transplant, nobody would be surprised, and nobody would know whether or not to blame the inotropic therapy, but what we would know is that if you withdrew it, things might look very bad under those circumstances.

I don't know how you would do a controlled

study to decide comparing -- not a controlled study, but try to impute whether these people are better off than not. I guess what leads me -- let me just finish -- what it leads me to wonder about is the appropriateness of perhaps nonindicated chronic inotropic exposure just to advance somebody on the list. That really does concern me.

DR. THADANI: But there is some data that at least we know a lot of patients are waiting for transplant die, and yet in the earlier days were put on the transplant list. Patient had been on long term inotropes in the hospital, for several days dobutamine, and they have not died of arrhythmic deaths, and that's what gave a lot of physicians the confidence to start intravenous home therapy.

So I buy your point there is some suggestion. As Milton said, we don't know the mechanism of death. We are invoking arrhythmias, and yet it was not seen so much because in hospital you would have picked it up. You know, they would have had VF. You would have known the data, and that's why physicians have gone and yet left them on IV inotropes so that they still meet the list criteria.

So I think there must be some data out there. Perhaps you know, we could mandate it or

people in the centers who are doing a large number of transplants could address that.

CHAIRPERSON PACKER: Ileana.

DR. PINA: You know, we looked at this in '95. We retrospectively looked at our admissions of patients who had come in decompensated and that we had done inotropic therapy and up-titrated their drugs, et cetera, and I can tell you that our arrhythmic events -- I don't have the numbers in my head -- were very, very small.

You're dealing though with a multi-approach to the heart failure issue. I mean these patients are on ACE inhibitors. They're well medicated. If they have any evidence of arrhythmias, many of them are on amioderone because of our EP group. Some have even had defibrillators put in.

Our mortality on the waiting list with our rather aggressive approach that we're known to have at Temple is about seven percent, which is actually quite lower than the quoted 11 or 14 percent, is it not, Lynne, the waiting list mortality?

The annual waiting list mortality is about somewhere between 11 and 14 percent -- with this very aggressive approach. So I think you're right. As long as you have the patients on the drip and you

haven't stopped them, which is what this population is, there is the data.

It's retrospective. We have it in abstract form, and are preparing the manuscript.

How are you going to do a controlled study in that group of patients? I don't think you can. You may want to compare one agent versus another, and we have trials like rematch trial now that will look at VADs versus inotropic agents at home.

I don't know how you --

DR. MASSIE: I think the interesting thing scientifically to do would be to look at the hearts of people withdrawn after chronic IV inotropic versus those that are not. Unfortunately they wouldn't be comparable patients necessarily, but you may be able to figure out the mechanism of what's going on during chronic exposure at the tissue.

DR. THADANI: Well, the patients on the transplant list are Class IV failures, right? So these are the most high risk patients, and yet you're not showing a very high mortality. So I think there's something missing in the equation of intermittent, and my worry is I don't think we have any clue that we can translate what happened in the oral therapy, which is continuous throughout the 24 hours, with the

intermittent therapy. We don't have data.

I'm not saying they are not harmful or useful. I think there's no data, and I think with the transplant issue, the data should have been available. I don't know why it's not.

CHAIRPERSON PACKER: Yeah. The transplant situation is a little bit -- I think everyone realizes -- very difficult to interpret because the patients who were put on IV inotropes to get transplanted or because they need inotropes because they are in desperate need of transplant is a patient population very different than the patient population who gets a transplant without IV inotropic therapy.

Now, in the past there has generally been a distinction made between UNOS I and UNOS II, but even so there is a difference in the severity of disease in a patient who the physician says needs inotropic therapy to get a transplant. So there would be no basis of doing a comparison here because there is no adequate control group unless you're prepared to randomize.

You can't find a control group of equal severity that you can use as an adequate matched control even retrospectively. So I assure you that if you looked at the mortality in the people who got IV

inotropes or looked at the hearts of people that got IV inotropes they would be worse, but they're worse to begin with.

Lynne.

DR. STEVENSON: I'm just trying to make a couple of comments.

Clearly, as you indicate, we do have our most experience from patients who are awaiting transplant. There's nothing in that experience which would give me what we would have called this morning reassurance that that's a safe therapy.

If we look, for instance, at Les Miller's experience of 25 patients on home dobutamine while awaiting transplant, two of those patients required LVADs. Six patients died. So that's clearly not something that would necessarily give us comfort, although perhaps shouldn't give us undue alarm.

I think there are many programs who do not use frequent home inotrope infusions that have similar out-patient mortalities to what Dr. Pina describes, and although I don't want to focus on this, this is just an example of the fact that we don't know what's involved.

There have been several reports now of series of patients on chronic dobutamine in whom

eosinophilic myocarditis has been demonstrated, which seemed clearly to be associated with worsening cardiac function, but I use that only as an example of the fact that we really do not know the safety of long term dobutamine even in this population that's closely monitored.

CHAIRPERSON PACKER: Okay. I understand that there are a few clinicians that -- actually two -- that Sanofi has asked to come and speak to the issue of IV therapy long term. Can you please identify yourself and the institution?

MR. HORNE: Sure. My name is Ron Horne from the University of Iowa.

I want to participate in the discussion that we just had and raise the issue of patient selection in our critical thinking of the trials that were outlined. I think that we would all agree that there's a significant minority of patients with advanced heart failure who have clinical and hemodynamic decompensation that either persists or rapidly recurs despite maximal vasodilator, diuretic, and short term intermittent IV therapy.

It's in this patient population that there's a large anecdotal experience of intermittent IV therapy to treat that episode of decompensation.

I think that this experience outlines the short term tolerability of this approach and suggests clinical stability.

I question the application of the existing data which examined chronic inotropic use, either IV or oral, to that patient population.

CHAIRPERSON PACKER: Because of the severity of disease?

MR. HORNE: Yes, yes. I think my experience with these trials is that there's a period of stability that's often required in the baseline phase prior to entry to the trial, and so the patients who I outlined would not fit in those trials.

So I understand that there is a similar lack of or that there is a lack of data, either positive or negative, examining the use of any type of inotropic therapy in the patient population that I just outlined.

CHAIRPERSON PACKER: Just for purpose of clarification, some of the long term trials of inotropic agents, in particular PROMISE, had very little, almost none in the way of stability criteria. The patients who were enrolled, that is a study in which if I remember 55 to 60 percent of the patients were Class IV, to begin with, and that's the patient

population, by the way, that suffered the greatest increase in mortality, a 53 percent increase in risk.

MR. HORNE: I don't know -- maybe you do -- how many of those patients fit the population that I just outlined, those who have --

CHAIRPERSON PACKER: I think a substantial portion of those fit precisely the criteria that you would enroll in an intermittent -- a trial of intermittent therapy.

MR. HORNE: I would look forward to looking at those data.

CHAIRPERSON PACKER: Marv?

DR. KONSTAM: You know, your point might have validity, that is, that there might be subsets of patients to which the control data set don't well apply, but I think that that argument would carry some more weight if there were any control data to support the effectiveness of these agents in particular populations.

So since there aren't any such data, I think we're relegated to look at the pretty broad data set that does exist that clearly points to excess mortality, and as Dr. Packer points out, particularly in the patient -- in a number of cases, particularly in the patients with Class IV.

And I think that, you know -- I think the point that you're raising, that perhaps this data set doesn't apply to subsets, I don't find that useful in the absence of any data that point to the contrary.

CHAIRPERSON PACKER: Please, and please state your name and affiliation.

DR. FRIEDMAN: I'm Dr. Abe Friedman. I'm an associate clinical professor of medicine at the University of Pittsburgh. I'm a critical care cardiologist at Shadyside Hospital, where I emphasize in treating congestive heart failure.

I think it's important when we look at the data to establish facts that are honest, and I think it's very honest to say that chronic oral inotropic therapy right now is potentially -- is dangerous, and the data is very clear that you presented, but we have to be careful because some of the inotropes that you did use were not purely Beta Is and were not purely phosphodiesterase inhibitors.

Vesnarinone with its rectifying potassium current; pimobendan with its calcium sensitization. So across the board there, you can even make critical comments about some of the studies that have been mentioned, particularly looking at potassium levels, magnesium levels, and digoxin levels, and chronic

therapy may be potentially dangerous.

Now, let's talk about the other issue of interchronic, intermittent therapy, and an honest comment here would be that there are no well controlled placebo studies to support it. There are a lot of clinical -- there's a lot of clinical data, probably an additional 14 other studies that you did not mention that do support its use, but none is well controlled and placebo controlled data.

I think it's important also that when we look at these populations, what populations are we really treating? I'm predominantly at Shadyside Hospital in Pittsburgh, and you'll excuse me. I'm a practicing clinical physician. I practice every day. I teach. I publish, but I'm in the infantry in taking care of these patients.

And in my patients, I treat predominantly the Medicare population. Now, this is the population with the most episodes of heart failure and also the most recurrent episodes of heart failure, and in my population, I do not have bridges to a transplant, and my bridge is potentially to stabilization.

I'd like to make comments about Class IV if you'll permit me using clinical data, not well controlled placebo data, but you're seeing the

patients because you've already alluded to them. These are the patients that you have stabilized on maximal medical regimen, which include the usual drugs, including even beta blockers, and you may have even given a course of inotropic therapy in our ICUs or monitored settings.

Now, what do you do within approximately one week or two weeks when these patients come back into the hospital? Now, this is a burgeoning population that continues to increase, and for us to make some sort of improvement in decreasing their hospitalizations, at the present time I personally do not know of any drug on the market that is available that is any better than what we have. Certainly on the horizon I don't know of anything better, including endothelial drugs.

So we have used quite heavily intermittent inotropic therapy. Now, intermittent inotropic therapy can be potentially dangerous, and we only use it in monitored settings. That means a low level monitor, and we do not start the therapy unless potassium levels are greater than four, magnesium levels are greater than 1.6, and digoxin levels are less than 1.5.

There are the patients that we do send

home on chronic home dobutamine therapy that cannot be monitored. These patients, however, are monitored fastidiously with electrolyte control.

So in these patients right now we feel that monitor therapy -- I feel that if we're going to approve any drugs in the future that they should be stated on monitors with only fastidious control.

Now, one study that everyone talks about is Dr. Dies' study from Lilly, the dobutamine trial, which was 48 hours. Now, why did these studies pick 48 hours?

If you look at the history of IV inotropic therapy, it starts with Liang and Overith, starting at 72 hours, subsequently coming with Applefield and Dies going 48 hours, and today coming to studies of approximately 24 hours, and in the Lesfield population, six hours as out-patient, and this is the tailoring that has been done by clinicians using this trial.

I recently contacted the Lilly Education Department and was kind enough to obtain some data on the Dies trial that wasn't published. Now, in all fairness to Dr. Dies, who's an excellent investigator, this was done -- this study was started in 1984 and went through 1986.

In his population, 12 of the dobutamine patients had potassiums less than 4.0, and the range went from 3.5 to 4.7.

In addition, seven out of the ten sudden deaths occurred on dobutamine infusion.

Now, we don't have any major specific markers for sudden death in this population. We know what can increase the incidence of sudden death, but when you're using larger doses of dobutamine, and in his trial the average dose was eight micrograms per kilogram per minute, upwards of 15 micrograms per kilogram per minute, is it a surprise that we had increased incidence of sudden death in that population?

And is it a surprise that we had increased incidence in the dobutamine group that had greater than four runs of ventricular tachycardia?

So, therefore, it is imperative that monitoring electrolytes be addressed.

In addition, today not only has the time period that we're treating these patients gone into a metamorphosis. The doses have gone into metamorphosis, and I use all three drugs. I start with dobutamine first because it's the cheapest drug available that is out there, but sometimes because of

arrhythmias and tachycardia and blood pressures, you have to go on to either using milrinone or amrinone.

So based on a clinician's input, when the FDA -- when you folks are making decisions in the future, I think it's very important that we look at all of these parameters, and we do need placebo, well controlled trials in order to help us, to guide us to those of us who are in the day in and day out care of patients.

Thank you very much.

CHAIRPERSON PACKER: Can you stay by the microphone?

Ileana.

DR. PINA: I'm in the trenches, too. We have 2,400 heart failure patients in our clinic, and of everybody that comes to us probably only 20 percent of patients eventually get transplanted. So I can share your frustration at patients that come back time and time again.

As we try to look at intermittent therapy in order to start protocols and to do it in a prospective fashion, we were met not only by the trials that you're stating where the potassium was low, doses were very high, but there's no consensus as to frequency, dosing. There are no well done trials.

So I'm not saying that it can't be done or that it shouldn't be done, but we've got to collect data in a much more perhaps intelligent, prospective, and organized fashion.

And I agree with you that the number of these patients is going to continue to go up. It's not going to go away, and this is not the population that you put in a study. This is a very, very sick population.

And in spite of all our medical therapy, they still get sick. So I share your concerns, but I also feel that we need some sort of perhaps not standardization, but some sort of dose ranging, protocols of frequency of monitoring, places of monitoring, and where these types of therapies should be done, if they should be done.

DR. FRIEDMAN: I agree with you 100 percent, and that's why my first sentence included the fact that there have not been well controlled trials, and those of us who are treating patients in the trenches sort of use, if you'll permit this term, clinical dosing ranges, not hemodynamic dosing ranges.

For example, our average dose in treating dobutamine is approximately 2.5 to five micrograms per kilogram per minute. If I give that patient 20

micrograms per kilogram per minute like the pigs were given, I know I'm going to be getting into trouble. There is no doubt in my mind that that's the case.

We have done similar dosing with milrinone and similar dosing with amrinone without loading because sometimes we see that loading not only causes some hypotension, but in itself may be arrhythmogenic, and how do we know? How do we find out how patients get better?

Well, I published 13 patients that were severe resistant Class IV, and we showed -- you know, 13 patients, not a lot of patients, but we certainly showed a decrease incidence in coming back into the hospital, and these are the papers that we're seeing.

When the patients are severe Class IV and they enter the hospital and they can't go to the bathroom without getting dyspneic, and then you're able to show at least clinically that they're improving.

Now, for example, how do I make a decision about when do I start intermittent therapy? That decision is made once that patient has failed maximal medical therapy, BUNs of 60 to 80, creatinines of approximately two to three, systolic blood pressures of approximately 80 to 100, given a course of

inotropic therapy, and then they rebound.

When I first was doing it, I was very frightened because there was no data at hand. It was 72 hours, but now we let that rebound occur within approximately one to two weeks.

CHAIRPERSON PACKER: Let me ask one question which I think is on the minds of everyone on the Committee. You sound like you're convinced that in the appropriate hands, used in the appropriate manner, with the appropriate monitoring, that intermittent IV therapy is going to be safe and effective for the -- as a long term management strategy -- for selected patients with heart failure.

DR. FRIEDMAN: I think that's a fair comment, Dr. Packer.

CHAIRPERSON PACKER: Why has there been no placebo controlled trial conducted to demonstrate such an effect?

DR. FRIEDMAN: I don't think you have any well controlled placebo trials to negate such an effect.

Number two, I am not a -- I am not an academician. All right?

CHAIRPERSON PACKER: Maybe I can rephrase the question. How do you know what you know in the

absence of a control group?

DR. FRIEDMAN: I'd like to say the same thing that Dr. Stevenson said just a little bit ago. I know, and I can only base that on how I've seen my patients, how I've treated them for the last eight years, and as I also told you, that I present to you not academic value with P values and confidence intervals. I'm speaking to you only as a clinician right now.

Do I have the data at hand? I go back to my first sentence. That data is not available. We need that data.

CHAIRPERSON PACKER: In fact, the data suggests a strong possibility of harm.

DR. FRIEDMAN: I beg to differ on that issue. Intermittent inotropic therapy has not necessarily been shown to show harm. You cannot extrapolate oral inotropic data to intermittent IV inotropic data. I don't think the studies are large enough.

CHAIRPERSON PACKER: Rob?

DR. CALIFF: Well, I just want to make one comment, and then I know Lynne wants to make some comments.

It's a difficult area, and I think a lot

of us have struggled with these patients. I actually don't see many patients these days. Other people on the panel are still pretty active clinically, but I used to see a lot of them.

And I would just -- the only comment I would make about your presentation, the commitment is obviously there, but the word "clinically" to a lot of us, I think, is a very charged word because, you know, I would replace that with anecdotally.

I mean many of us are clinicians and see patients, but we've learned that we can be fooled in our commitment by observations that we make without understanding what would have happened had we not used one or another therapies in our armamentarium.

And we can go through a whole list of things in cardiology where equally committed and well meaning people have come to conclusions such as yours and turned out to be wrong. There are also examples where they've turned out to be right.

But I would just urge not to fall back on the word "clinical" because to many of us the highest form of clinical practice is controlled observation where you can draw a conclusion and then practice based on the evidence, and I think what a lot of us are desperately seeking is some sort of confirmation

in the highest form that what we hope to be correct really is, that there is this group of patients that we treat and can help.

CHAIRPERSON PACKER: Lynne.

DR. STEVENSON: I would like to commend you for your incredible dedication to this really difficult job, but in terms of what you feel to be beneficial and what has been described in uncontrolled series of other people's experience with intermittent milrinone could well be attributed to the fact that these patients are seen on a regular basis. They're coming back.

They're followed extremely closely in terms of electrolytes and everything else, and the benefit of that type of intensive management program has been well documented, and the benefits observed from that are very similar to or superior to those which have been observed with the infusions of milrinone.

So I would suggest that the program is of critical importance, but we want to make sure that we're not somehow arranging that program by using a drug which itself might be deleterious.

DR. FRIEDMAN: It is very interesting though. When you -- I'm sorry. I was going to

respond. Maybe you'd better -- may I respond to that?

CHAIRPERSON PACKER: Sure.

DR. FRIEDMAN: There is no doubt that one of the criticisms of intermittent inotropic therapy is the fact that these patients are watched and they're seen by a physician and told, "Are you taking your lasix? Are you taking your medication? Are you restricting your fluids and you're restricting the salt?"

I feel though that that data is still weak, and it's very interesting. Over the years when we have stopped the medication for one or more reasons and are still seeing the patient -- the patient doesn't want to go into the protocol or doesn't want to go into the form of therapy -- even though they're being seen and examined, they generally rebound within approximately two months, and those patients that I have described, what I call my Class IV resistant, that they don't go out more than a few weeks.

CHAIRPERSON PACKER: JoAnn?

DR. LINDENFELD: I think that we've all seen these patients. Many of them are chronic patients who are very ill, and I think what makes me feel like we need more data as everyone has discussed is now the patients are asking us when they come in,

"Do I really need this? Will this help me? Is this going to make a difference in three months or should I just not come in the hospital?"

And I don't think I can tell them that. I don't have the same confidence that you do on this long term therapy, and I think we need those answers because I think the patients themselves are asking that question.

CHAIRPERSON PACKER: I think it would be fair to just remind ourselves that about ten years ago when oral milrinone was available under an investigational program, that there were many, many clinicians who used the drug in an open label fashion in patients with heart failure, many of them very, very sick, and swore by the drug, said the drug made people feel better, kept them out of the hospital.

When they compared the events and symptoms in patients receiving oral milrinone to patients -- to the period before they received the drug, there were dramatic, dramatic clinical benefits, symptomatic benefits: reduction in hospital days with what was deemed to be a very, very acceptably low mortality rate.

When milrinone was put into a large scale trial in this patient population, the drug did not

make anyone feel better, didn't reduce hospitalizations, increased hospitalizations, and increased mortality.

And it shows how difficult this situation is and how clinical judgment in the absence of a control group can give you misleading results, and your experience with IV milrinone is very reminiscent of the experience with oral milrinone.

DR. FRIEDMAN: Dr. Packer, I'm not here to give a selling point or an advertisement for IV milrinone. I use all three inotropes, and I'm not here to say -- I mean, I wish I had more data. That's what I'm telling you, and that's what I'm here to ask that we all do, that we do develop the studies to give us that information.

But at the present time I do not have any better ways to take care of these Class IV patients.

CHAIRPERSON PACKER: But that's what they said when oral milrinone was being evaluated. They had no better way of taking care of the patients.

The reality is they did have a better way. It was called placebo.

DR. FRIEDMAN: Dr. Packer, if I give my patients placebo, they will not get better. I'm talking about now Class IV resistant patients who are

on maximal medical therapy, and in that situation placebo is not going to take care of them.

And also, I don't think you can make -- you cannot make the transition from oral, chronic inotropic therapy to intermittent inotropic therapy, whatever drug you use.

DR. CALIFF: One thing that would be useful from my perspective would be just to get your point of view on how large of a difference you think intermittent inotropic therapy -- if you took 100 patients who fit your population that you described and treated, half with placebo and half with -- or 200, half with placebo, half with inotropic therapy, what would be the magnitude of the difference in symptomatology or staying out of the hospital that you would think would occur?

DR. FRIEDMAN: You're asking me to give you my, you know, personal opinion --

DR. CALIFF: Yea.

DR. FRIEDMAN: -- that's not found on any -- so if you'll permit me to do that and you won't come back at me saying that there's no data, I'm more than happy --

(Laughter.)

DR. FRIEDMAN: -- I'm going to be more

than happy to do that, but I want to make sure that the ground rules are fair.

In that situation, if you will give me those Class IV patients who are truly Class IV, I believe in the right hands and the right monitoring if it's done correctly that we will be able to keep them out of the hospital with recurrent admissions for congestive heart failure by giving them their 24 hours of intermittent inotropic therapy monitored.

DR. CALIFF: You mean you reduce hospitalizations by 50 percent?

DR. FRIEDMAN: If not more.

DR. CALIFF: And you would have no increase in mortality?

DR. FRIEDMAN: If done correctly, that is correct.

DR. CALIFF: Okay.

CHAIRPERSON PACKER: Well, a decrease in hospitalizations by 50 percent and no increase in mortality probably in Class IV patients would probably only take a couple hundred patients followed for four to six months.

DR. CALIFF: Until they die.

CHAIRPERSON PACKER: Yeah.

DR. CALIFF: I mean Class IV patients have

a mortality --

CHAIRPERSON PACKER: Pretty doable.

DR. CALIFF: Yeah.

DR. FRIEDMAN: And I believe in this Class IV -- severe Class IV population -- I think that you would be honest in saying that if you do nothing to these patients 30 to 50 percent are going to die within a year. Is that fair?

CHAIRPERSON PACKER: Yes.

DR. FRIEDMAN: Okay, without using inotropic therapy, et cetera.

CHAIRPERSON PACKER: Okay. Why don't we continue with the discussion on question nine? The question that's posed to the Committee is the paper on -- the review on long term treatment concludes that positive inotropic agents have not been shown to be effective or safe in the treatment of chronic heart failure during long term use whether given continuously or intermittently or whether given orally or intravenously.

Instead long term treatment has been associated with a consistent increase in the risk of hospitalization or death.

Do you agree? And we should actually go through and take a vote on this.

Yes, I'm sorry. Marv?

DR. KONSTAM: Well, I just -- you might change the last sentence to include the word "continuous." You know, the previous sentence says given continuously or intermittently. Instead long term treatment has been associated with consistent increase in risk for hospitalization and death.

I mean with the exception of the Dies study, if I'm not mistaken, everything else is based on chronic persistent oral use.

CHAIRPERSON PACKER: Yeah, we have the DICE study as well, which goes in the wrong direction.

DR. KONSTAM: That's the one exception, but that's not a pretty -- that' snot --

CHAIRPERSON PACKER: DICE and Dies are two different studies.

DR. KONSTAM: Oh, is that -- oh, DICE.

CHAIRPERSON PACKER: DICE.

DR. KONSTAM: Right. Okay, but I think where the data are crystal clear to the point of making a statement like this, it's chronic continuous use, I mean.

CHAIRPERSON PACKER: I don't think that the intent of this question is to have the Committee reach any opinion on the safety of long term

intermittent therapy. I think that the two sentences here are in themselves the conclusions of the review, which is that intermittent or continuous long term has not been shown to be safe or effective.

DR. KONSTAM: That's clearly true.

CHAIRPERSON PACKER: And second, that long term treatment has been associated with increased risk of hospitalization and death,a nd I think that's true, too.

DR. THADANI: Do you want to separate that into two parts? One is oral long term versus -- you're combining the whole issue now.

CHAIRPERSON PACKER: Well --

DR. THADANI: The last question was yes, but here I think you're combining the two.

CHAIRPERSON PACKER: Maybe the concept being embodied here is that the data exists with, let's say, definitive data is with oral.

DR. THADANI: Yes.

CHAIRPERSON PACKER: Continuous.

DR. KONSTAM: Yeah. To me though --

CHAIRPERSON PACKER: Second is -- second is the data with intermittent use long term is nondefinitive, but trends in the wrong direction.

DR. KONSTAM: How many patients in the

DICE? How many deaths in the DICE study? Three to five?

CHAIRPERSON PACKER: Three in five with three transplants in the dobutamine group.

DR. KONSTAM: You know, I don't have any --

CHAIRPERSON PACKER: No, no, the numbers are small.

DR. KONSTAM: Right. I mean --

CHAIRPERSON PACKER: The question is whether you think that there is any data on -- are you reassured by the intermittent data?

DR. KONSTAM: No, it's not that, Milton. Just in the spirit of saying what we know and what we don't know --

CHAIRPERSON PACKER: Right.

DR. KONSTAM: -- I think the previous sentence is clear. There are no data supporting -- no well controlled data supporting the use in either route, and then, you know, I'm a little bit more comfortable. It sounds like we're being pretty definitive in these sentences, and I'd like to be definitive, and I think where the data are definitive is in continuous use. You know, I don't know.

CHAIRPERSON PACKER: Okay. Then with the

sense that the second sentence, long term treatment with continuous oral therapy has been associated with a consistent increase in the risk of hospitalization and death, do you agree with both of those statements?

And we should begin at one end of the room. Cindy, do you want to begin?

DR. GRINES: I agree that the chronic therapy has been associated with increased risk of hospitalization and death.

CHAIRPERSON PACKER: Okay. There's two statements. Do you agree with both? The first means that neither intermittent or continuous has been associated -- has been shown to be safe or effective.

DR. GRINES: I share some of the same concerns that there are so few patients who have been treated with intermittent IV therapy that it's hard to draw firm conclusions. I agree that there's, you know -- it doesn't look positive.

CHAIRPERSON PACKER: No, no, no. I'm sorry. The statement as it reads is "has been shown to be effective or safe." Intermittent therapy has -- I understand the data is sparse -- hasn't been shown to be effective or safe, right?

DR. GRINES: Right.

CHAIRPERSON PACKER: So I mean, I'm sorry.

You're voting yes on one or both statements or --

DR. CALIFF: Say it again. Statement one is that intermittent or continuous therapy has not been shown to be safe or effective.

CHAIRPERSON PACKER: Right.

DR. CALIFF: It also -- I mean, the implication of that statement is also that it has not been shown not to be safe or --

CHAIRPERSON PACKER: It just says "has not been shown to be effective or safe."

DR. CALIFF: Yeah.

DR. FENICHEL: Milton.

CHAIRPERSON PACKER: Yes.

DR. FENICHEL: Maybe I can help this. I think maybe it's a matter of stress. The operative word in the first sentence, I think, the intended operative word is "shown." "Positive inotropics have not been shown to be effective," dah, dah, dah.

The operative word in the second sentence is, or operative words are "has been associated with." So in the one you're making -- the first assertion is there is the absence of a demonstration, and the second is almost there has been a demonstration, but at least there has been an indication.

So that's all that's being asserted, but

that is being asserted.

CHAIRPERSON PACKER: Okay. I think that to be fair this should be a statement that says -- that implies cyclic AMP dependent agents because the questions beneath it refer to other IV drugs, one of them a positive inotropic drug which is not cyclic AMP dependent. So we need to -- the review dealt only with cyclic AMP dependent agents.

Cindy. I guess the vote is do you agree with both statements as modified.

DR. GRINES: Well, we got past the first one, right? We're on the second one now.

If you say the cyclic AMP dependent drugs, I agree that the first one -- the first one hasn't been shown to be effective or safe. The second I still have a problem with the consistent increase in the risk of hospitalization and death, and I think we should maybe separate or clarify that since we have so little --

CHAIRPERSON PACKER: Marv suggested that long term treatment with continuous oral therapy --

DR. GRINES: Okay.

CHAIRPERSON PACKER: -- has been associated with a consistent increase in the risk of hospitalization and death. Do you agree?

DR. GRINES: I agree.

CHAIRPERSON PACKER: Okay. So we have yes on both.

John.

DR. DiMARCO: I'll agree with those as modified, both of them.

CHAIRPERSON PACKER: Lem?

DR. MOYE: I'm going to abstain on this one.

CHAIRPERSON PACKER: Rob?

DR. CALIFF: I mean the way they're both stated, they're both true from the absence of data on number one and the presence of data on number two.

CHAIRPERSON PACKER: JoAnn?

DR. LINDENFELD: I agree with both.

DR. KONSTAM: Yes.

CHAIRPERSON PACKER: Udho?

DR. THADANI: Yes for both.

DR. PINA: I agree with both statements as modified.

DR. RODEN: Yes.

DR. MASSIE: Yes.

CHAIRPERSON PACKER: Okay. The next -- does this conclusion apply to dig., nitroglycerin or nitroprusside? I think we can take all three at once.

DR. THADANI: What about the intermittent I --

PARTICIPANT: You have to go back to the intermittent.

DR. THADANI: Yeah, because you excluded the intermittent from the question completely now because you went to question 1(a). One (b) you changed it to only orals. What about intermittent? Because the whole discussion was on intermittent. So we have to make a statement we don't have data or there's some wrong directions. I think we can't --

CHAIRPERSON PACKER: Well --

DR. THADANI: -- just leave it up in limbo.

CHAIRPERSON PACKER: Yeah, I agree with you. We've already said in the first half that there are no data that says that the drug given -- that these drugs given intermittently are safe or effective. We've already said yes.

DR. THADANI: Or harmful. I mean we don't have enough data to make any conclusions, right?

CHAIRPERSON PACKER: Right. Says "has not been shown to be effective or safe during long term use." That applied to continuous or intermittent oral or intravenous.

DR. THADANI: Should we make another statement the data on intermittent is totally inadequate to address the issue?

PARTICIPANT: It says that.

DR. THADANI: I realize that, but you know, you're emphasizing the oral.

CHAIRPERSON PACKER: Yeah, it says it in the first question. We're actually going to deal with that in question number ten.

DR. THADANI: Ten? Okay.

CHAIRPERSON PACKER: The question here is do these tow conclusion apply to dig., nitroglycerine, or nitroprusside, and let me for the sake of simplicity ask if anyone thinks that either of these two statements applies to any of these three drugs.

DR. KONSTAM: The first sentence applies to nitroglycerine and nitroprusside, right?

CHAIRPERSON PACKER: That's correct.

DR. KONSTAM: The second doesn't.

CHAIRPERSON PACKER: Right. So that, Marv, you would vote it does not apply to dig. The first statement applies to nitroglycerine and nitroprusside. The second statement applies to none of the three.

DR. KONSTAM: Well, you know, it might be

worthwhile saying what we're talking about here. I don't know why we're bringing in nitroglycerine and nitroprusside at this point. We've been talking about drugs that have inotropic effect. Well, we were talking about cycle AMP dependent agents, right?

What are we trying to say here? You want separate statements about nitroglycerine and nitroprusside? Why are they even in there?

DR. LIPICKY: -- on IV inotropes --

DR. KONSTAM: Right.

DR. LIPICKY: -- we'll be asking the labeling question in the next question, and these two drugs are approved. So they might have to be relabeled.

CHAIRPERSON PACKER: Yeah.

DR. LIPICKY: We just want to see if the things you've been talking about in question nine are applicable to those other guys or not. Everything that went before is okay. We just want to dissect that out. Okay?

DR. KONSTAM: Yeah. Well, then in that spirit I understand.

Something -- that first part of the statement certainly is applicable to nitroglycerine and nitroprusside in that they have not been shown to

be effective or safe in the treatment of heart failure during long term use whether given continuously or intermittently.

CHAIRPERSON PACKER: Right, and the second statement does not apply.

DR. KONSTAM: Yeah. I mean the second statement should, right -- should -- you've again stuck in the point about cyclic AMP dependent agents.

CHAIRPERSON PACKER: Right, right.

DR. KONSTAM: So it would not apply.

CHAIRPERSON PACKER: Okay. Does anyone disagree with Marv's conclusions?

(No response.)

CHAIRPERSON PACKER: Okay. Question ten, should some of the conclusions of today's discussion be retrofitted into a labeling of intravenous medications now approved for the treatment of congestive heart failure?

And let me emphasize that the agency would like us to remember that the facts are different in each case and detailed wordsmithing is not appropriate, and only the sentences that apply in each example would be included.

For example, there is a statement about Class IV, and if the data didn't indicate that, that

sentence would not be included, and so we would tailor the wording to the appropriate -- in the appropriate way based on the data available for each drug.

Given that as a qualification, the proposed labeling change is as follows: Drug X is indicated for the intravenous treatment of patients who are hospitalized with acutely decompensated heart failure. In general, Drug X should be added to treatment with other drugs for heart failure, including dig., diuretics, ACE inhibitors, and carvedilol.

And so the first paragraph is a clarification of the indication.

The second paragraph: experience with intravenous Drug X in controlled clinical trials does not extend beyond 48 hours of repeated boluses and/or continuous infusions, and where applicable, this would be included in a multi-center trial of oral Drug X. Long term use was associated with an increased risk of hospitalization and death, and where applicable patients with Class IV symptoms appeared to be at particular risk.

Similar trials of other drugs with similar mechanisms of action have given similar results. There is no evidence that long term intravenous

regimens of Drug X do not carry a similar risk.

DR. MASSIE: Milt.

CHAIRPERSON PACKER: Barry.

DR. MASSIE: Going back to question nine, what you left out is the paragraph that there's no evidence of efficacy during long term intravenous --

CHAIRPERSON PACKER: No, we included that.

DR. MASSIE: What?

CHAIRPERSON PACKER: We included that.

DR. MASSIE: It's not on the statement you just read. No, I mean carrying forth the discussion and vote of question nine, there's nothing there that says that there's also no evidence of efficacy.

CHAIRPERSON PACKER: In question nine, the first sentence says --

DR. MASSIE: No, no, no. I mean in this relabeling. What I'm saying is that there ought to be some statement like that first sentence in question nine edit.

CHAIRPERSON PACKER: This is question ten. Is it ten? I'm sorry.

DR. MASSIE: What I'm just saying is included in these paragraphs --

CHAIRPERSON PACKER: Right.

DR. MASSIE: -- should be a statement like

the first sentence of question nine, which says that there is no evidence of efficacy either. Efficacy has not been shown of that approach.

CHAIRPERSON PACKER: Okay. Barry is suggesting that the sentence "not shown to be effective or safe in the treatment of chronic heart failure during long term use when given continuously or intermittently or orally or intravenously" should be embodied somewhere in the first paragraph; is that correct?

DR. FENICHEL: Isn't, Milton, isn't that a minor corollary of the first sentence in the second paragraph here? What we say is experience with intravenous so-and-so "in controlled trials does not extend beyond 48 hours," and so on. Well, a fortiori it doesn't provide evidence of safety or efficacy or nothing. I mean there it is. What could be a stronger statement than that?

DR. LIPICKY: You could have had mortality and symptom benefits in 48 hours. So that sentence doesn't say you don't have any efficacy.

DR. FENICHEL: No, no, no. What I take Barry's suggestion to be is that the thought from question nine that certain drugs have not been shown to be effective or safe, dah, dah, dah, during long

term use should be carried over.

Well, here we say there is no information at all about long term use from controlled trials. So of course they've not been shown to be safe and effective.

DR. MASSIE: Well, I think it's better to say than infer, first of all, but second of all, there is a lot of articles about long term use, and they aren't controlled trials, but a statement that this committee does not feel that they constitute evidence of efficacy, I think, is worth adding, I guess, because, yes, you can infer that if there's nothing about 48 -- exposure more than 48 hours, anybody would obviously read that as saying there's no evidence of efficacy.

I guess I would suggest being a little more literal.

DR. THADANI: Milton, just on the first part of the question, I think carvedilol is not approved for Class IV failure. So --

CHAIRPERSON PACKER: But the only --

DR. THADANI: But I think you're talking about decompensated failure in general.

CHAIRPERSON PACKER: Carvedilol has a question mark specifically for that reason. It's only

there because it's an approved drug.

DR. THADANI: Should we just exclude it and not be there at all?

CHAIRPERSON PACKER: Don't word smith. The concept here is -- and, by the way, one can have someone who is on carvedilol and then deteriorates to Class IV.

DR. THADANI: That's a different issue.

CHAIRPERSON PACKER: Which is a different issue. The agency will -- when this was first written, the parentheses "and carvedilol" was not included. It's included only -- it was added subsequently for completeness sake. Ignore it if it-- one way or another.

DR. THADANI: The reason I even brought it up, that could be a beta blocker if the guy is a post infarct patient who is on a beta blocker. So I think we should probably not mention that because somebody might take this and start their patient on carvedilol with no data.

CHAIRPERSON PACKER: Just take it out.

DR. THADANI: So I would suggest you take it out.

CHAIRPERSON PACKER: Just take it out.

Okay. The present recommendations have

been made, and we want to hear any other recommendations, aside from taking out the parentheses at the end of the first paragraph; that Barry would like to make the first sentence of the second paragraph more explicit by saying something similar to the question nine, which is the present evidence -- I'm sorry -- that the drug has not been shown to be effective or safe in the treatment of heart failure during long term use whether given continuously or intermittently or whether given orally or intravenously.

In other words, instead of or perhaps in addition to --

DR. THADANI: Orally would be out because you're talking about intravenous treatment.

DR. LIPICKY: Well, we can handle that. We can sneak something in.

CHAIRPERSON PACKER: Okay. With the understanding that the agency will sneak something in about a lack of evidence after the first sentence of the second paragraph, any other modifications of this paragraph?

DR. DiMARCO: Why do you need the last sentence? You have two negatives in the last sentence. There's no evidence of benefit. There's no

evidence of risk. It's just sort of hammering it, you know. I mean, how many times do you want to hammer the same?

CHAIRPERSON PACKER: The reason is it's actually supposed to be a clear statement that the experience with IV therapy cannot be viewed as being reassuring. That's the only way, John, that I know of of making that statement.

DR. THADANI: But the fact you are putting a second sentence, lack of evidence, do we need that? I mean there is no data, there is no data, either efficacy or risk. So I think we could even take the last sentence out and just leave the addition after the first sentence.

CHAIRPERSON PACKER: Yeah. We are really running out of time for today's meeting. So the agency will -- has really asked us not to do too much wordsmithing on this, and they'll incorporate any ideas that we have about this, but I guess the question is where clarity is indicated, clarity will be provided.

DR. LIPICKY: Yes, and so of the question is: should we relabel things that are approved? And that's a yes or no question. This is a kind of -- this is what the labeling would kind of look like, but

until you look at each individual drug and what is known about each individual drug, you can't quite write exactly what would need to be written. Everyone would be different.

CHAIRPERSON PACKER: Please understand the concept is not to wordsmith. The intent of the question here is should the agency seek to relabel existing drugs that fall into the category that we're talking about in a manner which would be guided by, although not precisely the same as, the wording in this paragraph.

DR. LIPICKY: Right.

CHAIRPERSON PACKER: Okay. Basically a yes or no answer. Barry?

DR. MASSIE: Yes.

DR. RODIN: Yes.

DR. PINA: Yes.

DR. THADANI: Yes.

DR. KONSTAM: Yes.

DR. LINDENFELD: Yes.

DR. CALIFF: Yes, and it's a great opening to get the label changed again very quickly with a fairly small clinical trial.

DR. DiMARCO: Yes.

DR. GRINES: Yes.

CHAIRPERSON PACKER: And yes.

So, Ray, it's 11 to zero -- I'm sorry -- ten to zero, one abstention. Lem abstained, and to recommend to the agency that existing IV drugs in the cyclic AMP category be relabeled as guided by the paragraphs on question ten.

DR. LIPICKY: Do you really mean those explicit words? You don't want to have nitroprusside relabeled or --

CHAIRPERSON PACKER: I think that --

DR. LIPICKY: -- IV dig.?

CHAIRPERSON PACKER: -- since it's nearly impossible to give nitroprusside long term, I think that the only evidence that we -- I think that we have no evidence about nitroprusside, but nor do we have concerns about nitroprusside.

DR. KONSTAM: But, I mean, the answer to Ray's question, I think, would be yes. I think it's giving a practical answer which --

DR. LIPICKY: Yeah, I thought this was truth in labeling, right?

DR. KONSTAM: Yeah.

DR. LIPICKY: You just want to let people know what is known.

DR. KONSTAM: There would be no reason not

to include --

DR. THADANI: I don't think anybody uses IV nitroprusside long term because it has such a potent hemodynamic effect. You can wipe out the pressure.

DR. KONSTAM: I agree.

DR. LIPICKY: But the labeling as it's rewritten here says you don't know it works short term either. You've got to pay a little attention to the words as they're written, and you don't know that giving it short term is not going to kill.

DR. THADANI: But if you give somebody IV nitroprusside in pulmonary edema, you can improve the patient very quickly. So, again, it depends on what you're using for acute decompensation where it says acute heart failure.

DR. LIPICKY: Well, that's fine. So then am I to take it that the Committee's recommendation to relabel is only in terms of the intermittent use and is not in terms of anything else?

CHAIRPERSON PACKER: No. The --

DR. LIPICKY: Okay. Then why not?

CHAIRPERSON PACKER: The therapy -- the Committee's recommendation is it's not -- it's not specific. It could be continuous use. The operative

word here is long term.

DR. THADANI: Long term.

CHAIRPERSON PACKER: The operative word is long term, and I think that it would be true from the Committee's point of view that to the extent that the questions in ten apply to nitroprusside, and many of them would not --

DR. LIPICKY: Okay.

CHAIRPERSON PACKER: -- that the drug -- the labeling for nitroprusside could be clarified.

DR. LIPICKY: Right. Okay.

CHAIRPERSON PACKER: Would anyone disagree with that?

(No response.)

CHAIRPERSON PACKER: A lot of what's on ten doesn't apply to nitroprusside, but to the extent that it does.

DR. LIPICKY: That's fine, but I mean, I could have saved us looking into three drugs, you know, to figure out what we wanted to do with three drugs if you had said, "No, don't worry about those three," but you say look at them and figure out whether you want to do something. If it's --

CHAIRPERSON PACKER: It wouldn't be the first thing you would do.

DR. LIPICKY: Right. I understand.

CHAIRPERSON PACKER: Okay. We are adjourned until tomorrow morning.

(Whereupon, at 5:44 p.m., the hearing was adjourned.)