think it's still a valuable drug. I think the liver toxicities, indeed, are unfortunate. I'm quite concerned with the discrepancy between the two sides and the actual figures showing how much liver toxicity there is, what's actually been reported versus what might be out there in the world, but I think that it's probably not quite as much as has been said to be what's out there in the world, and I think that's something that based on liver consultants, that we may be able to markedly reduce by appropriate monitoring in the patients.

CHAIRMAN BONE: Thank you.

Dr. Seeff, please.

DR. SEEFF: Well, not being a diabetologist I can't speak to the effectiveness of the drug, but from what I've heard from everybody, it sounds like a very good drug. It's not a great drug because we wouldn't be here if it were a great drug. We are faced with a problem with this hepatotoxicity.

I think that if the final decision, which is to retain the use of the drug, I think we need to spend a little bit more time -- and this is not the place to fine tune this -- but to spend a little more time trying to find out the best way to monitor for potential hepatotoxicity.

I'm not sure. I think that the job that was done is a very good one, but I think it could be improved upon.

I also think that if I were a patient, I would like to know that a drug I'm getting could kill me. I don't see anything that's directed to the patient. Even if it's uncommon, I don't want to be given something that might kill me, rare as it may be.

So I think that we should be not only educating the patients as to what they should be doing to look for the possibility, but to give them the option of knowing that they may receive a drug, that they are being offered a drug that could potentially cause their death, and they should then be able to make a choice as to whether or not they are willing to take that.

So I think it's a combination of the patient and perhaps a little more fine tuning on trying to monitor for hepatotoxicity.

CHAIRMAN BONE: Thank you.

Dr. Lewis.

DR. LEWIS: Yeah, that was well said, and I think, you know, we're talking about lots of discrepancies in the numbers, and I guess the only thing I would add is maybe we should try to do more in

terms of improving our reporting system, the structure of it and other things so that we don't have to rely on discordant numbers sometimes.

We say a lot about the fact it's a voluntary reporting system. There are other places around the world where it's mandatory. I'm not sure that's going to work here right away, but something in between maybe, and we would have the answers perhaps to very important questions about the incidence rates of very serious reactions that occur uncommonly. We need to collect that kind of information.

But, you know, I echo the comments of Dr. Seeff as well.

CHAIRMAN BONE: Thank you.

Dr. Illingworth.

DR. ILLINGWORTH: Yes. I would echo those comments also.

I think the drug does add to the therapeutic options of a patient with Type 2 diabetes, and we've seen data that clearly shows the drug does add to improved glycemic control when used in combination.

I think the informed patient is their own best advocate, and therefore, I would strongly endorse the previous comments that the more informed

the patient is about the potential side effects, the more informed they are about what symptoms are linked to hepatotoxicity, nausea, anything like that, and even give them potential flow sheets that can put down their blood values so that if they change doctors or they move, they've got baseline values with them; I think education regarding hepatotoxicity.

And then the other thing is education regarding potential drug-drug interaction. If somebody started on drug that we would know is metabolized by the cytochrome 3A4 system, have the patient made aware of that so they may go back to more frequent monitoring if they've been on the drug for a year.

CHAIRMAN BONE: Thank you.

Dr. Hammes.

MR. HAMMES: I'm going to put on my hat as a consumer's representative here. Basically my opinion is life is fatal. We're all going to die. People have different perceptions of risk. The best we can do is give them our best opinion of what risks are.

Some people will take the opinion that quality of life is everybody and other patients won't want to take the risk. So I second what was just said

about educating the patient. I think that's foremost in this.

I think the low levels of monitoring that we saw are an indictment of our medical system certainly, but I think they also reflect the lack of compliance on the part of the patient, and educating the patient will go a long way toward taking care of that end of the problem.

Along with educating the patient, clearly we need to do a better job with educating the physicians, and what I didn't hear much of today was educating pharmacists. They're seeing the patients more than the physicians, and a great deal of this education needs to go to them so that they can screen for some of these things in the pharmacy when prescriptions are being refilled.

So I think education needs to be a big component of this.

I think monitoring is something we need to do. There needs to be strong follow-up on this whole thing to narrow down these risk and benefit analyses. I think you have to look at risk in this regard as kind of a death incremental risk because clearly we saw that the risk of death from diabetes is very significant, and a small decrement in that death rate

will offset a rather large risk from hepatotoxicity.

But we need to quantitate those risks and continue looking at that very closely. Along those lines then, I think I feel quite strongly that monotherapy probably isn't what this drug ought to be used for. It's been clearly shown to me that it has a strong value in the patients for other therapies that failed. I don't know if this risk is worth it for a first line treatment.

CHAIRMAN BONE: Thank you.

Dr. Genuth.

DR. GENUTH: You have to excuse me. I had to check out.

I believe that everything we've heard that I know previously persuades me that troglitazone is effective enough therapy for Type 2 diabetes to accept some risk in its use if it's used wisely. I'm not persuaded that despite the new mechanism of action, which is certainly very provocative, that troglitazone produces better clinical results in the long term than any other single drug currently that we know about.

Obviously we need more data for long-term efficacy. So I'm a little bit divided mind about monotherapy.

There was a lot of emphasis comparing the

risks of liver injury and death with troglitazone, which I believe are real, to lactic acidosis risks with metformin. I didn't hear anybody comment on what I think is a very important difference between the two. Most of the cases of lactic acidosis due to metformin are probably preventable. They've occurred under circumstances that we know increases the risk.

And I think education can hopefully get that risk down to near zero, but I don't believe we can completely prevent liver toxicity from troglitazone because of the unpredictable nature of it, no clues who's going to get it, and I think logistically there's no monitoring scheme that can be dictated from above that will be carried out perfectly enough to prevent liver deaths either.

So with some reluctance I think we have to accept if we move forward with this drug; we have to accept the fact that some of us are going to write prescriptions for patients, and in a rare circumstance that's going to lead to the death or hepatic transplant of the patient.

That doesn't thrill me, but I think physicians, as has already been said, have that responsibility to make judgments and help the patient make proper decisions with good education.

So I'm all for continuing use of the drug as adjunctive to anything else in combination therapy, and I think that for monotherapy, the suggestions that the sponsor has already made about changing the labeling so as to define clearly how it should be used, for what length of time, and I would somehow try to add some definition of adequate response in terms of hemoglobin A1c or like glucose.

CHAIRMAN BONE: Thank you very much.

Dr. Braunstein.

DR. BRAUNSTEIN: Well, I, too, agree that this drug is efficacious, and this group of drugs is an important addition to the available treatments for diabetes. Obviously the liver toxicity is the major concern.

I do hope that with increased liver function testing, as suggested by our hepatologist consultants, that the risk or the requirement for transplant will be decreased. I hope that Dr. Graham's model is wrong. I don't think we have the data to really say that his model is right or wrong or the company's predictions that at the end of the year most of the risk is gone.

So I think we're just going to have to see with the collection of data over time, and I would use

whatever means the FDA has available to require that collection of data by the company.

My final thought is I know that there are a number of other drugs in the pipeline in the same group, in the same class, and I'm hopeful that one or more of those will prove not to be hepatotoxic, and then we'll let the marketplace tell us which is the best drug.

CHAIRMAN BONE: Thank you, Dr. Braunstein.

I find this weighing of risk and benefit in this situation troubling. We have impressive evidence for the efficacy of this drug, and it's clear that the reduction in indices of blood sugar control, that would be hemoglobin A1c, for example, are of a magnitude which based on all the other drugs that have been evaluated should be expected to produce very substantial reductions in morbidity and eventually mortality.

So we would expect that the use of this medication in patients whose diabetes couldn't be controlled without it should produce a very substantial incremental benefit. I think the evidence that it is superior for initial therapy is somewhat less impressive.

I think that the biggest problem for us is

trying to get our hands on this risk assessment, and what I think we've heard here is proof that it's very difficult to do that. The hard number that we have is the number of cases that the agency and the company have of patients who have ever died or required liver transplant, where it seems clear that the drug was at least likely, if not certain, to be the causae of the liver failure.

Everything after that is a problem. We have a little bit of a problem deciding what the denominator is, and we have a much greater problem if we decide how to adjust that denominator for all the factors that Dr. Graham expounded on so eloquently.

The risk estimate of something like one to two per 1,000 is a very high risk estimate for a fatal complication. It's on the order of surgery or general anesthesia. It's not -- most major operations carry a considerably higher mortality rate because there's also risk over and above what's associated with the anesthesia that has something to do with why people are being operated on in the first place, but it's in that range.

But there's a wide estimate or there's a wide confidence limit around that if we look at the extrapolations, for example, from the clinical trials

where the risk could be seven times as high or one-thirtieth.

And as was pointed out by the sponsor, this range is so wide that it actually incorporates the sponsor's estimate of the risk as well, making no adjustment at all for under reporting.

So this 200-fold span between the low and high end of that risk estimate makes it very difficult to get our hands on this risk, and I think this has troubled everyone.

The argument about the rate of under reporting has a certain circularity to it. What we don't have is a very hard population based comparison between reporting rates and actual occurrence rates. We don't have that absolutely solid, sorted out. It would be very helpful here if we had that.

We have information that gives us hints about this, but it isn't as solid as we would like. So this is really a matter of drawing inferences and trying to decide whether we really think the risk is that high or do we think it's somewhere near the middle of the range of estimates or even as low as the reported rate.

And I think these are the kinds of considerations that I'll be certainly taking into

account as I consider my vote and additional comments.

Is there any burning point that has to be made by the agency or the sponsor or the member of the Committee before we proceed to take the vote?

(No response.)

CHAIRMAN BONE: All right. Then let's go ahead with the vote.

DR. ILLINGWORTH: I'd just like to point out one thing with regard to monotherapy.

CHAIRMAN BONE: Only if it's a point of fact, please. Is it?

DR. ILLINGWORTH: It is a point of fact.

CHAIRMAN BONE: All right.

DR. ILLINGWORTH: And that is, of course, monotherapy needs to be kept in mind, is limited after two months to patients that do benefit.

CHAIRMAN BONE: Thank you.

DR. ILLINGWORTH: And that substantially changes then the risk-benefit ratio.

CHAIRMAN BONE: Point taken. Thank you very much.

All right. Anything further? Everybody's said their piece? Good. We're going to vote now.

Not everyone who is sitting at the table is a voting member of the Committee. So I will ask

the voting members of the Committee to vote, and we'll just, I think, start around the table from the right this time, starting with Dr. Illingworth.

And Question 1 has three parts, and then the editorializing or commenting has either already been done or mostly go into the answers to Questions 2 and 3.

So, Dr. Illingworth, Question 1.

DR. ILLINGWORTH: Question 1, based on the information with the current label indications, warnings and precautions, do the benefits outweigh the risks for (a) concomitant use with insulin? Yes.

Concomitant use with sulfonylurea? Yes.

Monotherapy? No.

CHAIRMAN BONE: Thank you.

Dr. Hammes.

MR. HAMMES: I would vote the same, yes, yes, no.

CHAIRMAN BONE: Thank you.

Dr. Genuth?

DR. GENUTH: Yeah, I think the benefits outweigh the risks for combining troglitazone with insulin, with sulfonylurea, with metformin, with a combination of metformin and sulfonylurea, and I think if the labeling is changed somewhat in the manner

suggested by the sponsor, for monotherapy.

CHAIRMAN BONE: Would that mean -- is that a no for this question for monotherapy?

DR. GENUTH: No. It's a yes with a --

CHAIRMAN BONE: Okay. It's based on the current labeling.

DR. GENUTH: -- contingency. No. Then it's a no based on the current labeling.

CHAIRMAN BONE: All right. Thank you.

Dr. Braunstein has left his votes, and we'll read those after everyone else has voted, and I will vote last.

Dr. Molitch.

DR. MOLITCH: I agree with Dr. Genuth, I guess. Yes and no with current labeling for monotherapy, but yes, if it gets modified as indicated.

CHAIRMAN BONE: Thank you.

Dr. New is in the same situation as Dr. Braunstein.

Dr. Kreisberg?

DR. BILSTAD: Henry, can I ask a question here? There's been a couple of statements about based on currently labeling. Do people really know what the current label says?

CHAIRMAN BONE: Well, it's been distributed.

DR. BILSTAD: Okay. Everybody is aware that it is already in there that it be discontinued after -- the way it's worded, let me read it.

CHAIRMAN BONE: I really think everybody has probably -- is there anyone here who's voting on this who hasn't read the labeling?

(No response.)

CHAIRMAN BONE: Okay. I think everybody has read it.

DR. BILSTAD: Okay.

CHAIRMAN BONE: Okay, Jim. Thanks.

Dr. Kreisberg has also voted in writing.

Dr. Cara.

DR. CARA: Yes, yes, no.

CHAIRMAN BONE: Good.

DR. COLLEY: Yes, yes, no.

CHAIRMAN BONE: This would be -- that was Dr. Cara, Dr. Colley.

We have a written vote from Dr. Marcus, and there'll be a vote from Dr. Hirsch.

DR. HIRSCH: Yes. I wish it had said -- it doesn't obviously -- but I wish it had said concomitant use when these other drugs are not giving

optimum effects.

So in that respect, I would say yes, yes, and definitely no.

CHAIRMAN BONE: Thank you.

Can we have the votes from those who had to vote in writing, please, from Kathleen Reedy?

MS. REEDY: Dr. Marcus: yes, yes, no.

Dr. Kreisberg: no, yes, yes.

Dr. New: yes, yes, and yes.

Dr. Braunstein: yes, yes, and a gentle yes.

(Laughter.)

DR. HIRSCH: Are you sure that Dr. Kreisberg one was right? No, yes, yes?

MS. REEDY: Yes.

CHAIRMAN BONE: All right, and my votes would be yes, yes, and no, I think, at the present time.

Question No. 2: if the answer to the first question was yes, can the current labeling be enhanced to further improve the risk-benefit relationship, and if yes, how?

I would ask you to -- we'll go around, and we'll ask you to address the items on which you voted yes, and then we'll come back and have people comment

on the items on which they voted no.

So Dr. Illingworth.

DR. ILLINGWORTH: I think the labeling, as I read it, I think is fairly comprehensive. I would just emphasize, as I emphasized earlier on, give the patient information as well so the patients are aware about what they need to do for monitoring. So I think that's my major focus in terms of improving the labeling and make sure patients are aware what are the symptoms of liver toxicity.

CHAIRMAN BONE: Thank you, Dr. Illingworth.

Dr. Hammes, comments on items on which you may have voted yes.

MR. HAMMES: The first two I voted yes. I would like to second that. I'd like to see a patient package insert type of thing developed explaining the risks, benefits, side effects for the patient's use, along with more extensive education of all the health care fields.

CHAIRMAN BONE: Dr. Genuth.

DR. GENUTH: Just the same as my colleagues.

CHAIRMAN BONE: Thank you.

Dr. Molitch.

DR. MOLITCH: I agree with the patient insert. I think that based on the information that we heard today that perhaps monthly monitoring perhaps ought to be extended out for a year and every two months for the next three times, say, for six months, and then quarterly thereafter since we are concerned about the duration of potential toxicity of this.

CHAIRMAN BONE: Okay.

DR. MOLITCH: So I'd like to see that monitoring extended.

CHAIRMAN BONE: Dr. Cara.

DR. CARA: Yes, I think current labeling can be enhanced, and what I would suggest is that there be very strong statements made that this treatment should not be considered for other conditions other than diabetes. I think that's very important until we have data regarding its efficacy and things like polycystic ovary syndrome and its potential side effects.

We need to be very, very cautious about this drug being used for other conditions.

I would also add that the medication should be only considered with failure of the primary, i.e., insulin or sulfonylurea or metformin, therapy alone.

The other thing that I would add is the need for continued monitoring. I don't think a patient insert is enough. I think there ought to be greater efforts at patient education and perhaps even a central registry where patients can be informed as additional information comes out so that they can take the appropriate steps to protect themselves.

I'm concerned about the delay between the findings and the information getting back to patients.

CHAIRMAN BONE: Thank you.

Dr. Colley.

DR. COLLEY: I would echo those comments that for insulin and sulfonylureas it should be restricted to patients who have failed to achieve their goal on maximal doses of the sulfonylurea.

And if I could just ask Dr. Bilstad to just explain briefly the Subpart H that you alluded to in your slide.

DR. BILSTAD: It would be a situation where the drug would be -- through a special distribution scheme, would not be distributed to patients unless they had actual evidence of having gotten the laboratory test.

DR. COLLEY: I would encourage that to be considered until we have more data on what the actual

risk is. It appears that the rate of adherence to the recommended laboratory monitoring is pretty abysmal, and that just encouraging that to be done is clearly not enough through the efforts made so far.

And as Dr. Cara said up front, patients should be informed of the risks. A patient insert I don't think is enough. They need to know this before starting the drug. They need to know what to expect in terms of symptoms that may arise. They need to know that they should be monitored, what the expectations are in terms of monitoring so that they know that they need to go to the lab, they need to have this done, and they need to hear back from their providers about it.

CHAIRMAN BONE: Dr. Hirsch.

DR. HIRSCH: I guess I would be much stronger in the labeling. I would like to see it stating that X deaths, whatever it is that we decided, or roughly X deaths have been reported and are believed to be attributable to this drug, reported during the year 1998, and the rough range that is covered by this is currently unknown. It may be equivalent or more than this in the future, and there may be a cumulative effect. It simply is not known, and for these reasons this is not to be used ever as

a first line drug in the treatment of diabetes until more information is available. It is only to be used after other drug failures occur, and then as an adjunct to those other drugs.

And when it is used, although not proven, it is currently prudent to obtain frequent sampling of blood for liver enzymes since this may assist in not having so many deaths or may be a helpful evaluation.

I would feel that that's extremely important to put all of those pieces of information into the labeling, which are not there now.

CHAIRMAN BONE: Thank you.

For myself, I would comment. I'm in agreement with several of the other comments, what is really a change in the indication.

I said that I found the balancing of risk and benefit here rather troubling because of the great difficulties we have in making those estimates with any confidence or precision in the precision. So I think that with the currently labeled indications, that's a much more difficult balance to draw than it would be if the indication were changed along the lines suggested, which would be that this drug is essentially to be used in patients which have failed to achieve adequate control on primary therapy, and

it's an adjunctive treatment, with the same kind of qualifications that others have mentioned.

And I think that's not just a passing comment. That's a specific recommendation about the indication, and I think that's a central point, I think, here. It goes beyond warnings and precautions, which of course I agree with the other comments on.

DR. HIRSCH: Could I just make one last comment exactly on -- we've had some difficulty -- I had -- today in following some of the data because sometimes we sort of think of the comparison as many of the anecdotes that came out as though this is the drug and we're comparing this versus no treatment. What we really should be comparing this against is optimal treatment with other drugs and looking for the additional incremental advantage of having this drug when those others fail.

CHAIRMAN BONE: Well, some of the clinical trials were designed in that way, as you know.

Yes, Dr. Fleischer.

DR. FLEISCHER: I'm not a voting member of the panel. I just am obviously concerned, as everyone here is, about the drug, but I would also just caution that you may, as someone who takes care of patients with diabetes, you make the restrictions on this drug

so onerous that for medical legal reasons no physician would dare give it to a patient. You might as well just ban it.

I mean, in other words, I think it should be properly done, but the language should not be so, you know, overly restrictive. That's all.

CHAIRMAN BONE: All right. So you would -- okay.

DR. FLEISCHER: And I think some of the concern really is going to be resolved with data hopefully.

CHAIRMAN BONE: Thank you.

All right. Then the next question is for those questions that were answered no, could modification of the current labeling result in the favorable risk-benefit relationship, and if yes, how or what other steps should be taken?

Again, we'll start with Dr. Illingworth. This would be -- I think you voted no on --

DR. ILLINGWORTH: On monotherapy.

CHAIRMAN BONE: -- on monotherapy, yeah.

DR. ILLINGWORTH: Well, I think we just need more data on what are the factors that are causing the liver toxicity. Are there some predisposing factors, drug interactions, genetic

variance in the cytochrome system? Are there other factors that can identify a patient who shouldn't be on this drug?

I think until we know that, if a person can be controlled on another medication, a sulfonylurea, metformin with a better safety record or less risk of hepatic toxicity, then that should be the recommendations.

CHAIRMAN BONE: Dr. Hammes.

MR. HAMMES: On the monotherapy, given our lack of precision on our risk estimates, I see no place for this as a first line treatment. If we get enough data to narrow these risk estimates down so at we can put a good handle on it, you know, that could certainly be reevaluated, but right now I don't think so.

CHAIRMAN BONE: Dr. Genuth?

DR. GENUTH: Well, like everybody else I find this very difficult to come to a precise and satisfactory conclusion. What I guess I would like to see is that in an ideal world other drugs with possibly better safety records be tried first, and if they don't work, the Rezulin given, but that's a Catch-22 because most of the studies have already shown that if a patient doesn't respond to one oral

drug, he's not likely to another oral drug.

So you would almost then be forced into the position of saying that Rezulin could only be used in combination therapy, and I'm not ready to abandon monotherapy, but I think it can be made safer with the restrictions that I mentioned before.

CHAIRMAN BONE: Right. Thank you.

Let's see. Next is Dr. Molitch. Did you vote no on anything?

DR. MOLITCH: I think I may have voted no incorrectly. If Dr. Bilstad is correct, then I didn't fully understand the restriction. In fact, I would vote yes based on what actually the labeling is.

CHAIRMAN BONE: I'm sorry. Clarify the point you're making here.

DR. MOLITCH: I think I'm voting yes, and I have no noes.

CHAIRMAN BONE: And the distinction you're drawing is?

DR. MOLITCH: For monotherapy that, in fact, there's this two-month window to document efficacy.

CHAIRMAN BONE: I see. All right.

Dr. Cara.

DR. CARA: No. No, there's nothing that

I would recommend to really make this a single use drug.

CHAIRMAN BONE: Thank you.

Dr. Colley.

DR. COLLEY: Nothing at this time until more data's available.

CHAIRMAN BONE: Dr. Hirsch.

DR. HIRSCH: No, and I have no verbal pyrotechnics to change it. So no.

CHAIRMAN BONE: The only thing that I could imagine that would change that would be something where you could actually predict who the sensitive people were or protect patients in some way here.

The fourth question is, and this, it seems like to me is a short answer rather than a yes or no question, is: does the Committee have any comments about the use of troglitazone in combination with a sulfonylurea and metformin together?

And we'll just go around the table, and short comments. We're not being asked to have an up or down vote on this.

Dr. Hirsch.

DR. HIRSCH: As before, us only when these are not doing the job adequately.

CHAIRMAN BONE: Thank you.

Dr. Colley.

DR. COLLEY: I would agree with Dr. Hirsch.

CHAIRMAN BONE: Dr. Cara.

DR. CARA: Agreed.

CHAIRMAN BONE: Dr. Molitch or Dr. Genuth. Well, no comment. Dr. Hammes or Dr. Illingworth?

MR. HAMMES: Yeah, I think there's real good data on using that as a combination again in the people that have failed the sulfonylurea/metformin therapy.

CHAIRMAN BONE: Thank you.

And Dr. Illingworth.

DR. GENUTH: I'd just like to add that's what I did say before.

CHAIRMAN BONE: Yes.

DR. GENUTH: That I would approve its use in combination.

CHAIRMAN BONE: I remember, yeah.

DR. ILLINGWORTH: I'd just endorse combination therapy in patients who are inadequately controlled on other drugs. The drug has a synergistic mechanism of action with other drugs used to treat diabetes. Use it synergistically with other

medications.

CHAIRMAN BONE: All right. The fifth question is what, if any, additional information is needed -- people may have suggestions -- to further evaluation the risks and benefits of troglitazone. Does the Committee have any recommendations for obtaining additional information about the hepatic effects of troglitazone?

So just sort of a two-part question, one more general about risks and benefits and one very specific about the hepatic effects.

We'll just start with Dr. Illingworth, I guess.

DR. ILLINGWORTH: For the first part of the question, additional information needed to further evaluate the risks and benefits of troglitazone, I think obviously anybody with any preexistent liver disease should be -- is contraindicated.

I think more information about potential drug-drug interactions will be helpful. Which drugs? Drugs for hypertension, lipid lowering drugs, particularly ones that are metabolized by the C3A4 system. Perhaps that may be a potential avenue for further exploration.

And the second portion of the question, I

would encourage the sponsors to look into more causation risk factors, genetic variance in the C3A4 system, differences in drug metabolism that may be predictive of risk.

I'd also explore further drug-drug interactions.

CHAIRMAN BONE: Thank you.

Dr. Hammes.

MR. HAMMES: I think perhaps an appear from the FDA and the company through professional associations to encourage pharmacists/physicians to report this would be helpful. I don't think requiring much more, and clearly we need to collect the data, you know, and we need just more longevity in the data.

CHAIRMAN BONE: Dr. Genuth.

DR. GENUTH: I have nothing to say about the liver. However, I would encourage the sponsors and other scientists to try and develop a clinically applicable way of determining which patients have the sort of insulin resistance that is most likely to respond to this drug or this class of drugs.

I think that's really the most logical way to approach the problem we have. We would reduce the risk if we narrowed the population to those most likely to benefit.

CHAIRMAN BONE: Thank you.

Dr. Hirsch, how about that?

DR. HIRSCH: In answer to the question, I think we're just sorely in need of new information. I've almost never had a meeting here in which there's something that had so -- that so confounded me, and this is not because of any malice of anyone, but I just think the information base is very inadequate to help us make the best conclusions about this, and therefore, I urge everybody involved to aid that, and I think it's true in both areas.

I think we need more information about the risk. That is, we need basic information on the mode of action of troglitazone on liver cells or whatever, any kind of basic thing.

But also we very much need information on whether the current surrogate endpoints that we're using like hemoglobin A1c and glucose are really as meaningful here as they are with other anti-diabetic agents. Very difficult to accumulate, but clearly if you're to do risk-benefit, this is what you have to have, and we don't have it.

CHAIRMAN BONE: Fair enough. Thank you.

Dr. Colley.

DR. COLLEY: I don't have anything to add.

CHAIRMAN BONE: Okay. Dr. Molitch.

DR. MOLITCH: I was encouraged by the liver function tests being a good indicator of patients going on to develop liver failure, but I'm still concerned about the fast risers, and I was intrigued by Dr. Marcus' idea of measuring ALT levels on a weekly basis using a filter paper method or capillary tube method.

I perhaps would urge the sponsor in one of their cohort studies to perhaps actually do that in a portion of patients to see if we could try to pick this up at an early point in time and see if it, in fact, is of benefit in identifying those patients at risk.

CHAIRMAN BONE: Thank you.

I think that the most crucial thing I can think of is to try to get hard population based data, and also to really look hard at this question of what happens with exposure past the first several months.

I think the models we've had, you know, are sharply disparate on these points, and having real information from large managed care organizations, perhaps Saskatchewan and some of the other systems where we can look at this, is crucial.

And I think the weighing or weighting that

everyone here on the Committee has done would be influenced heavily if we saw that kind of information either confirming or modifying any of the estimates that we've heard. I think that's the kind of thing that we really need very, very badly.

I'm going to ask the nonvoting members who are here if they have any additional comments before I summarize.

Dr. Seeff?

DR. SEEFF: I agree with you. This is an opportunity to learn more about this. We have to gather more facts about the frequency of hepatotoxicity. As I say earlier, as I mentioned earlier, I think that there will be an opportunity to look perhaps at a subgroup very carefully.

This, after all, is a drug that we do know causes hepatotoxicity, not at a high, tremendously high frequency, but enough that this would be a wonderful opportunity to look into this and try to learn more about this in terms of monitoring.

Excuse me. I've got laryngitis.

CHAIRMAN BONE: Right. Thank you.

Dr. Lewis, please.

DR. LEWIS: I agree. We need to learn now to monitor better, and this is one way to try and do

that.

I would just add that, I mean, there are confounders to monitoring: alcoholics who have elevated enzymes, patients with underlying liver disease. There's very little information, however, that patients with underlying liver disease are more at risk for an idiosyncratic reaction than people without that, but obviously it confounds the issue. There are certain drugs you don't want to give in patients who are alcoholic, and whatnot.

Well, we can use this as an opportunity to try and learn how better to monitor, whether it's more frequently or however.

CHAIRMAN BONE: Thank you.

Let's see. Ms. Killion, please.

MS. KILLION: I'm very encouraged by the emphasis on patient education because I think that's really the key to managing this disease from any aspect, and the idea of working in concert with your doctor with full information I think is really the only approach that a patient can take.

CHAIRMAN BONE: Thank you, and Dr. Fleischer.

DR. FLEISCHER: Well, I certainly hope that both the incidence and hopefully the way of

preventing the adverse effects of this drug can be clarified because this drug and I'm sure others in its class are truly very effective.

CHAIRMAN BONE: Thank you.

I will just try to summarize here just before we adjourn, and it's going to be challenging to summarize this meeting of the Endocrine and Metabolic Drugs Advisory Committee.

Basically we've been trying to weigh the risk and benefits of using troglitazone in diabetic patients under various circumstances, as outlined in Question 1. There is enormous concern about the evidence of hepatic toxicity.

There is no dispute about whether lightning has struck, as Dr. Graham has said. I think the members of the Committee have in many cases expressed concern about how well we can estimate the likely frequency of these lightning strikes, however, and this is weighed against the expected benefits of therapy based on the assumption that the long-term benefits with endpoints will be similar to the improvements that have been experienced by patients achieving improved glycemic control with other drugs, also the sparing of insulin effect.

And after a spirited and thorough

discussion, I think that the majority of the Committee -- and I don't have the counts here, do we? -- has voted 11 to one that the -- felt that with the current indications, warnings and precautions the benefits of troglitazone do outweigh the risk for concomitant use with insulin, and 12 to zero with sulfonylurea, but the Committee did not feel that the risks outweighed the benefits for monotherapy at this point, with the vote being four in favor and eight against.

Many of the Committee members have made suggestions about how the risk-benefit ratio could be enhanced further by changing in the labeling and prescribing practices and monitoring as they have outlined.

The majority of members of the Committee felt that their comments about combination therapy as in Question 1 would generally apply in Question 4, although this was not voted upon.

And the Committee very strongly indicated a need for additional epidemiologic and mechanistic information in order to better quantify the risk and better understand the mechanism of toxicity.

I want to thank the members of the Committee. I want to thank the presenters from Parke-Davis. I want to thank the agency. I want to

particularly thank Ms. Reedy and the group that manages the advisors and consultants process, and I want to thank the audience.

This session is closed.

(Whereupon, at 5:22 p.m., the Advisory Committee meeting was concluded.)

C E R T I F I C A T E

This is to certify that the foregoing transcript in the matter of: MEETING NO. 72

Before: ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE

Date: MARCH 26, 1999

Place: BETHESDA, MARYLAND

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

Irene Gray