something like that. I don't agree with that calculation. There was one case, as we discussed yesterday, where there was an elevation in a patient taking Avandia. This was the patient that subsequently was found to have serology for hepatitis A.

Whether it was due to hepatitis A or due to Avandia, there's no way of knowing. But what we do know for sure is that the elevation was very brief. In fact, it had already normalized before it was even realized that it was elevated. And so this case did not go on to jaundice. So, that calculation is wrong.

In my reading of 8,000 cases, there really is not a single case that, in my judgment, would have gone on to any evidence of liver failure related to these drugs. Now, 8,000 cases is not a million. I recognize that. But it still is, in my judgment -- and I've reviewed all of these cases in great detail -- I cannot find a single case that I think would have gone on to liver failure.

There is a difference between the USA and Japan. And this may be accounted for, to some extent, by the duration. But I think it's more than that. And this is not the right forum to discuss this. But we've seen this elsewhere in different trials and with different compounds. It would be interesting to speculate, but I think this is a real difference. I think that, for

whatever reason, patients in Japan are more sensitive to abnormalities in ALT elevation when they're given drugs.

The point here is that even breaking it does this way is really consistent. And both the pioglitazone versus placebo, you get the same data.

Then, finally, I just want to again reemphasize -- and I think we could put down pioglitazone and rosiglitazone down here -- all of which I think is very consistent, in saying that in a trial of roughly 6 months, roughly .5 percent patients will have an ALT elevation of greater than 3 times normal. And I think the difficulty we have to wrestle with is how to distinguish the potential rare case -- and I think it still is a potential for a long-term question of hepatotoxicity -- and I think that still needs to be discussed -- but how to distinguish those cases from the background elevation is what I think the problem is that we really need to address.

Thank you.

DR. BONE: Thank you very much, Dr. Misbin.

Are there questions from the committee?

Let me just ask about that one point about the calculation about liver failure. Maybe I can just see if I understood that comment by the sponsor in a slightly different way, and see if we can clarify that.

My understanding was that the sponsor was

applying really a rather speculative extrapolation, but one that's been employed in the past, whereas they calculated that if 1 out of about 10,000 patients treated with rosiglitazone or pioglitazone in clinical trials had an enzyme elevation of tenfold or so, they would expect 1 out of 100,000 to have jaundice and 1 out of a million to die. But they weren't, I don't think, saying that either of those events had actually occurred. This had to do with a kind of prediction. Is that correct?

DR. FRESTON: That's correct.

DR. BONE: And then, I take it that that's clear now.

DR. MISBIN: Just so that it's clear, I do not see a difference here between Avandia and Actos. And that has to be clear. Okay.

DR. BONE: Thank you. I wanted to make sure everybody had that point absolutely clear.

All right. I think Dr. Molitch was first to indicate that he had a question.

DR. MOLITCH: Just one question for Dr. Steigerwalt. You said that -- I can't remember what species it was -- that they noted extramedullary hematopoiesis. And I would think that that would actually be associated with true anemia rather than just a hemodilution effect. Can you comment more on that?

DR. STEIGERWALT: Again, this was sometimes sporadically seen. I recall mostly seeing this in the rats, as a species. And, again, it was generally at high doses. I think this might progress -- and I think it was also seen with rosiglitazone -- that at high doses, this might progress into some direct effects on the hematopoietic system. But, in general, around the doses for the humans, this appears to be a plasma volume expansion reaction.

DR. MOLITCH: So, you're really not concerned about this in humans?

DR. STEIGERWALT: No. I think it's related to the plasma volume expansion. And also, the issue of the necrosis and that sort of thing, these are very high doses, so it's not as relative to what's happening at the lower doses.

DR. BONE: Dr. Misbin, did the sponsor submit a red cell volume study, or similar study, to address this in humans?

DR. MISBIN: I don't believe so, no.

DR. BONE: The representative of the company is shaking her head no.

DR. SCHNEIDER: No, we did not supply a red cell mass study.

And I just wanted to add one point of

clarification about the difference in the calculation. For the upper limit of normal for the liver function parameters, ALT specifically, depending on the age and the sex of the patient, the upper limit would change. One upper limit would be 34 and then another, based on gender and age, would be all the way up to 43. For that particular patient, it fell right into the cusp between the two. So, if you used the one that was for that person's gender and sex, it fell into 8 times. But if you used the standard that Dr. Misbin applied for all the studies, because that's the way it's being done consistently, that's why there's a difference.

DR. BONE: Thank you.

Dr. Genuth.

DR. GENUTH: I'm glad that subject came up. I'd like to get one fact clear. How many standard deviations above the mean for ALT is 3 times the upper limit of normal?

DR. MISBIN: I think you'd have to ask the liver people. I can't answer that.

DR. GENUTH: I'd be glad to ask a liver person.

DR. BONE: Well, actually, it probably has to do with how the reference range is calculated. Is it 2 standard deviations, 2 and a half, or 3 for the reference laboratory that you used? I'll ask the sponsor. Because

that would give -- then, if it's 3 times or whatever --

DR. GENUTH: I just want to get an order of magnitude, a sense of that.

DR. BONE: Different reference laboratories will calculate their reference range differently, according to number of standard deviations.

DR. GENUTH: But yesterday we were told by one expert 2 standard deviations above the mean.

DR. HENRY: I'm Dr. Henry, from Covance Central Laboratories.

When we do our clinical trials reference range, this was a non-parametric analysis of clinical trials patients who were not on drug and who did not have any disease that was related to whatever analyte that we were looking at. This was done by Dr. Lee Thompson and Dr. Crevaling when Cycor, which was our former name, was started. So, what they did was to rank all of the 1,000 patients for this particular analyte. And then they took .5 percent off of each end. And that's our reference range.

DR. BONE: So, this would be a 99 percent confidence limit. Is that the answer?

DR. HENRY: Yes, 99.5, right.

DR. BONE: Okay.

DR. GENUTH: That's your reference range?

DR. HENRY: Yes.

DR. GENUTH: Okay. Now, how does 3 times the upper limit of normal compare to that in standard deviations? That is what I'm trying to find out.

DR. HENRY: I don't know. It's not the way we look at it.

DR. MISBIN: Let me just explain why this is likely to cause some confusion. The reason for doing all of this is when the post-marketing cases for troglitazone began to surface, many of the times -- it's very difficult to get information from post-marketing cases -- and sometimes, after many telephone calls, we would get a piece of paper, saying the patient had a value of 1,000. Now, what does one do with that number?

It was clear at the beginning that some consistent way of dealing with numbers like that had to be derived. And so what we did in classifying the cases was that if report came to us expressed as a multiple of the normal limits, we would accept that, whatever that is. But if a number came to us of 1,000, we would assume 34 was the correct number, and just make that calculation. And that seemed like the best way, most consistent way, of doing it.

Now, for reviewing of these NDA's, to eliminate any possibility of being criticized, of using a different standard from the way I treated the post-marketing data, I

decided to apply that value of 34 to all of the cases, recognizing that that, if anything, would overestimate the signal rather than underestimate it. And that's the genesis of all of this discussion.

DR. BONE: Perhaps Dr. Critchlow would comment on what the implication would be of a 99 percent confidence limit for a reference range, and then 3 times the upper limit.

DR. CRITCHLOW: Well, 99 percent, that would be 2 and a half standard deviations, so 3 times normal would be at least 7, 8, 10, depending on what the actual values are. But it's clearly several -- as I say, 7 to 10 -- standard deviations above normal.

DR. BONE: Does that answer your question, Dr. Genuth?

DR. GENUTH: Yes. Maybe it sounds mysterious, but what I'm really trying to get at was Dr. Misbin calculated a background rate in placebo- and other drug-treated patients of something like 0.6 percent from all the clinical trials. And I was trying to get some sense of how much that is above what would be expected in the distribution of normal subjects. And the only way to do that is to compare that, your 3 times upper limit, with the standard deviation.

DR. MISBIN: The other problem, I think, is you

have to worry about repeated measurements. These were in trials, so they had many measurements. Ordinarily, you don't do many measurements. So, it's not an easy question to answer. One could express the data in many ways.

DR. GENUTH: In a qualitative sense, is it right to believe that this background rate, rough though it might be, that you calculated is well above what would be expected from the normal distribution of a healthy population, as we think of health?

DR. MISBIN: All right, I can't answer that. That data is not available to me. That I would have to refer to the liver people. All I can tell you is that in all of the phase 3 trials -- and I think there are now five or six of them that I've listed -- the result is all pretty much the same.

DR. GENUTH: I'm sort of trying to guess, following Dr. Zimmerman's rule, how many of them are going to wind up jaundiced some day and die from it.

DR. MISBIN: It's only 3 times, I know, and his rule is 10 times.

DR. GENUTH: Maybe one of them has hepatitis C and will go on to develop something. But these patients were all parts of trials, and if something happened to them, we would have known about it -- at least if it would have occurred within 2 weeks of coming off of the drug.

And, by and large, the drug was continued, and this was not even considered to be a major event.

So, I did not mean to imply -- and I would like comments from the liver experts -- that any of these patients are going to go on to develop liver failure.

DR. BONE: I think, if I understood correctly, the Zimmerman rule was intended to apply to acute drug toxicity rather than to diabetic steatohepatitis; is that correct?

DR. FRESTON: That's correct, Mr. Chairman, and a very important point to make. However, it turns out that your calculation about the incidence of liver failure resulting in death or transplantation would come out to be about 1 in a million. As Dr. Graham told us last month, it's a similar frequency as being struck by lightning. It's 1 in a million.

And I'm pleased to have the opportunity to clarify that question about that one case of hepatotoxicity that occurred in the patient treated with Avandia. We, too, concluded that there was no way to know if that was due to the hepatitis virus or due to Avandia. We wanted, in our analysis, to stack the deck against the two new glitazones. And therefore we assumed, for purposes of projecting, that that was a real case of hepatotoxicity. And that's how we ended up with the 1 in a million.

DR. MISBIN: And the fact that the values normalized, though, within a few weeks, that particular patient is not going to go on to develop liver failure.

DR. FRESTON: Yes, we don't believe that. We were just trying to stack the deck.

DR. BONE: Okay. I think we've covered that point.

DR. GENUTH: I would just note that I can't resist, since the analogy of being struck by lightning was used last month and again today, of it being 1 in a million, and going through the deaths in clinical trials, one of the patients died being struck by lightning.

DR. BONE: Is that right?

(Laughter.)

DR. BONE: Okay. Well, maybe we can leave that out of the package insert.

(Laughter.)

DR. GENUTH: You don't have to put that in the package insert.

DR. BONE: I don't know.

Are there other questions from members of the committee concerning the presentations by the FDA presenters? Anything further?

(No response.)

DR. BONE: Fine. Well, then, I think what we

can do is have what I understand to be a relatively small number of open public hearing presentations, and then take a short recess before the discussion.

Are any of the people who registered to present, or indicated a plan to present at the open public hearing, present?

We have one presenter. And this, I believe, is Margaret Himelfarb, from Baltimore. Please state any affiliations you have, financial interests, or potential or possible conflicts of interest.

MS. HIMELFARB: Good morning. Thank you for allowing me to speak to you today. My name is Margaret Himelfarb, and I am a member of the International Board of the Juvenile Diabetes Foundation. I serve on the JDF Lay Research Review Committee, as well as its Research Advisory Board. I have no financial interest in the product under consideration today, and I appear at my own expense.

I am here not as a spokesperson for the Juvenile Diabetes Foundation or to endorse this specific product. Rather, I speak from the perspective of an informed health care advocate and the parent of a child with type 1 diabetes, a 22-year-old son, who has had diabetes for 18 years.

My comments this morning are borne of concern for the well-being of the 16 million Americans, 150 million

worldwide, who, like my son Michael, wage a daily battle to beat the odds against this killer disease. Diabetes, as you may know, is one of the most common and deadly diseases known to man. It affects 1 in 17 people in the United States, and frequently leads to serious complications that can destroy virtually every organ system of the body -- causing blindness, kidney failure, heart disease, nerve damage, and amputation.

In fact, every single day, 500 Americans die from diabetes and its complications -- mortality equivalent to the daily crash of a jumbo jet full of passengers.

The diabetes complications and controlled trial proved that maintaining optimal blood glucose control can reduce the likelihood of diabetic complication by as much as 76 percent. However, many individuals with diabetes are unable to achieve normal glycemia with existing treatments. More effective medications are desperately needed.

Rezulin, the first of a new class of type 2 drugs that enhance insulin sensitivity at the receptor level, was greeted with high expectations. In its first 2 years on the market, it has become one of the most widely prescribed type 2 agents, helping 750,000 Americans gain control over their diabetes. No drug is 100 percent safe. But unfortunately, Rezulin, we soon learned, can have an unpredictable, sudden and sometimes lethal side effect --

acute liver failure.

The risk factors of Rezulin-associated liver failure are unknown, and few, if any, warning signs exist. Despite the FDA recommendation that Rezulin users test their liver enzymes monthly, two deaths have occurred so quickly after testing that the fatalities were virtually unpreventable.

Furthermore, one study suggests that less than half the doctors who prescribe this medication regularly test for liver toxicity. So great is the concern that the FDA recently convened a rare special hearing to reevaluate this drug, and further restrictions were recommended.

So, on a case-by-case basis, how does one weigh the risk of complications from poorly controlled diabetes against the odds of potentially undetectable drug-induced liver toxicity? Several physicians with whom I have spoken, who are aware of the facts, are conflicted and apprehensive. Yet, lacking viable alternatives, many practitioners continue to prescribe this powerful drug for their type 2 patients.

Type 2 diabetes and insulin resistance are now appearing with increasing frequency in children, whose diabetes, on average, is even more challenging to control than that of adults for a variety of reasons. In fact, at a diabetes workshop last week, I was told by a researcher

that, in California, with its large Hispanic population, the average age of the individual with type 2 diabetes is 21 years old. In such early onset cases, complications manifest sooner and with more devastating consequences. The threat to our youth, coupled with the fact that diabetes is becoming a worldwide epidemic, makes the need for a safe, effective type 2 treatment all the more imperative.

Actos and Avandia allegedly belong to the same class of drugs as Rezulin, and also operate at the receptor level to increase insulin sensitivity. If this panel's careful review determines that either or both of these drugs are safe as well as efficacious, I urge you to recommend approval as expeditiously as possible.

Thank you.

DR. BONE: Thank you very much.

I have 10:57. We will resume at 11:10.

(Recess.)

DR. BONE: We're going to resume the meeting now, and the people who aren't here will just not hear the next part of the meeting, I think. Will everyone please immediately take your seats. Thank you.

The meeting is now back in session. We're going to have discussion by the committee on the information we've heard earlier and other topics that

members of the committee may wish to discuss. I'm sure there will be opportunities, if additional points of clarification are necessary, for the committee members to ask specific questions of the agency or the sponsor.

We're going to be leading up to the questions, and so we'll try and keep those questions in mind as we discuss. The questions are in the short-answer essay format rather than votes. The committee will not be voting on anything today.

For anyone who doesn't have a copy of the questions, the first question is: What comments do you have from the safety standpoint about the effects of pioglitazone on the liver, lipids, hemoglobin, heart? And I'm sure members of the committee may wish to add additional comments. If they do, we will.

And do we have any recommendations for the labeling relating to safety, other than for possible effects on the liver? This would be specifically regarding pioglitazone. Then we will have an opportunity to revisit the two class labeling questions which were discussed yesterday, about labeling regarding hepatic effects. So, that's just to give an idea of what we'll expect to accomplish in the next hour or two.

I guess I would just like to have the members of the committee open their discussion, comments, reactions

to anything that they've heard this morning. Would anyone care to initiate this discussion?

(No response.)

DR. BONE: Since there don't seem to be an immediate plethora of questions and comments, maybe I'll ask a question here that relates to some comments of the sponsor. Is it the sense of the committee that, for purposes of our discussion at the present time, from the standpoint of liver safety, rosiglitazone and pioglitazone appear to be roughly similar, so that they could be discussed together rather than making any distinction between them at this point?

Can anyone comment on that?

Dr. Molitch.

DR. MOLITCH: Certainly the data seem to suggest that. Yes.

DR. BONE: Several committee members are nodding. Does anyone take a different view?

DR. ILLINGWORTH: No, I agree. And notably, they're both metabolized by different enzymes in the liver than troglitazone is.

DR. BONE: Thank you, Dr. Illingworth.

Do other members of the committee wish to make a comment?

DR. HIRSCH: I agree.

DR. BONE: Dr. Hirsch has indicated agreement. Others are nodding. So it seems that, at least for the moment, we kind of regard those two as being not distinguishable. Let's put it that way. And that may help us with some of our later discussions.

I think Dr. Molitch had a comment or a question.

DR. MOLITCH: I had some questions before for the sponsor -- I don't know whether they've had time to address them -- about the specific high-risk subgroups that may have had predispositions to some of the complications that we may have seen with the drug, such as edema formation in those individuals who had edema at entry into the study; changes in LDL cholesterol in those who had elevated LDL cholesterol at entry into the study -- I think this would be of interest -- patients who had diastolic hypertension at entry into the study. Was there any aggravation of that in any patients?

DR. BONE: Is the sponsor going to be able to help us with some information on those questions?

VOICE: That's the two questions you asked earlier?

DR. ILLINGWORTH: Yes.

VOICE: No.

DR. BONE: You're not going to be able to.

Okay. I think they had some concern about the ability to get a reliable answer within the time space that we have here.

Dr. Genuth.

DR. GENUTH: If I had known you wanted a plethora of questions, I would have worked harder during the break.

(Laughter.)

DR. BONE: I know you worked very hard, Dr. Genuth.

DR. GENUTH: You should have given us that direction.

I wanted to get back to the problems of monitoring. I would sort of like to ask all the assembled wisdom, is there some better monitoring scheme or a quick way to distinguish false positives from true positives? Again, referring to Dr. Misbin's background estimates of 0.6 percent, and it's been pointed out, you would have to identify a lot of false positives to pick up one true positive.

So, I guess I'd like to ask the hepatic people, is there something we could build in that would quickly and reasonably assure us that a positive test was a false positive from the background? For example, if you had a value greater than 3 times the upper limit of normal, but

say less than 10 times the upper limit of normal, if you repeated the test in some standard period of time -- 1 week, 2 weeks; I don't know the right number -- but if you repeated the test and it was back down to normal, as occurred in these trials, would that provide any significant reassurance that you could continue the patient on that drug for the benefit it obviously does provide?

DR. FRESTON: Yes, indeed, it would provide reassurance. The down side is that that now imposes a second round of follow-up testing on all those patients who didn't need it in the first place. And we don't have an alternative test for being more specific with respect to what caused those ALT rises.

DR. GENUTH: Well, I wouldn't agree that we didn't need it in the first place. And it would impose that on 0.6 percent of the people, not all the people.

DR. FRESTON: Yes. It certainly is reassuring, if one continues the drug and the ALT comes back to normal, that the cause wasn't the drug.

DR. GENUTH: Well, how would you feel about it if the drug were stopped as soon as the physician knew the first test was positive, and 1 week or 2 weeks later it was down to normal, would you conclude it was caused by the drug?

DR. FRESTON: No.

DR. GENUTH: Or would you conclude that it was a random event and the drug could be started again?

DR. FRESTON: Well, the data that have been presented indicate that it's just as likely that the value is going to come down with discontinuation of the drug as continuing the drug. So, it's like flipping a coin with respect to what you'll learn from it.

However, if the second part of the question is then to restart the drug, then that constitutes a re-challenge. And that provides a lot of information. It also provides ethical dilemmas.

DR. BONE: Dr. Illingworth.

DR. ILLINGWORTH: A question going back to drug metabolism. Pioglitazone is metabolized by the cytochrome 2C8 and 3A4 systems. Have you done any studies to assess whether or not drugs that we know are metabolized by a cytochrome P3A4 system, like erythromycin or giving patients grapefruit juice, which makes the intestinal drug metabolism, do you get a rise in pioglitazone levels if you give a drug or a compound that's known to affect metabolism by this enzyme system?

The reason for the question is because of drug interactions with drugs are known to go through this pathway.

DR. CHARNEY: We have done a series of drug

interaction studies that were not included in the presentation, clinical studies. And they included glipizide, which I believe is metabolized by the same enzymes, warfarin, metformin, and digoxin. And none of these studies showed any interactions between, or any effects of pioglitazone, on the other drugs. And there was also an in vitro study in which there were 10 of the isozymes that were tested, and pioglitazone did not inhibit any of those.

And even though, for simplicity, on the preclinical slide, it was said that those two isoforms were involved in the metabolism, there are really three or four others that are minor contributors to the metabolism. So there isn't any one single predominant isoform involved in the metabolism. This is our data.

DR. ILLINGWORTH: But you haven't specifically addressed does giving a drug chronically, that's known to be metabolized by the C3A4 system, raise the blood levels of pioglitazone?

DR. CHARNEY: That would imply chronic administration of both drugs and --

DR. ILLINGWORTH: As in a patient who's taking a lot of grapefruit juice.

DR. CHARNEY: No, that was not done specifically.

DR. BONE: Maybe I could ask the FDA people what their assessment is of the currently available information on pioglitazone with respect to drug interaction studies in general, from the standpoint of the adequacy of the information in comparison with what we usually have at this stage and the quality of the information, and what level of comfort would they see in that?

DR. MISBIN: With respect to comparison to other products at this stage in development, I think we have certainly as much information as in general. Whether that is adequate information is a different question, which I will not answer.

(Laughter.)

DR. BONE: Yes, I think we'd always like to know a little more about drug interactions. But is it about on a par with our usual level of information?

DR. MISBIN: If anything, more. They did several formal studies. Those drugs have been mentioned. So I think, if one has to put it on the scale, I think we know more about the interactions with pioglitazone than we do with many other compounds.

DR. BONE: And nothing of concern so far?

DR. MISBIN: I wouldn't go that far. As I said, the review is not completed, and I'm not ready to

comment on that specifically.

DR. BONE: All right. I didn't want to go beyond today's information.

Yes, sir.

DR. WEI: Well, in terms of drug interaction with pioglitazone --

DR. BONE: Who is speaking?

DR. WEI: Jim Wei from FDA, pharmacokinetics.

DR. BONE: Thank you.

DR. WEI: I'm a reviewer in the human PK section.

In terms of drug interaction, the drug pioglitazone involved, two P450 isoforms. One is 2C8, one is 3A4. P3A4 is a dominant drug metabolism enzyme involved with more than 65 common drugs. However, in the company's submission, they only picked the five commonly, potentially co-administered drugs for the drug interaction study, not specifically designed for targeting like yesterday for compounds.

I would like to include like erythromycin, because drug interaction depends on the dose that is used. Erythromycin is a very commonly prescribed antibiotic, and also the dose is significantly large. Generally it is about 2 grams a day. We see many cases in which we do not see significant drug interactions among the other three or

four compounds. However, we do see a significant plasma level increase when erythromycin is co-administered.

So, I would like to see or suggest the company do specific drugs interaction study, targeted to a very specific substrate, like erythromycin and also grapefruit juice drug interactions.

DR. BONE: Thank you.

Does that respond to your question, Dr. Illingworth?

DR. ILLINGWORTH: Yes.

DR. BONE: Other discussion, comments or questions from members of the committee?

Dr. Genuth.

DR. GENUTH: Another question occurs to me. We haven't touched on this yet at all, to the best of my recollection. If we monitored all drugs in this class and a patient taking one of the drugs had a positive test, do the hepatic experts think that that should foreclose that patient receiving any drug in this class? Is my question clear?

DR. KAPLOWITZ: Yes. It's actually an important question. The evidence that exists would suggest that the hepatotoxicity of troglitazone is an idiosyncratic reaction, it's not a hypersensitivity reaction, meaning not an immunological-mediated reaction. So, on the grounds of

cross-reactive immunologically, there would be no reason to be concerned.

On the other hand, if you're proposing that there could be a potential for class hepatotoxicity on the basis of the mechanism of action of the drug, for which the evidence today would not be strongly supportive of that, then I think you would have to argue not to use the drug. So, my view would be, for the moment, the prudent thing to do would be not to use the drug in an individual who had hepatotoxicity from any drug in the class, particularly if you're going to go ahead and monitor. It would just seem the prudent thing, and it would be a rare occurrence.

DR. BONE: Well, I don't know if it would be completely rare. There is a certain incidence of elevation of liver enzymes with troglitazone. And it's not inconceivable that patients who had been taken off troglitazone because of enzyme elevation might be considered for other therapies. So, I think it's a practical question that Dr. Genuth is asking.

DR. KAPLOWITZ: Yes, I take the point. And it's an impossible question to answer. The prudent thing, I suppose, would be not to use it. If one were going to use it, one would have to be exceedingly careful and closely monitor such circumstances to see if there was any evidence of cross-reactivity.

DR. MISBIN: Could that be done as a phase 4 study? Would that be a feasible study?

DR. KAPLOWITZ: Yes, I think it would be a good study.

DR. MISBIN: That would potentially answer some very important questions.

DR. BONE: Dr. Levitsky.

DR. LEVITSKY: I guess in the last comment, I'm detecting a logic which I'm not able to follow. The previous hepatology speaker suggested that there was no hepatotoxicity demonstrated from these drugs because it was not a class phenomenon, but was rather related to that side chain, which was different and was metabolized differently. If that is so, then why would it be suggested that the prudent thing is not to give one of these drugs? And why is there no suggestion for screening? I'm missing something I think. Although I understand the emotional content of the statement about prudent behavior.

DR. KAPLOWITZ: Yes. You know, you're right. And I'm hedging a bit on this issue. Because we have no information on cross-reactivity, it is my opinion that the drugs that were presented today and yesterday have a very low hepatotoxic potential, and one that was so low that we couldn't see it within the framework of the clinical studies.

What I don't know is what the mechanism of action of troglitazone-induced liver disease is. I can't be 100 percent sure that it's not a hypersensitivity reaction, although the circumstantial evidence suggests that it's not. Therefore, the prudent thing, in my opinion, would be if you had an individual who had been withdrawn, where troglitazone had been withdrawn for potential adverse liver event, that it would be wise, until we have more information, to watch that individual a little bit more carefully. It would be a wonderful phase 4 study, because it would give us that very information, as to whether there is a cross-reactivity.

So, normally I would say that the incidence of liver adverse events are very low with pioglitazone, and therefore it was our opinion that surveillance would be not likely to identify very many patients above the placebo background.

On the other hand, if one is dealing with a selected group of individuals who have had an adverse event from one of these drugs, it would be good information to obtain what the cross-over possibilities of adverse events are. We have no data on that. And it would give us considerable insight.

DR. FRESTON: Again, yesterday, you heard the comment about I respectfully disagree. In this case, I

don't respectfully disagree, I respectfully agree, but would like to add an additional facet.

I mentioned earlier that this is no longer a scientific question, it's an emotional question. Hence, the comment "prudent." We don't pretend that we know everything about these drugs. They're young in their development and certainly young in their clinical usage. The available evidence we have suggests that this is a idiosyncratic, unpredictable reaction. And those, historically, do not cross-react within a class.

But the way to identify additional information on this whole issue, including the new one that Dr. Kaplowitz just introduced, and that is that maybe when we know more about the Rezulin reaction, there is an immunologic basis for it. We don't know that yet, but maybe there would be. The way to find out is to deliberately test these patients with another drug in the class in a controlled trial, where you can gather important information to answer the question once and for all.

DR. BONE: Other comments from the committee concerning this?

It would be interesting to see the consent form for that trial.

(Laughter.)

MS. KILLION: Yes, I sort of have a comment

directed along that vein. I think that it's an emotional issue for patients -- for everyone, perhaps, but especially for patients -- because simply we don't know why we have this. It is idiosyncratic. We don't understand the mechanism that causes this acute liver failure. And so the patient is at risk, does not have information readily available to assess the risk, and then has to proceed sort of on a gut level or in consultation with a doctor. To arrive at some kind of comfort level, when you don't have information, is something that's very difficult.

And once you've dodged the bullet once, I think you have an extremely heightened response to exposing yourself to something, even if you can be -- I don't want to say convinced -- but if it can be argued that your risk is lower -- you know, once burned, twice shy. So I think that would be a very difficult study to conduct. And I'd like to see what the response among the patients is.

DR. GENUTH: Can I comment on that?

DR. BONE: Dr. Genuth.

DR. GENUTH: You have to remember that the patient may have individually benefitted from taking the first drug, and that's a factor in the equation we haven't talked about much. If the patient has in fact had a big drop in their hemoglobin A1C, a symptomatic improvement, particularly if that hadn't occurred with other therapies

of their type 2 diabetes, then they would in fact have a personal incentive to use another drug in that class if it was possible that it could be used more safely. And the odds of a bad outcome would be exceedingly low, given the great degree of attention and monitoring, I presume, the protocol would require.

So, I don't think it's an entirely irrational idea to study it, if you studied those patients only who felt they had a lot of benefit.

MS. KILLION: Well, I didn't mean to imply that it was irrational. I think it's something that has to be done if you want to progress in this arena. But it's going to be something that is a challenge. It's going to be a real challenge.

DR. GENUTH: I think "irrational" was the wrong word. "Emotionally unattractive" probably would have been more accurate.

(Laughter.)

DR. BONE: All right. Thank you.

Dr. Molitch. And just before Dr. Molitch asks his question, it just occurred to me, the sponsor was not able to answer the question in the time allotted that Dr. Molitch had asked earlier, but do you have numbers or could you look and see if we have figures, on worsening of edema? If you just have an AE list for worsening of edema,

that should be listed as a separate topic in your adverse experiences, and that would probably be fairly responsive to his question, if not perfectly so.

Dr. Molitch.

DR. MOLITCH: I would just like to come back to this particular issue. I think it's worth discussing here more, because if we're going to be recommending future studies for this, I think this would be one that would be very well worthwhile. And I think that I have become gradually convinced over the last 2 days that maybe this is not a class effect overall.

And realizing that with troglitazone we were having a 1 to 2 percent risk of ALT abnormality, but even with that group, it's actually a very small fraction of that group goes on to liver failure. So that you could almost justify a re-challenge with troglitazone in a very carefully controlled study, but I'm not sure anybody here would truly advocate that. But I think it probably would be a very well worthwhile study to use these other drugs where, in fact, the null hypothesis is that it would not cause a rise in transaminases with the use of the other alternative drug in the class.

DR. BONE: I didn't mean by my remark to imply that that wasn't an excellent idea and something we ought to do. It's just that it's going to be something where

issues of the patient understanding the potential risk and being able to fit these individual participants in the trial will require particular attention, I think, in the total context.

Dr. Hammes.

DR. HAMMES: Remembering back to our troglitazone meeting -- and we haven't really had this come forward in the last 2 days too often -- was this phenomenon of the rapid risers, where even with the troglitazone people, if you had been monitoring more frequently, we wouldn't have picked up a couple of the deaths. And I think that puts this whole monitoring in a little different perspective.

On the other hand, it keeps ringing in my hears what Dr. Seeff said yesterday, that even these people with 2 and 3 times the upper limit of normal, they have a disease process going on that needs to be diagnosed. Now, today, we have a lot more data that suggests that in this population they can take these drugs and take them safely, and they may go on to improve, and that we have this baseline rate in diabetics of something like .6 percent that might have these elevated enzymes.

What this whole thing suggests to me is that it seems rather economically foolish to be testing the 99.4 percent of the people that do not have those elevated

enzymes. On the other hand, it suggests that perhaps a baseline before we start is certainly prudent and perhaps an annual or something reasonable would be prudent. And if we have an elevated ALT, these people need to be followed, they need to be diagnosed and find out why, but not necessarily withdrawn from the drug. Maybe there is some other level -- 10 times or whatever it is; I don't know -- where we need to withdraw the drug and re-challenge or something like that.

But I guess I'm kind of changing my opinion. As Dr. Molitch said, this probably isn't a class thing, and I don't think it's probably economically justified to be testing everybody.

DR. BONE: Dr. Hirsch.

DR. HIRSCH: I feel very differently about it, and I don't think it's an emotional or an irrational feeling. But let me tell you why I feel differently, and that is this is a totally new class of drugs. Now, I agree with you, we don't know whether the troglitazone thing and other hepatotoxicities represents a class effect that can spill over to the other drugs or not. Nor do we even know whether monitoring, if assiduously done, is all that terribly useful, since people may begin with a high level and just proceed to hepatotoxicity no matter what you've done -- even stopping the drug. That's not crystal clear

to me.

But, nevertheless, I favor the monitoring until we can learn more about this new class of drugs. I just don't think it's asking that much. These drugs do other funny things that we don't understand now. They do some things to the arterial or capillary bed or whatever. It isn't clear to me why the body doesn't respond adaptively and make a little more of the plasma protein when there's dilution. It certainly does it with all kinds of pheresis experiments. It's not clear to me why red cell mass is conserved but dilutes out in this way without an appropriate kicking in of reticulocytosis, et cetera.

So, we are dealing with a totally unknown thing in terms of the novelty of this class. There is a lot of information that's already available, but I think it's very prudent and good for sort of learning about this to follow these patients exceedingly carefully. And on the liver end, I think monitoring is the thing to do. And on the other end, I think a lot of phase 4 studies or other interests in defining this. We don't even know whether they get fat or not because the appropriate compositional studies have not been done, even though one would predict that might happen.

So, I favor being very careful about this at the present time. I think it will be good for us to learn

more about these drugs before we wash our hands and say, they're safe, go ahead and do whatever you want.

DR. BONE: Dr. Critchlow?

DR. CRITCHLOW: I would have to agree that some type of monitoring should be done, at least as Dr. Hirsch says, until more information is available. I find it hard to accept the notion that if you say monitoring is not warranted in any aspect, that you are saying that detection of elevated enzymes is not worthwhile, that you wouldn't want to know or that you don't need to know that a patient has either transient, or not, elevation in enzymes.

What's unclear is the frequency with which monitoring should be done, because if the development of acute toxicity is such that monitoring at -- I don't know even know what the interval would be -- is not going to pick it up, then clearly you're looking at those transient or chronically, or mildly, elevated enzymes or going after that. Then the question is, well, what do you do about it when you find it?

DR. BONE: Thank you, Dr. Critchlow.

Dr. Genuth?

DR. GENUTH: Yes, I'd like to support both of my colleagues in still advocating monitoring by some scheme, even though I think it's kind of, whatever schedule is used, it's applying one random process to another random

process, and hoping that, once in a while, you'll get a coincidence that will save a patient from a catastrophe.

The other argument that occurs to me. I think we've all agreed that these are effective drugs in treating type 2 diabetes, and I would hate to lose this class of drugs. If we did no monitoring, and it just turns out there is some class effect and we have another sort of wholesale post-marketing incidence of bad events, we might lose then this whole class of drugs.

And one reason that I don't want to lose it is the first drug in the series has now been reported to reduce the intimal/medial thickness of the carotid arteries. This is a study reported, I think, in 1998, in the Journal of Clinical Endocrinology and Metabolism.

And although I'm not as conversant with it, I think there's some in vitro data, too, that troglitazone may have some effects, independent of or in addition to, lowering glucose levels. It may be something to do with decreasing insulin resistance, but it may have some additional effect that would be beneficial for cardiovascular complications.

And conceivably, the other two drugs in this class have the same effect. Nobody has reported on it today. Maybe nobody has looked for it yet. But I daresay they're in the process of looking, because it's a very

intriguing observation if it's true.

So, I don't want to risk, frankly, having something bad happen with the next drug in this class that's approved, and then have a reaction that says these are terrible drugs, they kill people, make them very sick, and we just can't abide them.

DR. BONE: Dr. Sobel.

DR. SOBEL: I just want to ask Dr. Genuth if studies, such as you've mentioned on carotid intimal thickness, do you feel this is a unique characteristic of troglitazone, or do you feel that's a class effect?

DR. GENUTH: I have no way of knowing.

DR. SOBEL: And the reason I'm saying this is that we always have to provide a certain look at a class in which despite down sides, there may be up sides. Not that I'm favoring such a thing, but you've introduced an idea where we're cumulating, say, a group of advantages, which may be attributed to the, quote, to the drug that has more hepatic effect. I don't know. This is something which we should consider.

DR. GENUTH: I haven't the slightest idea, in answer to your question.

DR. SOBEL: I haven't either. I just wanted to know what you were thinking.

DR. GENUTH: I am only citing one peer-reviewed

observation.

DR. SOBEL: Okay.

DR. BONE: Presumably sponsors of the other two drugs are immediately designing trials to evaluate this question.

(Laughter.)

DR. GENUTH: I think they read that journal, they already know it, and the studies are in progress.

DR. BONE: I'm sure.

I guess the knotty problem here, it seems for everybody involved, is how to find out as efficiently and expeditiously as possible whether there is a problem that is sufficiently infrequent to have escaped detection during the clinical trials, the phase 3 and phase 2 clinical trials, but nevertheless would be one which would have to be considered in the long-term use of the drug. And we've talked about surveillance and various approaches to that, monitoring, sort of an amplified, intensified surveillance carried out, however well it would be carried out.

I guess my question is, in light of the experience of the FDA, and its epidemiology specialists especially, have had with the previous drug in this class of concern, is there another approach that anyone has come up with that might quickly and convincingly answer this sort of question? I say this almost as a rhetorical

question, because I'm sure we would have heard about it if they did. But I'm going to ask that anyway.

DR. BILSTAD: Yes, you would have heard about it had we had any good ideas.

Yesterday, we touched upon the two approaches to it. One is if you have periodic monitoring recommended in the labeling, and then you rely on the spontaneous reporting system to report cases and try to make some judgments about the incidence based on that. And there's a lot of assumptions that go into that, under-reporting being a big one, and also the concern about the degree to which monitoring is really taking place, as used in the community, as opposed to a clinical trial. And with a clinical trial, the problem obviously is the feasibility of doing one to detect such rare events.

So, ideally, under controlled conditions, doing monitoring and making sure that monitoring is done, that could give you an answer. But the number of patients that would need to be included is large enough to make that a formidable undertaking.

DR. BONE: Having noted the position of the sponsor that monitoring is not required, I would not be surprised if, nevertheless, some consideration has been given to how some monitoring program could be combined with other efforts in order to really amplify the efficiency of

the reporting system with regard to a particular drug in order to get as much information as possible in a relatively short period of time. And I would be very interested to know, and I'm sure that my colleagues would, whether the sponsor has any ideas along those lines.

DR. SCHNEIDER: As the incidence or potential occurrence of this type of event is exceedingly rare, when we had our trusty statistician try to figure out how many patients it would take to do it, it seemed like it would be about half of the market in the United States in like the first year. And we said, okay, we can't do it that way.

DR. BONE: You don't expect to get half the market in the first year?

(Laughter.)

DR. SCHNEIDER: Ask them.

(Laughter.)

DR. SCHNEIDER: And what we really thought was one of the most important things is to get information out to the clinicians in the field. And we really thought that spending some time with both our field sales force and also our marketing partner Lilly's sales force, who already know all the diabetologists and the endocrinologists, and spending some time with them and explaining that we really are very sensitized to this issue and we want to make sure that any cases of elevated LFTs -- or that they explain to

their patients about the symptoms associated with liver dysfunction and that we hear about them as soon as possible within the company, and that we are able to incorporate that information into a database, but have it immediately reviewed by our external hepatology panel just to make sure that we're not misunderstanding something or misinterpreting something, so that we can get the warning signs as quickly as possible.

I do think that the post-marketing report system has really been sensitized to this issue. The fact that there was a public hearing about Rezulin a month ago, the fact that I think the Wall Street Journal has articles, the Los Angeles Times has articles, and there have been a lot of lay press about this, I think that for both this drug and Avandia, you will probably see very prompt post-marketing reports if there should be something that happens, and then having the extra safeguard of having an outside panel look at these very objectively would be very helpful.

DR. BONE: For example, have you considered two possible things that you might want to keep in mind? One would be ways in which the companies marketing the product might encourage patients to comply with some kind of follow-up regimen, and also the possibility that your sales force would be in a position to not only solicit the

responses from the prescribing physicians, but also not only then to provide a numerator for the denominator because I'm sure you will have a very good idea of how many patients those individual physicians would be treating with a particular drug. This would be, it strikes me, one possibility. Have you considered something along those lines?

DR. SCHNEIDER: At the moment, we sort of are two separate companies, so we have the R&D group in Princeton and we have our sales and marketing folks in Chicago. And we're trying to figure out all the pieces that go along with this. And that specific idea we haven't discussed, but I think that could be something that can easily be discussed, again, not only with our sales force, but also our colleagues from Lilly.

DR. BONE: It strikes me we've got this tension here, the less intense effort we make, the longer the question -- or whatever lingering aroma -- will take to go away. And at the same time, we have to trade that off against the burdens of doing the monitoring and making the effort. And I think this is the question that will be probably discussed for some time before it's resolved.

Other questions or comments from the committee?

Dr. Hirsch and then Dr. Genuth.

DR. HIRSCH: Just briefly. I take it, from my

own standpoint, it seems almost sure that the two newest drugs have less hepatotoxicity in the short run than the first drug. I think that's a reasonable conclusion that I've come to.

So, one might say, what's the fuss about this? Well, the fuss about it is we don't understand all the things we should about these drugs, and there's a very real possibility that later in the game, at 9 months or 1.2 years or something, we may see something popping up. We don't know that. And there are even some theoretical reason as to why, remotely, that could be a possibility.

So, this speaks strongly for some sort of continuous but attenuated monitoring system, because you can't obviously keep this going forever, but at least in the short run, or in the immediate future, to have some kind of monitoring going. I think, just as an aside, given our health care system, the stipulation that there be some kind of monitoring as a recommendation is wise, rather than leaving it up in a more nebulous way to the good wishes of competitive health care systems or whatever.

DR. BONE: All right. Dr. Genuth.

DR. GENUTH: Yes. I think, Henry, you really have an ingenious suggestion there for some incentive system. If the company would give 1 month's free supply of the drug every time the patient keeps an appointment for

monitoring -- and you did that for 6 months or so; maybe a year -- in the end, I think everybody would benefit, even profit.

DR. BONE: The company may wish to consider the magnitude of that incentive.

(Laughter.)

DR. BONE: Dr. Illingworth.

DR. ILLINGWORTH: One suggestion in this vein would be to have some kind of a patient registry. This would allow patients to be identified who are on the drug, who have been started on it, to get a numerator of how many patients are being treated, and then get follow-up on those patients, and also look for potential drug interactions. As we saw earlier on, two of the rises in transaminases occurred when antibiotics were started. And clearly, you will get rises in liver enzymes that are often due to drug-drug interactions or other drugs added concurrently. You want to get a good history.

DR. BONE: Other comments on this point? And then we'll go on to just review some of the other topics, and then go through the questions, I think.

Dr. Molitch.

DR. MOLITCH: I think that this is a problem that's probably going to surface again for other drugs in the future, and some thought really needs to be given to

how to do large-scale screenings of patients. Whether companies will want to contract with some sort of managed care organization or a large pharmacy -- Walgreen's type of a group -- where patients can come in with a filter paper and stick their finger, put a piece of filter paper in a tube and give it to the pharmacist at the time they collect their new monthly prescription, so that it eventually gets run and collected.

I think some creative ideas have to be given to trying to create a method like this to do this, not just for this drug, but that might then be applicable for other things, as well, in the future. And my guess is that we're probably going to need to start with this one for these two.

DR. BONE: Thank you.

Do committee members have any further discussion on the other topics that we were asked to address? I don't know if the edema question is -- if you had a chance to look at whether you had emergence of -- well, let's say -- worsening of edema as a significant AE.

DR. SCHNEIDER: It's actually a problem with the dictionary terms or the dictionary terminology. Edema, as a new phenomenon, would code to edema, and worsening edema would code to edema.

DR. BONE: I see.

DR. SCHNEIDER: So, we have to go back to the original cases, and then we'll let you know. So, it's just a dictionary problem.

We can tell you that absolutely the number is no bigger than the number that we showed you. But I can't tell you which one of those had preexisting edema.

DR. BONE: Thank you.

DR. SCHNEIDER: But we'll be more than happy to provide the information to the advisory committee. It's just not something that we can put together today.

DR. BONE: Fair enough. Thanks for trying.

Obviously that phenomenon seems to underlie at least two of the questions which we were asked to address, which had to do with the decline in the hemoglobin and hematocrit concentration and the cardiac questions. Let's talk for a second or two about the adequacy of the echo study. There was a point made by the medical review that this was designed and conducted a little bit differently from the way in which the other drugs in the class were evaluated.

And I guess I'm wondering if members of the committee have any thoughts on that topic. For example, should the study be done over or is it acceptable as it is, even if it doesn't have the same kind of comparison?

(No response.)

DR. BONE: Committee members do not seem to be responding.

Dr. Molitch, do you have a response?

DR. MOLITCH: I think the fact that it was done against placebo as opposed to active drug, in fact, works against -- they might be seeing a worsening effect with the placebo group, and there really wasn't any difference seen between the two. If there's an increase in plasma volume that occurs with the drug that wasn't seen with the placebo, that would have a worsening effect, but they didn't see anything. I'm not sure it's a critical defect.

DR. BONE: I see. So, you think that that consideration might offset the point that Dr. Misbin made about the fact that the diabetes might be affecting the cardiac status of the placebo patients?

DR. MOLITCH: I don't think so in that short a period of time.

DR. MISBIN: I didn't quite understand. Could you explain it again, please?

DR. BONE: He's saying if the placebo patients didn't accumulate any fluid or gain any weight, that that might counterbalance the effect. Is that right?

DR. MISBIN: Yes. I'm not sure that there would be that much worsening over a 26-week period.

DR. BONE: Dr. Levitsky.

DR. LEVITSKY: In studies we did some years ago in children, if you improve diabetes control, you can show rather remarkable changes in echocardiogram in a period of 4 months. I'm not sure that that's necessarily true.

DR. BONE: Can the sponsor provide us with information about the change in diabetic control experienced by the two groups during the study? In other words, was there an improvement in the diabetes control of the pioglitazone group in comparison with the placebo control group?

DR. SCHNEIDER: In a word, yes.

DR. MISBIN: Remember, you have established a rule that we don't discuss efficacy.

(Laughter.)

DR. BONE: Well, we're going to make a special exception, without modifying, only to know whether it answers the specific safety question.

DR. SCHNEIDER: There was improvement in HbA1c, statistically significant improvement, from baseline in the three highest-dose groups -- 15, 30, and 45.

DR. BONE: Okay.

DR. SCHNEIDER: And there was an improvement in the lowest-dose group, but it did not reach statistical significance.

DR. BONE: So this leaves, I guess,

Dr. Misbin's concern unanswered.

DR. SCHNEIDER: Right. That's why we're doing the additional analyses, based on levels of glycemic control that were achieved. There are some patients who -- about 70 percent, 75 percent, of the patients do respond to this agent. But there are patients who don't respond to the agent, and sometimes they will stay in clinical trials for the duration. So, we will have people in a dose group who were considered responders, and we also have people who were not considered responders. And we can do an analysis based on level of hemoglobin control.

In addition, in the long-term follow-up study, we will be providing a lot more longer-term data. We now have echoes for patients who have been treated with the drug for in excess of 2 years.

DR. BONE: So, in effect, the sponsor is trying to address Dr. Misbin's concern by essentially doing a statistical analysis to try to adjust for the effect of glycemic control in this. Is that a fair statement?

DR. SCHNEIDER: That's correct.

DR. BONE: Thank you.

DR. MOLITCH: One question along those lines.

DR. BONE: Dr. Molitch.

DR. MOLITCH: Is there a difference in the glucose responders with respect to the fluid retention

problem and the decreased hematocrit that occurs?

DR. SCHNEIDER: There was no relationship between both the small changes in hematocrit and response.

DR. MOLITCH: So you could get the same change in hematocrit without a glucose response?

DR. SCHNEIDER: That's correct.

DR. BONE: Thank you.

Dr. Hirsch.

DR. HIRSCH: I'm sorry, I may have just missed a point about the echocardiogram. You did baseline echoes and then echoes at 26 weeks, or whatever, both in the treated and the placebo groups. Did the placebo group show any echocardiographic deterioration? I thought that's what we wanted to find out, so we knew what the meaning of the lack of change in the echoes of the treated group is, if you see what I mean.

DR. SCHNEIDER: Yes, I see what you mean. And there were no changes from baseline to end of study in essentially in any of the treatment groups.

DR. HIRSCH: In either group?

DR. SCHNEIDER: That's correct.

DR. BONE: Okay, thank you. I think we've covered that fairly thoroughly now.

Are there any additional remarks that members of the committee wish to make before we go ahead and

discuss the specific questions that we were asked to address?

(No response.)

DR. BONE: There do not seem to be any such remarks. Very well, we'll proceed.

I'm going to take a little bit of a liberty here, I think, with the order of the questions. And that is because we are going to have a chance to discuss this class issue, I'm going to ask that when we deal with question 1a, which is, again, a short-answer question -- nobody is voting on anything -- can we also then address specifically pioglitazone first, as asked in that question, and then ask for members of the committee to have the opportunity then to comment again on questions 1 and 2 that were regarded as class-labeling questions, so we can dispose of that topic altogether, otherwise I think we'll be repeating ourselves. And this will also give members an opportunity, if they wish, to distinguish between drug-specific and class points with greater clarity, I expect.

Now, the two class-labeling questions are being passed out for the benefit of anyone who used theirs yesterday. Does anyone here at the table need one?

(No response.)

DR. BONE: Everybody has got one. Fine.

The first question that is drug specific is: What comments do you have from the safety standpoint about the effects of pioglitazone on the liver? And the class-labeling questions are, one: Should the labeling for members of the thiazolidinedione class of drugs, apart from troglitazone, address the subject of hepatotoxicity observed with troglitazone? And, if so, how? And should the labeling for other members of the class specify that liver testing should be performed at periodic intervals? And, if so, how frequently?

These are questions we discussed yesterday with the advantage of most of the information on rosiglitazone and this sort of preview of today's results that they were substantially similar. So we're going to deal with that topic first and then go on through the other questions.

I'm going to also suggest that one question which we routinely ask be included at the end. And that being comments about recommendations for phase 4 studies. And this will enable committee members to put phase 4 recommendations in that box, if you will, rather than trying to mix that into the other questions.

So, perhaps we'll just go around the table as we usually do, responding to question 1a, on the liver, and those two other questions about class labeling for liver, first, with respect to pioglitazone, and then the two

comments on the class as a whole. And perhaps we'll start with Dr. Illingworth.

DR. ILLINGWORTH: I think, based on the data that we've seen presented this morning, the safety profile in terms of the liver adverse effects is comparable to placebo. So, I'm not concerned that the drug has a high-profile liver toxicity. So I think, to comment from a safety standpoint, the effect on the liver, it's comparable to placebo.

For the class labeling questions, I do think there's been enough publicity concerning troglitazone, and we don't know yet data from 10,000, 20,000, 50,000 people whether pioglitazone is going to have rare adverse effects. I do think there should be something in the labeling about this is what we've learned from troglitazone. We don't have data yet on pioglitazone. Therefore, we need to monitor patients and see what happens. And I think it's going to be reassuring from the patient's point of view, as well.

DR. BONE: Would you, in that labeling, allow the manufacturer to distinguish between its pre-approval experience with a notation of the limitations of that information?

DR. ILLINGWORTH: I would. And I'd also emphasize perhaps in the labeling that the drugs are

metabolized by different pathways, with troglitazone going to the C3A4 almost exclusively, and this one not. So it does potentially have a safer metabolism pathway.

DR. BONE: Thank you.

Dr. Hammes, first, with the compound specific, and then the general.

DR. HAMMES: In terms of the pioglitazone, I am still concerned with that doubling in incidence rate we saw with the long-term studies. I'm concerned in that the total number of patients that were studied seems to be less with this drug than the other agents. Everything we've seen certainly indicates that it's comparable to placebo. I think we need a larger patient base to say that for sure.

And that leads me into the class thing. I think the labeling certainly ought to indicate that other class in this drug was associated with fatalities and that it needs to be considered as a possibility with this drug.

DR. BONE: What about monitoring?

DR. HAMMES: In terms of monitoring, I'm certainly not convinced that the frequency of monitoring needs to be what we were talking about with troglitazone. I'd like to see certainly baseline and perhaps whenever the patient is in for a routine follow-up, if it's quarterly or annually. If they're well maintained, there needs to be some less-intense monitoring.

DR. BONE: One of the points that was raised yesterday was about having a different monitoring approach for patients who had mild enzyme elevations prior to treatment. Would you distinguish between the two?

DR. HAMMES: Definitely, if they're elevated at treatment, they need to be intensely monitored, both for their own sake and for the drug.

DR. BONE: Dr. Critchlow.

DR. CRITCHLOW: I agree with those comments. And I would just like to add that with respect to this drug versus placebo, clearly there was no difference in the short run, but we've only had -- what is it -- 1,200 patient years, 1,600 patient years worldwide of exposure, much of which is in short-term exposure, 3 to 4 months. So, we really don't know the long-term effects or what the effect of cumulative exposure would be.

And in that sense, I would recommend caution in the sense that some type of certainly baseline assessment and probably some monitoring, 6 months, 12 months. Again, you're going to miss the transient elevations, but would then pick up those mildly elevated chronic elevations that you might need to do something about.

DR. BONE: Thank you.

Ms. Killion.

MS. KILLION: I think that it's fairly clear

that there are no significant red flags with this particular substance. I have less concerns about it than I did with troglitazone. I think that we've learned from troglitazone, and therefore we should include some information with respect to that in the labeling. I think that would be appreciated by patients.

As far as monitoring goes, I am a proponent of monitoring. I think that patients are rational actors, and that if the perceived benefit of the drug outweighs the onerous nature of the requirements -- again, I think if you're trying to set a standard of requirement for monitoring that is not too onerous, then you will get compliance on the part of the patients. And I think then you'll get the information that you need and you'll be able to make progress in this area where it's really required.

DR. BONE: Thank you.

Dr. Molitch.

DR. MOLITCH: I agree with the prior speakers. I think the amount of liver toxicity with this drug is certainly no greater than so far that we've seen from placebo, although I don't think we can clearly say that in the larger scheme until more data is obtained. But there are certainly no red flags now, I would agree with you.

My recommendation for the labeling would be, I agree that I think some mention ought to be made that other

members of this class have been shown to show liver toxicity and even deaths from liver disease, although nothing at this point would suggest that this necessarily is the same with this particular drug. Nonetheless, to be prudent, I think that I would advocate monitoring of this drug perhaps in a similar fashion to troglitazone and to rosiglitazone for a period of time -- perhaps a year -- and that that would be included in this.

DR. BONE: What frequency did you have in mind for monitoring?

DR. MOLITCH: Perhaps monthly for the first 8 months.

DR. BONE: I see. So you would treat just the same way.

DR. MOLITCH: Until we know for sure that it's --

DR. BONE: Dr. Levitsky.

DR. LEVITSKY: I would have to concur. I certainly think the labeling should be as was previously discussed. And although I see no evidence of increased hepatotoxicity with this drug, I don't think we have enough information yet. And if it's going to come to market reasonably soon, I would think that the best interests of the public would be served by having a monitoring scheme similar to troglitazone until more information is

available. But I think we have to be very flexible about discontinuing the monitoring scheme as soon as that information is available. And that would probably take a year or so.

DR. BONE: Thank you.

Dr. Genuth.

DR. GENUTH: I think, based on limited preclinical studies with relatively small numbers of patients and relatively short durations, there is no evidence that pioglitazone is toxic to the liver. Based on the preclinical pharmacology data, I'm still concerned that dogs don't like it if they get huge doses. So, that still worries me slightly. But certainly the clinical trial data, I think pioglitazone doesn't show any evidence of toxicity.

I think that, like my colleagues, the labeling should indicate that one member of this class was associated, is associated, with serious hepatic toxicity in rare instances. And I think it is reasonable to use some wording that introduces the notion that not all drugs in the same class necessarily will be associated with serious liver toxicity -- however you word that.

And I think monitoring should be done monthly for the 8 months that's being done now with troglitazone. I think when a large enough experience has been accumulated

after marketing, to quell our concerns about another troglitazone-type problem, then I think monitoring should stop.

I also am still kind of attracted to the idea that there be some specific guidelines about retesting within 1 week if the value of ALT is 3 times above the upper limit of normal. I am also somewhat encouraged with the notion that if the second test is normal that the drug could be continued.

DR. BONE: Dr. Hirsch.

DR. HIRSCH: I think we've already been through the first question so many times that I would just say, keep going, whatever. I agree with everyone.

The issue of labeling, I feel very strongly, and not for any emotional reason, but just as a physician. I feel that the labeling should indicate that these new drugs are members of a class of drugs, the first of which, or one of which, did produce serious liver problems. I think that should be noted.

I also feel that there should be monthly monitoring, and I think we ought to make a very definite recommendation for that the patient be monitored thereafter perhaps for an additional year, quarterly. And also I think a strong statement should be put in there that patients should be advised, or be aware, of the fact that

certain symptoms should be promptly reported to their physician.

Obviously jaundice is one of them. And I don't know what other presenting symptoms there were at the time of the troglitazone thing, whether nausea and vomiting or weight loss or whatever, but that congeries, that constellation of symptoms, the chief of which and most menacing would be the presence of skin discoloration or discoloration of the urine, however one would want to put this into appropriate terms.

DR. SOBEL: Could I have a clarification? In other words, a patient package insert also for these new members. Is that correct?

DR. HIRSCH: Correct, absolutely.

DR. SOBEL: That's the sense of the committee?

DR. HIRSCH: Well, it's my sense. I don't know about the others.

DR. MISBIN: Is it your suggestion then that, really, we just adopt the same labeling we have for troglitazone, both patient package insert as well as the professional package insert, the same monitoring, but a statement saying that this is based on data that occurred with a different drug in the class and at the moment we don't have any evidence to say that it would occur with this drug?

DR. HIRSCH: Well, I would even be stronger and say preliminary data indicate that in the short run, for the 6-month period, there has been less of this problem, if it exists at all. It's unclear whether this -- however, there are no data at the present time on longer periods of time. And because of this possibility, recommend --

DR. MISBIN: But rather than negotiating every word, is it your sense that really the label that exists with troglitazone already goes through the issue of jaundice and abdominal pain and all these other things. It would seem that that language could just be taken but, in addition, that this is related to a different drug and the other cautionary statements that you mentioned.

DR. HIRSCH: I think that's an important piece of information to give both the physician and the patient, yes.

DR. BONE: I'm going to ask the people on the right-hand side of the table, who didn't -- the answers have matured as we went around a little bit. I'm going to ask Drs. Illingworth and Hammes and Critchlow to address the question of frequency of monitoring, which is I think what Dr. Illingworth was about to do.

DR. ILLINGWORTH: Yes, this came up yesterday. I really do think that the clinical data that we have been provided with indicates that troglitazone, compared to

rosiglitazone and pioglitazone, is different in its metabolism and its toxicity. And I would, therefore, not favor applying the same monthly rule for pioglitazone as is applied now for troglitazone.

And obviously it's important to get baseline liver enzymes. I wrote down a potential algorithm: baseline, every 6 weeks times 2 for 3 months, and then every 2 months for say another 6 months, and then every 3 months for another 6 months, and then perhaps once every 6 months.

I think diminishing frequency will pick up the people who are going to do well. And also emphasize to patients and to physicians the risk of potential drug interactions. We've seen two cases of liver enzymes going up. And therefore, get a good history when you add a new drug. Make sure the patients are aware that there may be a drug interaction that we don't know about.

DR. BONE: Thank you.

Dr. Hammes.

DR. HAMMES: I would tend to lean toward that scheme of monitoring rather than the monthly, with the additional caveat that if we have an elevated test that it is followed perhaps weekly at a much more intense level.

And I also want to say that I am strongly in favor of the PPI for the class of drugs, and also the

statement that we have not identified the severe liver problem with these later two drugs should be part of it.

DR. BONE: Dr. Critchlow, please.

DR. CRITCHLOW: I would have to also say perhaps starting out at relatively more frequent -- and I know monthly seems like a lot, but perhaps monthly for the first 3 months, and then quarterly, and then annually after the first year might seem reasonable.

DR. BONE: Thank you.

For myself, with regard to question 1a, I think that we do not have evidence of a clinical hepatic safety problem with pioglitazone, although we take note of the FDA toxicology comments on preclinical data. And I think that, based on the information available, I would not distinguish between pioglitazone and rosiglitazone at this point.

With regard to the class labeling comments, I think that it is clear that we will need to discuss in the label the fact that the pioneer compound in this class did have a significant hepatic toxicity. I think it's fair to allow the distinction to be made between that compound and the others based on the information available, but this must be qualified by indicating that we only have pre-marketing information at his point on the other compounds. And this may simply be unrealistic to think that we're going to detect a rare event in any realistic

pre-marketing safety package.

The labeling as far as testing, I think this is really problematic. We have, as I mentioned yesterday, kind of a mixed purpose in this monitoring. I think when we monitor a patient on troglitazone, we are monitoring for that patient's specific benefit. And the risk is certainly perceived to be high enough to warrant that.

In this case, we're monitoring for a mixed purpose with these other drugs -- partly for the protection of the patient and partly in order to amplify the efficiency of the reporting system. This may be a slightly more complicated answer. To my mind, the intensity that we would apply for the second purpose, the intensity of monitoring that we would require for the second purpose, would be influenced by the efforts that were made by the sponsors of rosiglitazone and pioglitazone to improve the efficiency of the reporting process on the other end.

So, I could imagine that a less frequent monitoring consideration for patients who didn't have priority elevation of enzymes would be plausible if substantially more than the typical passive effort were very well structured as an arrangement to follow those.

So, I think there's interaction there. One, we have somewhat less concern about individual risk, at least at this point, but recognize that that doesn't eliminate

the risk of a rare event. On the other hand, our need for surveillance is another topic that I've just discussed.

One other consideration here with regard to monitoring for both purposes is that if the hypothesis that cumulative dose may influence risk and that the one reason why the more potent drugs are safer is that the amount of compound taken is less, then we may have to think about perhaps widening the interval of monitoring, but extending it for a period of time before we have the greatest assurance.

So, I think this is something where, frankly, some very careful epidemiologic calculations would bear on my exact answer for frequency of monitoring. I would adopt the troglitazone monitoring schedule for patients with prior elevation of enzymes on general principles rather than because of a specific problem. Both of these drugs have shown that patients with preexisting enzyme elevations get better. And it's entirely plausible that that's actually a therapeutic effect.

So much for question 1a and questions 1 and 2 on the other topic that are from the other list.

If we'll now just go through the comments on, what comments do you have from the safety standpoint about the effects of pioglitazone on lipids? And perhaps we'll just start with Dr. Illingworth again and see what he has

to say on the topic, if he has something to say.

DR. ILLINGWORTH: Well, lipid changes -- and I asked earlier on -- the drug apparently does have a slight PPAR alpha effect, which would suggest it has an effect that mimics the effect of fibric acid derivatives in a slight effect. This may explain why if you look at the lipid results in study 001, where the plot of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides is given separately rather than a ratio, which that value is worthless, we do see a significant reduction in triglycerides, a rise in HDL, and a very slight rise in LDL.

But this parallels what you see with any drug that reduces VLDL production or enhances lipolysis. If you lower triglycerides, generally you have a slight rise in HDL, as seen with the fibrates.

So, I think the lipid changes are beneficial. There isn't a significant rise in LDL. I think further studies need to be done, though, to look at well-defined patient groups, patients with normal triglycerides, which are hard to get in diabetics, and patients with more severe degrees of hypertriglyceridemia -- how much of a triglyceride effect do you get? And then also look at some mechanisms -- does the drug activate lipoprotein lipase, the effect on hepatic lipase, effects on VLDL metabolism,

and even postprandial lipemia studies will be interesting to look at. So, I find the effects on lipids to be beneficial.

DR. BONE: Thank you.

Dr. Hammes.

DR. HAMMES: I really can't add much to what Dr. Illingworth said. I'd second that.

Again, my comment that the studies we looked at today were 26 weeks as opposed to 52-week studies that we had looked at yesterday. And comparing the two is difficult on that basis, and I won't even try.

DR. BONE: Thank you.

Dr. Critchlow.

DR. CRITCHLOW: I can't add anything to the previous two speakers, but clearly, on the basis of the data presented, I would have no concerns about the safety or lack thereof in any way with the drug with respect to the lipids.

DR. BONE: Thank you.

Dr. Hirsch.

DR. HIRSCH: Well, I have nothing to add with the lipids except that in the labeling it might be noted that a lipid screen or a lipid analysis before starting the study would be useful to do, and give the data that the drugs have done X, Y, Z.

DR. BONE: Thank you.

Dr. Genuth.

DR. GENUTH: I don't see any problem with the lipids from the data we were given. But I would just add the comment that in the monotherapy study, only 54 percent of the patients on placebo and 62 percent on the active drug completed the study. So, the data is a little bit flawed.

DR. BONE: Dr. Levitsky, comments on lipid safety?

DR. LEVITSKY: I don't see any problems with the lipids either. I concur with the others.

DR. BONE: Dr. Molitch.

DR. MOLITCH: I agree.

DR. BONE: Ms. Killion.

MS. KILLION: I have no additional comments.

DR. BONE: And the Chair sees no evidence that there's a safety problem with regard to lipids.

DR. ILLINGWORTH: Henry?

DR. BONE: Dr. Illingworth.

DR. ILLINGWORTH: Just one additional comment. Given the fact there was one patient with a major increase in creatinine kinase on atorvastatin, and thinking to the risk of myopathy with fibrates and statins that are metabolized by the C3A4 system, perhaps further studies

should be done to define is there an increased risk of myopathy in a patient on a statin who is given this drug.

DR. BONE: Thank you.

DR. SCHNEIDER: Dr. Bone, could I make a comment?

DR. BONE: Well, it would be unusual to comment in the middle of the comments, but I guess if you could make it very concise, since we've gone around the table on this.

DR. SCHNEIDER: Very concise. We looked at all the rest of the patients who were on lipid-lowering agents, HMG CoA reductase inhibitors, and that's the only patient that had that one little blip. Nobody else had anything even 3 times the upper limit of normal. So, just for reassurance.

DR. BONE: Thank you.

The next topic we're going to be asked to comment on is the -- and I guess these are related topics. I'm going to once again exercise my prerogative to add the topic of edema, because that did come up, and I think it's related at least in some people's minds to C and D. So, maybe what I will ask people to do, as we go around, is to comment on what comments do you have from the safety standpoint about the effects of pioglitazone on the hemoglobin level, the heart and if they wish to make an

additional comment on edema, just treat all three together.

And perhaps we'll start with Dr. Molitch.

DR. MOLITCH: I think that the effects that we've seen today are similar to what we've seen as a class effect for these medications. I don't see anything striking that worries me except for the one comment that I think probably ought to be in the label, that in occasional patients who have underlying significant congestive heart failure that a significant worsening of this may occur.

DR. BONE: Ms. Killion, why don't you comment, and then we'll come back down the rest of the table.

MS. KILLION: I have no comments with respect to hemoglobin or heart, but as far as edema goes, I think I observed that there was an increase in edema in patients that were on insulin. And that does have some concern for me, as well. So that is something that I would like to see addressed. And certainly I'd want to know that in going in.

DR. BONE: Thank you.

Dr. Levitsky,

DR. LEVITSKY: I don't have any additional comments. I agree with what has been said.

DR. BONE: Dr. Genuth.

DR. GENUTH: I agree with Dr. Molitch word for word.

DR. BONE: Dr. Hirsch.

DR. HIRSCH: I agree. I am concerned a little bit about the long-term effects of this whatever it is -- increase in plasma volume -- and what this augurs in respect to the complications of diabetes, the nephropathy and the retinopathy. It may make it better. It may make it worse. I don't think we have any idea. I have no idea right now. And this is a very important thing, obviously, for phase 4 studies, if there are any surrogates of these, like albuminuria or whatever, that can be studied, this will be very important.

But in terms of what should go into the label, I think it should be pointed out that many patients will experience an increase in plasma volume, and therefore a small reduction in hemoglobin, hematocrit, et cetera, and that for this reason, individuals with congestive heart failure or with edema should be made aware that this can be a very important problem for them.

We've also not touched on the weight issue, which is I guess a part of this same thing, and the issue of people who may be more responsive to adipocyte hyperplasia or differentiation or whatever this may do -- namely, adolescents and children in puberty. Now, I don't know -- what's the troglitazone label? Does it say you shouldn't use this in children, or is there anything about

that?

DR. MISBIN: Much of this topic we've been discussing really is already in the troglitazone label. It doesn't specifically say you shouldn't use it in children, but it does talk about the fat cell hyperplasia, and the heart issue, as well. There are already statements warning patients with grade 3 heart failure that troglitazone should not be used. And since the data seem identical, I think the preliminary plan was to use the same labeling for those issues unless --

DR. HIRSCH: I'd be particularly concerned about using this during the pubertal and adolescent years for those reasons.

DR. MISBIN: All right. To the best of my recollection, that is specifically not there. It could be, but I think, unless there is some disagreement, that is a class effect. So, that kind of statement would have to be in all three labels, unless I misunderstand.

DR. BONE: We had some discussion along very much the same general lines about childhood and adolescent use and so forth yesterday, and I think the transcript will reflect rather extensive discussion on that point, as well.

Dr. Illingworth.

DR. ILLINGWORTH: I agree with Dr. Molitch's comments. I think the patients with congestive heart

failure need to be monitored very closely. And anybody with any sort of history of edema needs to be obviously monitored closely, too. Otherwise, no. The effects are due to fluid retention, and that's why the hematocrit goes down.

DR. BONE: Dr. Hammes.

DR. HAMMES: I agree with what's been said, with the emphasis that it quite clearly is a class effect and all the labels ought to be the same.

DR. BONE: Dr. Critchlow.

DR. CRITCHLOW: I agree with the previous speakers.

DR. BONE: From my point of view, the expansion of the extracellular space is important. It appears, as best we can --

DR. HIRSCH: Excuse me. I don't think it is ECF. There's no evidence for that. It's only plasma volume expansion. Is that correct? Has anyone ever measured ECF, extracellular? There are obviously wonderful ways and, simply, one should.

DR. MISBIN: There's date on troglitazone in normal volunteers.

DR. HIRSCH: On ECF specifically?

DR. MISBIN: Well, I don't remember that.

DR. HIRSCH: Thiocyanate, bromide, whatever?

DR. MISBIN: I just don't remember that. That, as far as I know, is the only definitive data.

DR. BONE: I don't see how plasma volume expansion alone would cause edema. I think it must be an ECF expansion to account for the edema.

DR. HIRSCH: I think the measures they've had are only of plasma volume expansion. Is that correct?

DR. BONE: Yes, but edema fluid is extravascular. So, I think it must be, although we haven't specifically had data on that point. But I think it must be, from the description of the physical examination.

DR. HIRSCH: I think the plasma volume increase, without -- I don't wish to belabor it -- without the edema, from what I understand, as people have had these little drops in hematocrit, et cetera, even in the absence of edema.

DR. BONE: Yes.

DR. HIRSCH: So, this may be an additional point.

DR. BONE: Well, either or both.

I think that's an important phenomenon. And it clearly seems to be a class effect, needs to be reflected in labeling, and needs to be studied. I think it's absolutely essential that we understand what the actual mechanism of this is for the reasons that Dr. Hirsch

elucidated, in terms of the long-term potential benefits or possibly adverse effects in diabetic patients. If this is something that affects vascular permeability or whatever, it needs to be figured out.

Question 2, major question 2, which has no subparts, is: Do you have any recommendations relating to safety for the labeling of pioglitazone other than for possible effects on the liver? And I think we could say, other than comments already made, as well, concerning labeling.

And perhaps Dr. Critchlow would begin, and we'll go around in a slightly different order.

DR. CRITCHLOW: I actually don't have any additional comments.

DR. BONE: All right. I think we've had a lot of discussion about a lot of these points in the course of the other questions.

Dr. Hammes, do you have any additional points to make about safety-related labeling?

DR. HAMMES: Nothing additional. I would just reemphasize the PPI.

DR. BONE: Thank you.

Dr. Illingworth.

DR. ILLINGWORTH: I think we discussed the issues that I feel need to be addressed in the labeling.

And, again, Dr. Misbin pointed out there is a precedent with what troglitazone has got in their labeling, and that should perhaps be used as the model, with exceptions where exceptions are justified.

DR. BONE: Additional comments, Ms. Killion?

MS. KILLION: No additional comments.

DR. BONE: All right. Dr. Molitch?

DR. MOLITCH: No.

DR. BONE: Dr. Levitsky?

DR. LEVITSKY: No additional comments.

DR. BONE: Dr. Genuth, any further comments?

DR. GENUTH: Just to reemphasize the importance of congestive heart failure and edema in the labeling. And I forgot the phase 4 part of the question. Can I just add --

DR. BONE: We're going to get to that in a minute. We're going to have one more comment, which isn't on the list, but I've added an opportunity to make phase 4 recommendations separate from the labeling. I didn't want to get those mixed up.

Dr. Hirsch?

DR. HIRSCH: No further comments.

DR. BONE: We'll all probably think of something later and we'll communicate with the agency, but I don't have any further suggestions at the moment for

labeling.

Now, this is the opportunity to make specific recommendations for phase 4 studies that we think are important. And the ones we've already mentioned we may just refer to or elucidate further as necessary, and anything that hasn't been mentioned, please do.

And perhaps Dr. Hirsch will begin this round.

DR. HIRSCH: Yes, I think I've been through this already. I think the emphasis on adolescents and children, differential effects on them from adults is a very important potential for a phase 4 study.

The issue of whether individuals who have responded to troglitazone in one way can now be looked at in terms of these drugs, to try to determine whether or not this is or is not a class effect would be a very important thing to do.

DR. BONE: You mean the liver effects?

DR. HIRSCH: The liver effects, yes.

And then, finally, also the data from the monitoring and so on obviously are, to some degree, a phase 4 whatever. But the other phase 4 studies involve all of the cardiac and the hematologic things that we've talked about considerably, and also the nature of the body weight increase, in terms of fat. I think these are just crying to be done by well-known physiologic techniques.

DR. BONE: Dr. Genuth, additional recommendations for phase 4 studies?

DR. GENUTH: Yes, I have two positive recommendations and one negative recommendation. I think the combination of repaglinide and pioglitazone should be studied. I think the triple combination of sulfonylurea, metformin, and pioglitazone should be studied. And I don't think you should study the combination of pioglitazone and troglitazone.

(Laughter.)

DR. BONE: Good. Thank you.

DR. LEVITSKY: Well, as the pediatrician on the panel, I'll restrict myself simply to making the plea that children and adolescents not remain orphans in terms of their drug status, and that the pediatric and adolescent studies be phase 4 studies, with particular attention to body composition, anemia, and the volume issues that were discussed.

DR. BONE: Thank you.

Dr. Molitch.

DR. MOLITCH: In addition to what's already been mentioned, I'll again reiterate what I said yesterday, that I was concerned about the one monkey study with rosiglitazone, suggesting that there may be some effect on ovulation, and that there be some sort of phase 4 study,

looking at ovulation or fertility or something along those lines, to be sure that that's not impaired with pioglitazone, as well.

DR. BONE: Would you look at that as an animal study or a human study?

DR. MOLITCH: I think it could be looked at as a human study, looking at just ovulation of people who are not on contraception, looking at fertility rates, et cetera. It would be nice to have an animal study, too.

DR. BONE: Would you be satisfied with an animal study?

DR. MOLITCH: I think if the study were done on the same species of animals that was done and showed the defect, and showed absolutely no defect at all, and with adequate statistical numbers, I probably would be satisfied with that.

DR. BONE: That might present fewer problems than treating ovulating women in terms of the conduct of the trial in a certain way.

DR. MOLITCH: Well, is there anything in the label to say that ovulating women should not be treated at the present time, for troglitazone, for example? There's nothing that demands that contraception be used currently?

DR. BONE: No. The trials were all done on contraception, weren't they?

DR. SCHNEIDER: Yes, they were.

DR. BONE: Yes, the sponsor replies in the affirmative. Okay.

DR. STEIGERWALT: The class for troglitazone is currently category B. There were not significant animal findings for troglitazone.

DR. MOLITCH: So that I think that it will be used in ovulating women. And if it's going to be used anyway, it would be nice to collect some data.

DR. BONE: Thank you.

Ms. Killion, recommendations for phase 4 studies?

MS. KILLION: I support all the recommendations that have been already presented.

DR. BONE: Thank you. It's great to be able to generate a wish list, isn't it?

(Laughter.)

DR. BONE: Perhaps Dr. Critchlow?

DR. CRITCHLOW: I think it would be interesting, but it also depends on what ends up in the label regarding monitoring. But I thought Dr. Bone did an excellent job crystallizing the nature of the conflict with the aims of monitoring. But it would be of interest to -- I guess I would just want to reemphasize that the concept of what it is that we're really trying to accomplish with

monitoring, and perhaps set up some different kinds of monitoring schemes, just to see what one might gain with different scenarios, that might be worth pursuing.

DR. BONE: Thank you.

Dr. Hammes.

DR. HAMMES: I would agree with the suggestions up to now. And I also would suggest a drug interaction study with the 3A enzyme would be in order.

DR. BONE: Dr. Illingworth.

DR. ILLINGWORTH: Yes, I would agree with what's been mentioned previously. And I think the idea of having some long-term studies with this drug used alone, with appropriate control, and used in combination therapy, followed for, say, 2 or 3 years would be very informative. In those kind of studies, perhaps looking at vascular reactivity or carotid ultrasound or some measure of vascular atherosclerosis parameters, and obviously follow the lipid profiles, follow the other things.

And the other thing is, again, going back to the effect on perhaps a slight effect on PPAR alpha, is there any effect on coagulation parameters? When you lower the triglycerides, do you affect fibrinogen, PAI-1, things like that? Those could be looked at in long-term studies, too.

DR. BONE: I think we've got everybody's except

for mine. I think there are a couple of points.

One is that we have just received the data comparatively recently from the large U.K. study of type 2 diabetes, using drugs of other classes, with results which were very encouraging. But we don't have, and for obvious reasons, the kind of outcome measurements that we would like to have for a new class. We've made reasonable projections about the benefits of therapy based on the reduction in glycosylated hemoglobin. And these seem very likely to be correct.

But I think that outcome studies, looking at the same kinds of endpoints would be extremely helpful and a very important contribution. And I think those will be expected, really, by the diabetes community, both from the patient and physician side of that.

I think that we've had a theme here of emphasizing mechanistic studies to look at phenomena such as the edema and so forth, and I fully endorse all of those. This may seem like a fairly long list of things that the committee are recommending for phase 4. But when we consider the scope of the problem of diabetes and the various manifestations of diabetes and its complications, and in fact the very large market that awaits effective drugs for the treatment of diabetes, I think that these are very reasonable proposals that we will be expecting to see

addressed.

Are there any final comments from members of the committee?

Dr. Illingworth.

DR. ILLINGWORTH: One comment that was raised yesterday -- in any long-term trials, you could not use, ethically, a placebo group, unlike in the U.K., where I think we recognize that we need to have active therapy and compare, ideally perhaps, two therapies -- one of which is perhaps slightly more effective than the other one -- but basically treat the patients.

DR. BONE: Obviously one of the groups would be something along the lines of one of the U.K. interventions, I suppose, or more than one perhaps.

Well, then, if there are no further comments, I will try to summarize.

The questions for the committee were in the nature of comments rather than any up or down vote. And I want to reemphasize the point that today we were only trying to address safety issues, and that the FDA will be considering the efficacy questions and risk/benefit questions, comparing those considerations, as they go on with the review, and that this in no way implies anything about or should any inferences be drawn about the efficacy data from this somewhat unusual way we did this. This is

for a specific reason.

The committee's comments in response to the first question, which is, what comments do you have from the safety standpoint about the effects of pioglitazone on the liver, generally reflected the favorable safety experience to date, which is similar to that of rosiglitazone. I think it was the general view of the committee -- and please, anyone, correct me if I've made a mistake -- the general view of the committee that labeling for drugs in this class at this point should reflect the experience with troglitazone, permitting a distinction to be drawn between the experience with troglitazone and the experience with other members of the class to date, with the qualification of the duration and scope of exposure.

There were additional questions asked about class labeling for monitoring. And the committee generally recommended that relatively frequent monitoring be carried out, recognizing that the experience so far has been good with drugs other than troglitazone in this class.

The drug, in question 1b, does not appear from the basis of information available to pose any safety hazard from the standpoint of lipids. The problem of declining hemoglobin and questions about cardiac function were regarded as linked to the retention of fluid. That seems to be a class effect that's not well explained at

this point. And while serious complications of this were not experienced in the clinical trials, the committee generally felt that the label should reflect the possible risk to patients who have either heart failure or other edematous diseases, such as nephrosis, for example, nephrotic syndrome.

With regard to additional recommendations relating to safety for the labeling pioglitazone, these I think constituted the major recommendations of the committee, with a number of additional points that were raised and are in the record about areas in which information is limited.

And the committee made a number of recommendations for phase 4 studies, directed at better understanding of mechanisms of some of the phenomena described above, and as a complement to the monitoring for greater assurance about the safety with respect to the liver. A number of additional suggestions were made, and again, these will be reflected in the record, but this was the major thrust, I think, of the recommendations for phase 4 study in the broadest sense.

If there are no amendments or additions by the committee, I want to thank the sponsor for their presentation and their flexibility in working with us on this slightly altered format. I want to thank the agency

for their excellent presentations and information. I want to thank the committee members for their participation. I wish to again thank the Executive Secretary, Kathleen Reedy, and the Office of the Advisors and Consultants, staff, for their excellent work in organizing the meeting. And I want to thank all of the audience for their respectful attention, and the comment also from the member of the public who spoke.

Thank you. This is adjourned.

(Whereupon, at 12:58 p.m., the committee was adjourned.)